Interventions for preventing the progression of autosomal dominant polycystic kidney disease

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Interventions for preventing the progression of autosomal dominant polycystic kidney disease (Review)

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[Intervention Review]

Interventions for preventing the progression of autosomal dominant polycystic kidney disease

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ABSTRACT

Background

Autosomal dominant polycystic kidney disease (ADPKD) is the leading inherited cause of kidney disease. Clinical management has historically focused on symptom control and reducing associated complications. Improved understanding of the molecular and cellular mechanisms involved in kidney cyst growth and disease progression has resulted in new pharmaceutical agents targeting disease pathogenesis and preventing disease progression. However, the role of disease-modifying agents for all people with ADPKD is unclear. This is an update of a review first published in 2015.

Objectives

We aimed to evaluate the benefits and harms of interventions to prevent the progression of ADPKD and the safety based on patient-important endpoints, defined by the Standardised Outcomes in NephroloGy-Polycystic Kidney Disease (SONG-PKD) core outcome set, and general and specific adverse effects.

Search methods

We searched the Cochrane Kidney and Transplants Register of Studies up to 13 August 2024 through contact with the Information Specialist using search terms relevant to this review. Studies in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE, conference proceedings, the International Clinical Trials Registry Platform (ICTRP) Search Portal, and ClinicalTrials.gov.

Selection criteria

Randomised controlled trials (RCTs) comparing any interventions for preventing the progression of ADPKD with other interventions, placebo, or standard care were considered for inclusion.

Data collection and analysis

Two authors independently assessed study risks of bias and extracted data. Summary estimates of effects were obtained using a random-effects model, and results were expressed as risk ratios (RR) and their 95% confidence intervals (CI) for dichotomous outcomes and mean difference (MD) or standardised mean difference (SMD) and 95% CI for continuous outcomes. Confidence in the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Main results

We included 57 studies (8016 participants) that investigated 18 pharmacological interventions (vasopressin 2 receptor (V2R) antagonists, antihypertensive therapy, mammalian target of rapamycin (mTOR) inhibitors, somatostatin analogues, antiplatelet agents, eicosapentaenoic acids, statins, kinase inhibitors, diuretics, anti-diabetic agents, water intake, dietary intervention, and supplements) in this review.

Compared to placebo, the V2R antagonist tolvaptan probably preserves eGFR (3 studies, 2758 participants: MD 1.26 mL/min/1.73 m^2, 95% CI 0.73 to 1.78; I^2 = 0%) and probably slows total kidney volume (TKV) growth in adults (1 study, 1307 participants: MD -2.70 mL/cm, 95% CI -3.24 to -2.16) (moderate certainty evidence). However, there was insufficient evidence to determine tolvaptan's impact on kidney failure and death. There may be no difference in serious adverse events; however, treatment probably increases nocturia, fatigue and liver enzymes, may increase dry mouth and thirst, and may decrease hypertension and urinary and upper respiratory tract infections.

Data on the impact of other therapeutic interventions were largely inconclusive. Compared to placebo, somatostatin analogues probably decrease TKV (6 studies, 500 participants: SMD -0.33, 95% CI -0.51 to -0.16; I^2 = 11%), probably have little or no effect on eGFR (4 studies, 180 participants: MD 4.11 mL/min/1.73 m^3, 95% CI -3.19 to 11.41; I^2 = 0%) (moderate certainty evidence), and may have little or no effect on kidney failure (2 studies, 405 participants: RR 0.64, 95% CI 0.16 to 2.49; I^2 = 39%; low certainty evidence). Serious adverse events may increase (2 studies, 405 participants: RR 1.81, 95% CI 1.01 to 3.25; low certainty evidence). Somatostatin analogues probably increase alopecia, diarrhoea or abnormal faeces, dizziness and fatigue but may have little or no effect on anaemia or infection. The effect on death is unclear.

Targeted low blood pressure probably results in a smaller per cent annual increase in TKV (1 study, 558 participants: MD -1.00, 95% CI -1.67 to -0.33; moderate certainty evidence) compared to standard blood pressure targets, had uncertain effects on death, but probably do not impact other outcomes such as change in eGFR or adverse events. Kidney failure was not reported.

Data comparing antihypertensive agents, mTOR inhibitors, eicosapentaenoic acids, statins, vitamin D compounds, metformin, trichlormethiazide, spironolactone, bosutinib, curcumin, niacinamide, prescribed water intake and antiplatelet agents were sparse and inconclusive. An additional 23 ongoing studies were also identified, including larger phase III RCTs, which will be assessed in a future update of this review.

Authors' conclusions

Although many interventions have been investigated in patients with ADPKD, at present, there is little evidence that they improve patient outcomes. Tolvaptan is the only therapeutic intervention that has demonstrated the ability to slow disease progression, as assessed by eGFR and TKV change. However, it has not demonstrated benefits for death or kidney failure.

In order to confirm the role of other therapeutic interventions in ADPKD management, large RCTs focused on patient-centred outcomes are needed. The search identified 23 ongoing studies, which may provide more insight into the role of specific interventions.

PLAIN LANGUAGE SUMMARY

Which therapies are the most effective for preventing the progression of autosomal dominant polycystic kidney disease?

Key messages

• For people with autosomal dominant kidney disease (an inherited condition that causes fluid-filled sacs called cysts to develop in the kidneys), the medicine tolvaptan probably preserves kidney function and slows the total volume growth of the kidney.

• Targeted low blood pressure and the use of somatostatin analogue medication (which aims to suppress growth factors) probably slow the total volume growth of the kidney but have little or no effect on kidney function.

• The small number of people enrolled in these studies, the wide range of treatments used, and the outcomes reported made it difficult to interpret the results. Larger, well-designed studies with common outcomes and longer follow-ups are needed.

What is autosomal dominant polycystic kidney disease?

Autosomal dominant polycystic kidney disease is an inherited condition that causes fluid-filled sacs called cysts to develop in the kidneys. These cysts can grow very large. The most common symptoms include high blood pressure, back or side pain, bleeding, and a swollen abdomen. Many people with this condition will develop kidney failure (a condition where the kidneys no longer function well enough to

keep a person alive) at some point in their lives. Treatments include medication to control blood pressure, pain relieving medication, and cyst removal.

What did we want to find out?

We wanted to find out which treatments help slow or stop the formation and growth of cysts in the kidney, the progression to kidney failure, and the harms of these medications.

What did we do?

We searched for studies that assessed the benefits and harms of randomly allocated treatments for preventing autosomal dominant polycystic kidney disease progression. We compared and summarised the results of the trials and rated our confidence in the information based on factors such as trial methods and sizes.

What did we find?

We found 57 studies that randomised 8016 people to 18 different treatments. Studies were conducted around the world, mainly in Europe and the United States. Treatment duration and follow-up ranged from two days to seven years. The types of interventions included medication that alters the way the kidney concentrates the urine, medication aimed at stabilising the volume of the cysts and preventing them from growing, blood pressure-lowering medication, lipid-lowering medication, fish oil, and dietary changes such as the amount of water a person drinks.

Compared to placebo (dummy medicine), tolvaptan (a class of medicine known as vasopressin 2 receptor antagonists) probably preserves kidney function and slows the increase in total kidney volume; however, it may increase dry mouth and thirst and probably increases waking at night to urinate and fatigue.

Reducing blood pressure to lower than standard targets and somatostatin analogues (a medicine aimed to suppress growth factors) probably slowed the growth of the kidneys; however, they probably do not result in any difference in kidney function. Somatostatin analogues probably increase hair loss, diarrhoea, dizziness and fatigue, while reducing blood pressure probably does not result in more side events. Their effect on death was uncertain. Other treatments investigated had unclear results, with data being sparse and inconclusive.

What are the limitations of the evidence?

The small number of studies per comparison and the small size of the studies were limitations in this review. Not all the studies provided data about the outcomes we were interested in.

We are moderately confident that tolvaptan preserves kidney function and slows total kidney volume growth. We are also moderately confident that targeted lower blood pressure and somatostatin analogues decrease total kidney volume but have little or no effect on preserving kidney function.

We are very uncertain about any of the other treatment options.

How up to date is the evidence?

The evidence is current to August 2024.

Summary of findings 1. Summary of findings table - V2R antagonists compared to placebo for autosomal dominant polycystic kidney disease

V2R antagonists compared to placebo for autosomal dominant polycystic kidney disease

Patient or population: autosomal dominant polycystic kidney disease
Setting: outpatients
Intervention: V2R antagonists
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with V2R antagonists				
Death follow-up: mean 12 months	1 per 1000	**0 per 1000** (0 to 12)	**RR 0.34** (0.01 to 8.22)	1370 (1 RCT)	⊕⊝⊝⊝ Very low[a,b]	--
Kidney failure - not reported	-	-	-	-	-	--
Mean change in eGFR follow-up: mean 20 months	The mean mean change in eGFR was **-3.6** mL/min/1.73 m^2	MD **1.26 mL/min/1.73 m^2 higher** (0.73 higher to 1.78 higher)	-	2758 (3 RCTs)	⊕⊕⊕⊝ Moderate[a]	--
Total kidney volume follow-up: mean 36 months	The mean total kidney volume was **5.5** mL/cm	MD **2.7 mL/cm lower** (3.24 lower to 2.16 lower)	-	1307 (1 RCT)	⊕⊕⊕⊝ Moderate[a]	Additional results NOCTURNE 2020 "The pooled tolvaptan treatment groups (MR+IR) (–2.07%, P = 0.0127), the tolvaptan MR 80 mg group (–2.55%, P = 0.0108), and the tolvaptan MR 50 mg group (–2.46%, P = 0.0155) each exhibited a significantly greater mean percent decrease in TKV from baseline to week 3 versus the placebo group (0.09%)." Schafer 2019: In a paediatric population (4-17 years old) tolvaptan therapy did not result in a significant difference in height-adjusted TKV
Serious adverse events	129 per 1000	**137 per 1000** (88 to 215)	**RR 1.06** (0.68 to 1.66)	3076 (4 RCTs)	⊕⊕⊝⊝ Low[c,d]	--

follow-up: mean 15 months	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_443878750952935637.

[a] Serious risk of bias: Due to study limitations
[b] Very serous imprecision: Large confidence intervals
[c] Serious inconsistency: Results distributed either side of the no effect point
[d] Serious imprecision: Due to large confidence intervals

Summary of findings 2. Summary of findings table - Somatostatin analogues compared to control for autosomal dominant polycystic kidney disease

Somatostatin analogues compared to control for autosomal dominant polycystic kidney disease

Patient or population: autosomal dominant polycystic kidney disease
Setting: outpatients
Intervention: somatostatin analogues
Comparison: control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control	Risk with somatostatin analogues				
Death follow-up: mean 30 months	0 per 1000	**0 per 1000** (0 to 0)	**RR 3.02** (0.12 to 73.55)	309 (1 RCT)	⊕⊝⊝⊝ Very low[a,b]	--
Kidney failure follow-up: mean 33 months	50 per 1000	**32 per 1000** (8 to 124)	**RR 0.64** (0.16 to 2.49)	405 (2 RCTs)	⊕⊕⊝⊝ Low[c,d]	--

Change in GFR follow-up: mean 26 months	The mean change in GFR was **-5.13** mL/min/1.73 m^2	MD **0.1 mL/min/1.73 m^2 lower** (0.7 lower to 0.5 higher)	-	404 (3 RCTs)	⊕⊕⊕⊖ Moderate[c]	Additional data from Temmerman 2012: Quote: "In ADPKD patients, there was no significant difference in GFR between placebo and both treatment groups (LAN 90 or 120 mg) (Mann-Whitney Rank Sum test: P = 0.09)"
Total kidney volume (TKV) or height adjusted TKV follow-up: mean 20 months	-	SMD **0.33 lower** (0.51 lower to 0.16 lower)	-	500 (6 RCTs)	⊕⊕⊕⊖ Moderate[a]	--
Serious adverse events	134 per 1000	**243 per 1000** (136 to 437)	**RR 1.81** (1.01 to 3.25)	405 (2 RCTs)	⊕⊕⊖⊖ Low[a]	--

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; **SMD:** standardised mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_443880215154316389.

[a] Serious risk of bias: Due to study limitations
[b] Very serious imprecision: Due to single study and large confidence intervals
[c] Serious inconsistency: Due to results distributed either side of no effect point
[d] Serious imprecision

Summary of findings 3. Summary of findings table - Low blood pressure targets compared to standard blood pressure targets for autosomal dominant polycystic kidney disease

Low blood pressure targets compared to standard blood pressure targets for autosomal dominant polycystic kidney disease

Patient or population: autosomal dominant polycystic kidney disease
Setting: outpatients
Intervention: low blood pressure targets

Comparison: standard blood pressure targets

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard blood pressure targets	Risk with low blood pressure targets				
Death follow-up: mean 5.65 years	7 per 1000	**1 per 1000** (0 to 30)	**RR 0.21** (0.01 to 4.30)	558 (1 RCT)	⊕⊖⊖⊖ Very low[a,b]	--
Kidney failure - not reported	-	-	-	-	-	--
Change in eGFR follow-up: median 6.5 years	The mean change in eGFR was **-3** mL/min/1.73 m^2	MD **0.1 mL/min/1.73 m^2 higher** (0.32 lower to 0.52 higher)	-	557 (1 RCT)	⊕⊕⊕⊖ Moderate[c]	--
Change in total kidney volume follow-up: mean 60 months	The mean change in total kidney volume was **6.6** mL/cm	MD **1 mL/cm lower** (1.67 lower to 0.33 lower)	-	558 (1 RCT)	⊕⊕⊕⊖ Moderate[c]	--
Serious adverse events follow-up: mean 5.65 years	278 per 1000	**253 per 1000** (192 to 331)	**RR 0.91** (0.69 to 1.19)	558 (1 RCT)	⊕⊕⊕⊖ Moderate[c]	--

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_443878394135892135.

[a] Serious risk of bias: Due to study limitations
[b] Very serious imprecision: Due to single study and wide confidence intervals
[c] Serious imprecision: Due to single study results

BACKGROUND

Description of the condition

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited disorder that affects kidney function. ADPKD is characterised by uncontrolled growth of kidney cysts that alter normal kidney structure and progressively impair kidney function. This may result in the requirement for dialysis or kidney transplantation in people with late stages of ADPKD, and cardiovascular death is high. ADPKD accounts for about 5% of new patients commencing kidney replacement therapy (KRT) in the US (USRDS 2008) and 3% to 10% in Europe (ERA-EDTA 2011). By the age of 60 years, about half of all people with ADPKD develop kidney failure (Torres 2009). The incidence of the condition ranges from 1:400 to 1:1000 in the general population (Lewis 2014).

ADPKD is a heterogeneous genetic disorder commonly caused by mutation of the *PKD1* (on chromosome 16p13.3) or *PKD2* (on chromosome 4q21) genes, which encode two different polycystins. *PKD1* mutations account for about 85% of all ADPKD cases and are usually associated with a more severe phenotype, characterised by an earlier appearance and greater numbers of cysts, and faster progression to kidney failure. Other rare genetic mutations recently identified in *GANAB* and *ALG9* suggest the genomics of ADPKD is more complex than originally considered (Besse 2019; Cordido 2017). As the condition progresses, an increase in cyst numbers and size leads to complications such as hypertension, bleeding, infections, discomfort and pain. Cyst expansion is a major factor in the progressive loss of functional kidney tissue, which results from both direct (parenchymal compression) and indirect (fibrosis) mechanisms.

Description of the intervention

Although several interventions have been proposed for the management of ADPKD, the only disease-modifying therapy is the vasopressin type 2 receptor (V2R) antagonist, tolvaptan. However, its widespread use is limited by side effects, high cost, and restricted availability. Other therapeutic management for people with ADPKD focuses on controlling secondary conditions arising from kidney failure, particularly hypertension, to alleviate morbidity and prevent death.

How the intervention might work

The mechanisms of cyst growth are complex, and various potential therapeutic targets have been proposed. Cyclic adenosine monophosphate (cAMP) plays a central role in cystogenesis (Hanaoka 2000). Arginine-vasopressin (AVP) is the main inductor of cAMP production, working to activate an enzyme, adenylate-cyclase, via V2R binding. Administration of V2R antagonists has been shown to reduce cyst and kidney volume and prevent kidney function impairment in experimental polycystic kidney disease (PKD) (Gattone 2003). cAMP levels can also be lowered by reducing the amount of circulating AVP by increasing water intake to reduce serum osmolality that can suppress the central release of AVP. Consistent with this, experimental findings show that chronic high fluid intake limits cyst growth (Nagao 2006).

cAMP accumulation is prevented by stimulating the somatostatin receptors (SR) SST2 (Masyuk 2007). The unexpected finding that somatostatin administration was effective in stabilising cyst volume in an ADPKD patient with pituitary adenoma (a type of brain tumour) prompted interest in testing the efficacy of SR-agonists (octreotide, lanreotide) using systematic approaches (Torres 2007).

A protein, tuberin, a regulator of mammalian target of rapamycin (mTOR) kinase, is another potential target. This was initially investigated following a retrospective analysis that showed both liver and kidney volume decreased amongst people with ADPKD who received rapamycin therapy following kidney transplantation (Qian 2008). This was confirmed by experimental models (Wahl 2006; Wu 2007), where the administration of mTOR inhibitors limited cyst enlargement and slowed the progression of chronic kidney disease (CKD). Additionally, activation of the AMP-activated protein kinase (AMPK) leads to inactivation of the mTOR pathway. Metformin has also been found to activate AMPK, potentially impairing cyst growth in ADPKD (Takiar 2011).

Other interventions, including dietary supplements of niacinamide (Zhou 2013), vitamin D (Rangan 2013), long-chain omega-3 polyunsaturated (eicosapentaenoic) fatty acids (Ogborn 2000), and administration of statins (Gile 1995), have demonstrated efficacy in slowing kidney impairment and contract cyst growth in different experimental models of PKD. Interventions broadly used to slow CKD, such as angiotensin-converting-enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB), may also produce similar beneficial effects on kidney function in people with ADPKD (Schrier 2009).

Why it is important to do this review

Kidney cyst growth usually precedes glomerular filtration rate (GFR) decline by several years (Grantham 2006; Grantham 2008). This suggests that early approaches targeting ADPKD biology could be helpful to slow the progression of ADPKD and improve patient outcomes. Given the limited treatment options currently available for ADPKD, an up-to-date evaluation of therapeutic agents considering their potential place in therapeutic management is important for patient and clinician decision-making.

OBJECTIVES

Our objectives were to evaluate the benefits and harms of interventions to prevent the progression of ADPKD and the safety based on patient-important endpoints, defined by the Standardised Outcomes in NephroloGy-Polycystic Kidney Disease (SONG-PKD) core outcome set (Cho 2017) and general and specific adverse effects.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) looking at interventions directed at preventing the progression of ADPKD were included, without duration restrictions. The first period was only considered for randomised cross-over studies. There were no language restrictions.

Types of participants

Inclusion criteria

Studies enrolling patients (adults or children) with a clinical diagnosis of ADPKD (assessed by magnetic resonance imaging (magnetic nuclear imaging) or echo tomography fulfilling Ravine criteria) confirmed or unconfirmed by genetic tests, with kidney and cyst volumes of any dimension, and CKD stages 1 to 4, as defined by the US National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines were eligible for inclusion.

Exclusion criteria

ADPKD patients with CKD stage 5 (GFR < 15 mL/min/1.73 m^2), receiving dialysis, or having undergone kidney transplantation were excluded from our analysis. Patients with autosomal recessive polycystic kidney disease (ARPKD) or other liver or kidney cystic diseases different from ADPKD were also excluded from the review.

Types of interventions

- V2R antagonists
- Somatostatin agonists
- mTOR inhibitors
- Anti-diabetic agents (including metformin or pioglitazone)
- Antihypertensive agents (including ACEi, ARBs, calcium channel blockers (CCB), beta-blockers)
- Diuretics
- HMG-CoA reductase inhibitors (statins)
- Antiplatelet agents
- Low blood pressure (BP) targets
- Increased fluid intake
- Low osmolar diets
- Supplements (including vitamin D or vitamin D derivatives, curcumin, eicosapentaenoic acid, niacinamide)

Types of outcome measures

Outcomes were analysed at the end of treatment, and as change from beginning to end of treatment, where applicable.

Primary outcomes

Change in kidney function

- Serum creatinine (SCr) (mg/dL)
- Measured or estimated (e) GFR (mL/min or mL/min/1.73 m^2)
- Creatinine clearance (CrCl)
- Doubling of SCr
- Kidney failure (including the need for KRT or transplantation).

Secondary outcomes

- All-cause death
- Kidney pain (rate of episodes or subjective perception as assessed by any analogue pain scale)
- Quality of life (QoL) (assessed by validated scales or any other instrument as reported by authors, such as SF-36 or KDQOL-SF questionnaires)
- Fatal and nonfatal major adverse cardiovascular events including, but not limited to, myocardial infarction (MI), cerebrovascular accident (CVA), congestive heart failure (CHF)
- BP: systolic (SBP) and diastolic (DBP) (mm Hg), mean arterial BP (MAP) (mm Hg)
- Total kidney volume (TKV) (mL or L), total cyst volume (mL or L), and total parenchymal volume (mL or L) assessed by magnetic nuclear imaging scan, echo tomography or computed tomography
- Any admission to hospital and duration of hospital stay (if long-term data were available from the studies)
- Urinary protein excretion: 24-hour proteinuria or 24-hour albuminuria (mg/d) or urine protein-creatinine ratio (UPCR) (mg/g or g/g) or urine albumin-creatinine ratio (UACR) (mg/g or g/g)
- Urine osmolality
- Adverse events: including but not limited to dizziness, diarrhoea, abdominal cramps and nausea (all treatments), hypernatraemia, thirst, dry mouth, transaminases elevation, headache (V2R antagonists), angioedema, hyperlipidaemia, anaemia, oral ulcers and infections (mTOR inhibitors), alopecia (somatostatin agonists), hyperkalaemia (ACEi and ARBs).

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Group's Specialised Register up to 13 August 2024 through contact with the Information Specialist using search terms relevant to this review. The Cochrane Kidney and Transplant Group's Specialised Register contains studies identified from the following sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials CENTRAL
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of kidney-related journals and the proceedings of major kidney conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney journals
6. Monthly searches of the International Clinical Trials Registry Platform (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register have been identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of the Cochrane Kidney and Transplant Group. Details of these strategies, as well as a list of hand-searched journals, conference proceedings and current awareness alerts, are available in the Specialised Register section of information about the Cochrane Kidney and Transplant Group.

See Appendix 1 for search terms used in strategies for this review.

Searching other resources

1. Reference lists of review articles, relevant studies and clinical practice guidelines.
2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

The search strategy described was used to obtain references relevant to the review. Titles and abstracts were screened independently by two authors (KSP, DJT) who discarded studies that were not applicable. However, studies and reviews that might include relevant data or information were retained initially and reviewed in detail. The same two authors independently assessed retrieved abstracts and, if necessary, the full text of these studies to determine which satisfied the inclusion criteria.

Data extraction and management

Data extraction was carried out independently by two authors (KSP, BC or DJT) using a standardised electronic data extraction form. Studies reported in non-English language journals were translated before assessment. Where more than one report of one study existed, reports were grouped together, and the report with the most complete data were used in the analyses. Where relevant outcomes were only published in earlier reports, these data were used. Any discrepancies between reports were highlighted.

Assessment of risk of bias in included studies

The following items were assessed independently by two authors using the risk of bias assessment tool (Higgins 2022) (*see* Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Was incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at risk of bias?

Measures of treatment effect

For dichotomous outcomes (kidney failure, commencement of KRT or transplantation, all-cause death, cardiovascular events, hospitalisations, adverse effects), results were expressed as risk ratio (RR) with 95% confidence intervals (CI). Where continuous scales of measurement were used to assess the effects of treatment, results were reported as mean difference (MD) or standardised mean difference (SMD) if different scales were reported (SCr, GFR, proteinuria or albuminuria, BP, cyst and organ volumes, QoL, kidney pain).

Unit of analysis issues

Data reported at the end of the first period of randomised cross-over studies were considered.

Dealing with missing data

Any further information required from the original author was requested by written correspondence (e.g. emailing the corresponding author), and any relevant information obtained in this manner was included in the review. Evaluation of important numerical data such as screened, randomised patients as well as intention-to-treat, as-treated and per-protocol population were carefully performed. Attrition rates, such as drop-outs, losses to follow-up and withdrawals, were investigated. Issues of missing data and imputation methods (such as last-observation-carried-forward) were critically appraised (Higgins 2022).

Assessment of heterogeneity

We first assessed heterogeneity by visual inspections of the forest plot. We quantified statistical heterogeneity using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.10 used for statistical significance, and with the I^2 test (Higgins 2003). A guide to the interpretation of I^2 values was as follows.

- 0 to 40%: might not be important
- 30 to 60%: may represent moderate heterogeneity
- 50 to 90%: may represent substantial heterogeneity
- 75 to 100%: considerable heterogeneity.

The importance of the observed value of I^2 depends on the magnitude and direction of the treatment effects and the strength of heterogeneity.

Assessment of reporting biases

If possible (i.e. greater than 10 studies), funnel plots were produced to assess the potential of small study bias, and further statistical testing of publication bias Eggers tests were performed. (Higgins 2022).

Data synthesis

Data for treatment effects were summarised using the random-effects model. The statistical method used for dichotomous outcomes was the Mantel-Hanszel inverse variance for continuous outcomes, and for time-to-event data reported as hazard ratios (HR) (95%), we have used a generic inverse variance.

Subgroup analysis and investigation of heterogeneity

We attempted to analyse heterogeneity through subgroup analysis. Heterogeneity amongst participants could be related to age (adults or children), stage of kidney disease (stage 3 to 5 not requiring dialysis), and severity of ADPKD (PROPKD score, cyst and kidney dimensions at baseline, presence or absence of CKD), genetic background (mutations in PKD1 or PKD2 genes) and study follow-up duration, were effect modifiers of the interventions studied.

Sensitivity analysis

Sensitivity analyses were performed to explore the influence of the following factors on effect size.

- Repeating the analysis, excluding unpublished studies
- Repeating the analysis, taking account of the risk of bias
- Repeating the analysis, excluding any very long or large studies to establish how much they dominate the results
- Repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), and country.

Summary of findings and assessment of the certainty of the evidence

We have presented the main results of the review in summary of findings tables. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schünemann 2022a). The summary of findings tables also include an overall grading of the evidence related to each of the main outcomes using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach (GRADE 2008; GRADE 2011). The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Schünemann 2022b). We have presented the following outcomes in the summary of findings tables.

- Death
- Kidney failure
- eGFR
- TKV
- Serious adverse events

RESULTS

Description of studies

The following section contains broad descriptions of the studies considered in this review. For further details on each individual study (Characteristics of excluded studies; Characteristics of included studies; Characteristics of ongoing studies).

Results of the search

The original 2015 review (Bolignano 2015) included 30 studies (2039 participants; 69 records) and excluded four studies; five studies were ongoing, and there were three studies awaiting classification. Authors of some included studies were contacted for additional information with respect to study methods and/or unreported data; four investigators responded to queries (LOCKCYST 2009; Soliman 2009; Temmerman 2012; Walz 2010).

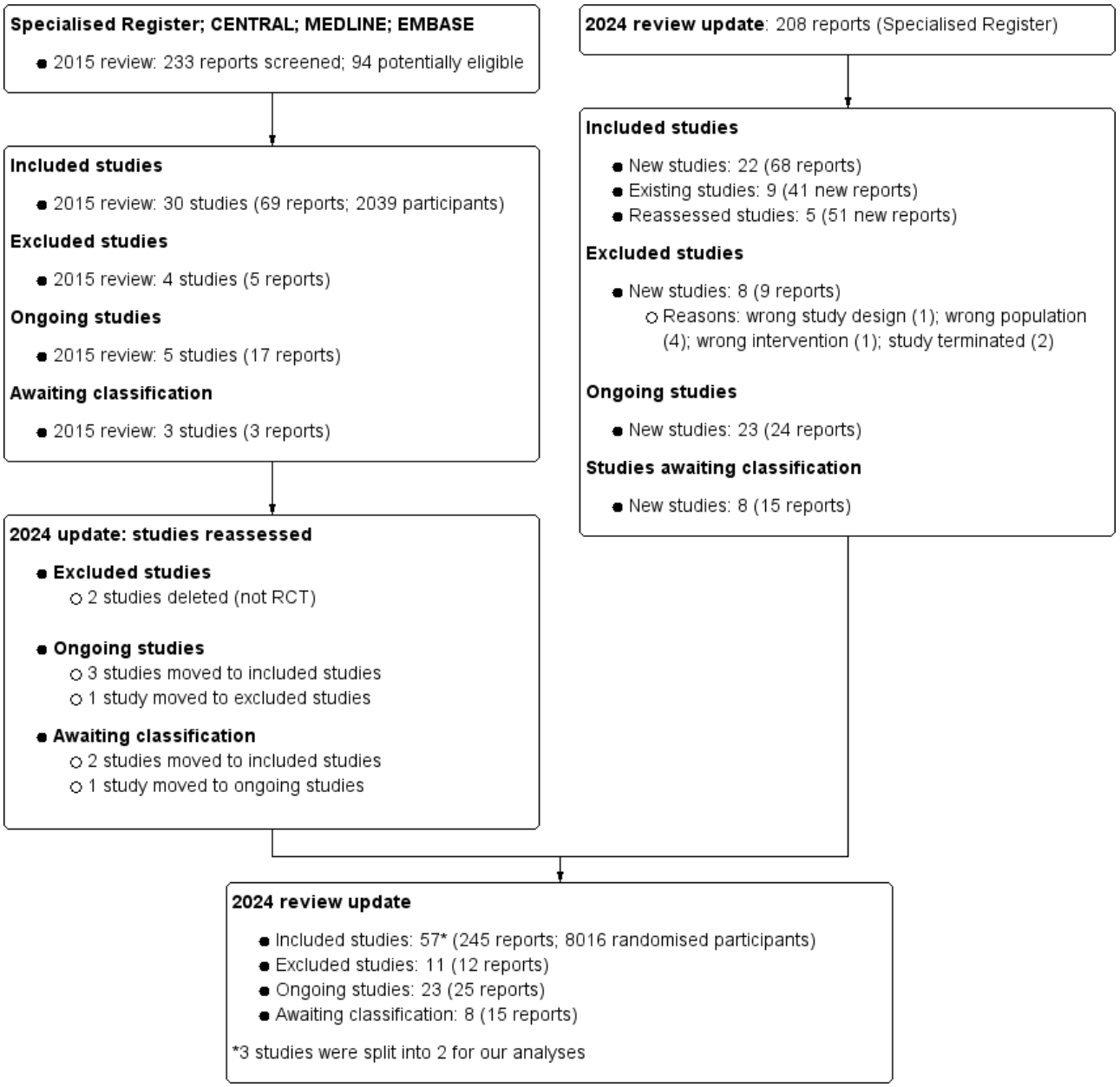
The latest search (13 August 2024) identified 208 new records. Twenty-two new studies (68 reports) were included, eight studies (nine reports) were excluded, 26 studies (35 reports) are ongoing, and there are three studies awaiting classification (four reports) (abstract-only publications or recently completed with no published results). We also identified 41 new reports of nine existing included studies and one report of an existing ongoing study.

We reassessed and reclassified five previous ongoing and awaiting classification studies (51 new reports) as included; one ongoing study was moved to excluded; one study awaiting classification was moved to ongoing; and we deleted two excluded studies which were not randomised.

A total of 57 studies were included (245 reports, 8016 randomised participants), 11 studies were excluded, 23 studies are ongoing, and eight studies are awaiting classification. These ongoing studies and studies awaiting classification will be assessed in a future update.

See Figure 1 for the study inclusion and exclusion process.

Figure 1. Flow chart showing study selection



Included studies

Eight studies were cross-over studies (Al Therwani 2017; Blazer-Yost 2021; Kramers 2020; Perrone 2020; Ruggenenti 2005; SIRENA 2010; Uchiyama 2021; van Dijk 2001). In five studies (AIPRI 1996; ELATE 2011; Hogan 2010; LOCKCYST 2009; Temmerman 2012), ADPKD patients represented a subpopulation of the study cohort, but separate data for the main study outcomes were only available in two (ELATE 2011; LOCKCYST 2009). The number of participants was not specified in Watson 1999. Except for five studies (Cadnapaphornchai 2005; Cadnapaphornchai 2011; Nowak 2020; Mora 2013; Schaefer 2019), all studies were performed in adults. Study duration ranged from single-day interventions to 60 months.

ADPKD and kidney volume assessment at baseline and end of treatment were performed by echo tomography in 12 studies (Biao 1997; Cadnapaphornchai 2005; Ecder 1999; Fassett 2010; Nakamura 2001d; Nakamura 2012a; Nutahara 2005; Uchiyama 2021; van Dijk 2001; van Dijk 2003; Watson 1999; Zeltner 2008), computed tomography in 10 studies (ALADIN 2 2019; ELATE 2011; Higashihara 2008; Hogan 2010; LOCKCYST 2009; Pasari 2019; Ruggenenti 2005; SIRENA 2 2016; SIRENA 2010; Temmerman 2012), and magnetic nuclear resonance imaging in 24 studies (ALADIN 2013; Braun 2014; Blazer-Yost 2021; Brosnahan 2022; Cadnapaphornchai 2011; Chaudhary 2021; DIPAK 1 2014; El Ters 2020; Nowak 2020; HALT-PKD Study A 2014; Melemadathil 2013; Mora 2013; NOCTURNE 2020; PREVENT-ADPKD 2018; RAPYD 2012; Schaefer 2019; Soliman 2009; SUISSE ADPKD 2007; TAME-PKD 2018; TEMPO 250 2011; TEMPO 3:4 2011; Tesar 2017; Vendramini 2021; Walz 2010). Methods of assessment were not specified in the remaining 11 studies.

All studies excluded patients with eGFR < 15 mL/min/1.73 m^2. Mean eGFR ranged from 26.8 to 124 mL/min/1.73 m^2 in adult ADPKD patients and from 102 to 142 mL/min/1.73 m^2 in children.

Total kidney volume was estimated in 30 studies (ALADIN 2013; ALADIN 2 2019; Blazer-Yost 2021; Braun 2014; Brosnahan 2022; Cadnapaphornchai 2005; Cadnapaphornchai 2011; Chaudhary 2021; DIPAK 1 2014; ELATE 2011; Nowak 2020; HALT-PKD Study A 2014; Higashihara 2008; Hogan 2010; LOCKCYST 2009; Melemadathil 2013; Mora 2013; NOCTURNE 2020; PREVENT-ADPKD 2018; RAPYD 2012; Ruggenenti 2005; Schaefer 2019; SIRENA 2 2016; SIRENA 2010; Soliman 2009; SUISSE ADPKD 2007; TAME-PKD 2018; TEMPO 3:4 2011; Vendramini 2021; Walz 2010) with mean values ranging from 576 to 2845 mL in adults and from 157 to 534 mL in children.

Total cyst volume was analysed in six studies (ALADIN 2013; Melemadathil 2013; RAPYD 2012; Ruggenenti 2005; SIRENA 2 2016; Walz 2010) with mean values ranging from 140 to 1709 mL. Total parenchymal volume was calculated in five studies (ALADIN 2013; Melemadathil 2013; Ruggenenti 2005; SIRENA 2 2016; Walz 2010) with values ranging from 242 to 680 mL.

The following comparisons were investigated.

- V2R antagonists
  - Tolvaptan versus placebo
  - High versus low dose tolvaptan
  - Immediate release versus modified release tolvaptan
  - Tolvaptan versus placebo during infusion of L-NG-monomethyl-arginine administration
  - Tolvaptan in combination with either hydrochlorothiazide, metformin, or placebo
  - Trichlormethiazide versus no thiazide diuretics in tolvaptan treated participants
- ACEi (enalapril, ramipril, lisinopril, or benazepril) were compared to the following:
  - ACEi versus placebo or standard care
  - ACEi versus calcium channel blocker (amlodipine)
  - ACEi versus ARB (losartan or telmisartan)
  - ACEi versus beta-blockers (atenolol or metoprolol)
  - ACEi (lisinopril) plus placebo versus ACEi (lisinopril) plus ARB (telmisartan)
- ARB (candesartan) versus calcium channel blockers (amlodipine)
- Long-acting somatostatin analogues were compared to the following:
  - Octreotide or lanreotide versus placebo
  - Octreotide alone versus octreotide plus everolimus
  - Lanreotide subcutaneously once every four weeks versus standard care only
- mTOR inhibitors were compared to the following:
  - Rapamycin/sirolimus or everolimus alone versus placebo or standard therapy
  - Rapamycin plus ramipril versus ramipril alone
  - Sirolimus plus telmisartan versus telmisartan alone
- Metformin versus placebo
- Pioglitazone versus placebo
- Spironolactone versus placebo
- Low versus standard blood pressure targets
- Dilazep dihydrochloride versus placebo
- Bosutinib versus placebo
- Eicosapentaenoic acids versus standard therapy
- Statins (pravastatin or simvastatin) versus placebo or standard therapy
- Calcitriol versus traditional Chinese medicine
- Cholecalciferol versus placebo
- Curcumin versus placebo
- Niacinamide versus placebo
- Low-osmolar diet and adjusted water intake to achieve urine osmolality ≤ 280 mOsm/kg water versus no intervention
- High water intake versus ad libitum intake.

Excluded studies

In this update, eight new studies were excluded. The reasons for exclusion for all studies were:

- Wrong population (Davis 2018; Dinh 2023; Hogan 2016; NCT05281328)
- Wrong intervention (Elue 2018)
- Outcomes of interest not part of the study design (Doulton 2006; Nakamura 2005a)
- Study terminated (FALCON 2021; ISRCTN57653760; MANGROVE 2022)
- Wrong study design (pharmacokinetic study) (Naver 2023).

Ongoing studies

There are 23 ongoing studies.

- Metformin versus placebo or standard care (CTRI/2022/05/042904; IMPEDE-PKD 2021)
- High water therapy versus tolvaptan (CTRI/2022/09/045945)
- Traditional Chinese Medicine versus placebo (Gan 2019)
- Statin (pravastatin, atorvastatin) versus placebo (Gitomer 2024; NCT05870007)
- Modified Atkins diet versus normal calorie diet (GREASE II 2020)
- Diuretics versus placebo (HYDRO-PROTECT 2024)
- Dopamine antagonist (rotigotine) versus standard care (NCT06291116)
- Retinoic acid receptor antagonist (tamibarotene) versus placebo (jRCT2011230055; NCT06289998)
- NG-monomethyl-L-arginine versus placebo (NCT00345137)
- Renal sympathetic denervation versus antihypertensive drugs (NCT01932450)
- Somatostatin agonists (lanreotide) versus placebo (NCT02127437)
- Sodium chloride versus placebo (NCT05228574)
- Immediate versus delayed renal denervation (NCT05460169)
- SGKT2 inhibitor (empagliflozin) versus placebo (NCT05510115; NCT06391450; NCT06435858)
- RGLS8429 versus placebo (NCT05521191)
- Daily caloric restriction plus increased physical activity versus standard advice (NCT06496542)
- Time-restricted feeding versus normal healthy eating (Steele 2023)

- mTOR inhibitor (sirolimus) versus placebo (Vienna RAP 2015).

Studies awaiting classification

Eight studies are awaiting classification: six studies are either published protocols or abstract-only publications with no extractable data (BEET-PKD 2022; IMPROVE-PKD 2023; KETO-ADPKD 2023; Nowak 2021; Rastogi 2023; Staged-PKD 2020) and two studies were identified prior to publication (Trillini 2023; WATER 2024).

- Beetroot juice versus nitrate-deplete beetroot juice (BEET-PKD 2022)
- Dopamine antagonist (rotigotine) versus standard care (IMPROVE-PKD 2023)
- Ketogenic diet versus water diet versus normal diet (KETO-ADPKD 2023)
- Caloric restrictions versus intermittent fasting (Nowak 2021)
- KD019 versus placebo (Rastogi 2023)
- Tolvaptan plus octreotide versus tolvaptan plus placebo (Trillini 2023)
- Glucosylceramide synthase inhibitor (venglustat) versus placebo (Staged-PKD 2020)
- Low salt/low protein versus low salt/regular protein versus regular salt/low protein versus regular salt/regular protein diets (WATER 2024)

Risk of bias in included studies

Risk of bias assessments were performed using Cochrane's risk of bias assessment tool (Appendix 2). Figure 2 summarises the overall risks of bias for the studies, and Figure 3 reports the risks of bias in each individual study.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

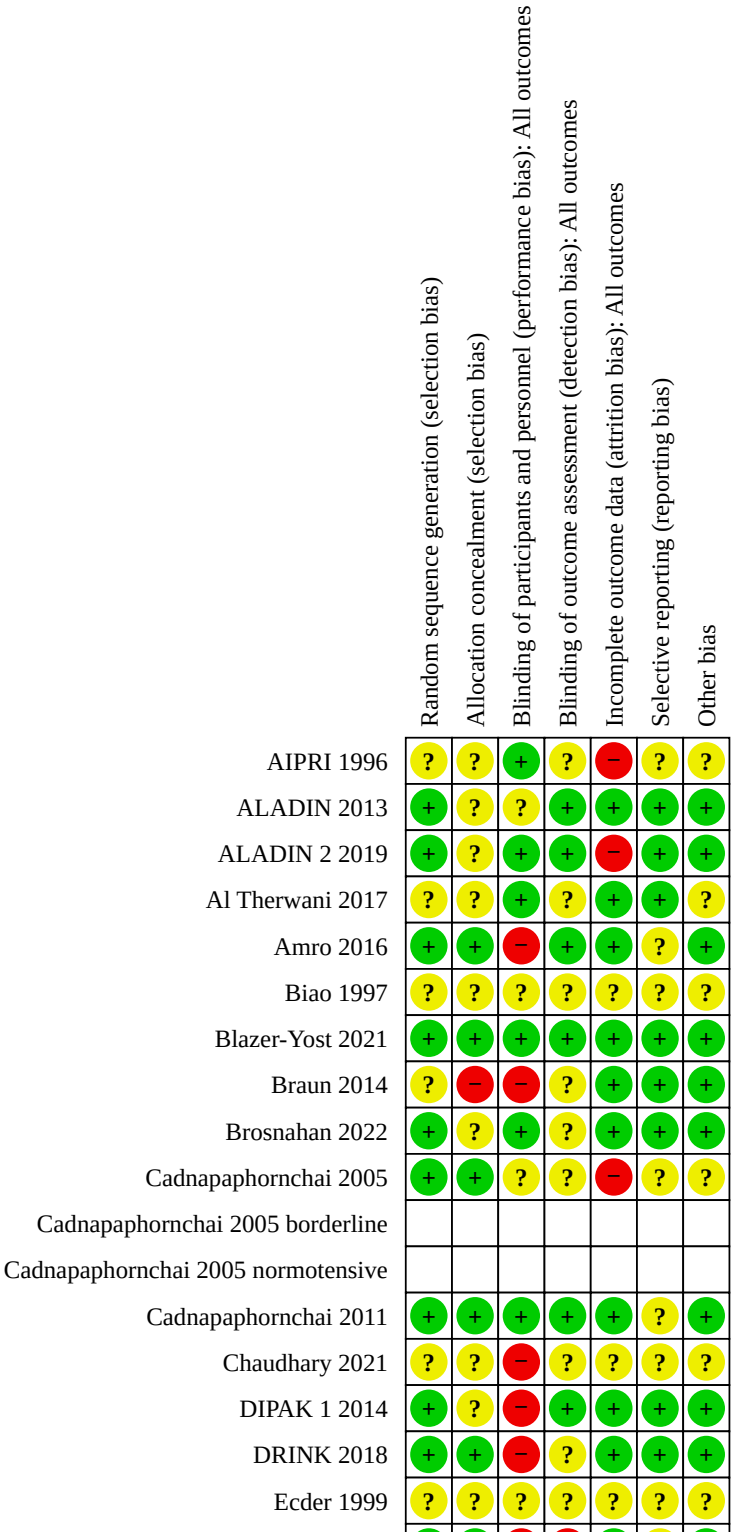


Figure 2. (Continued)

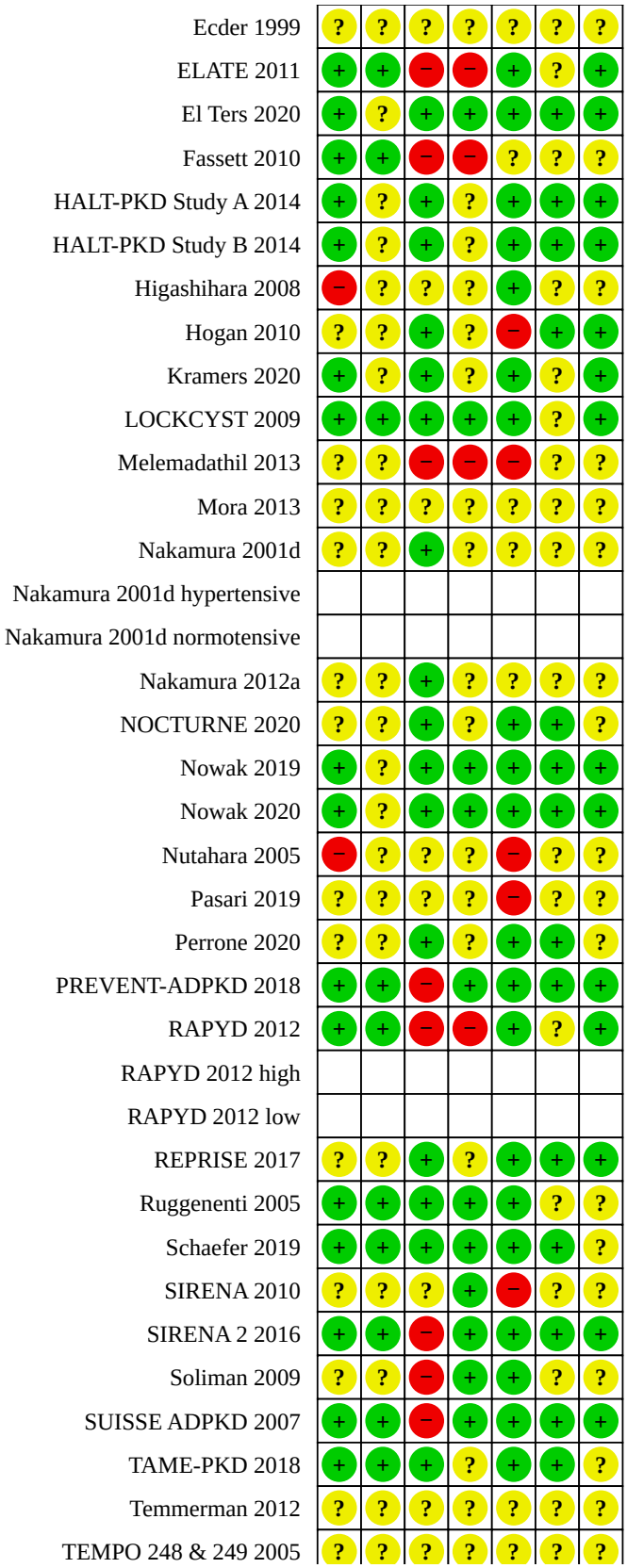


Figure 2. (Continued)

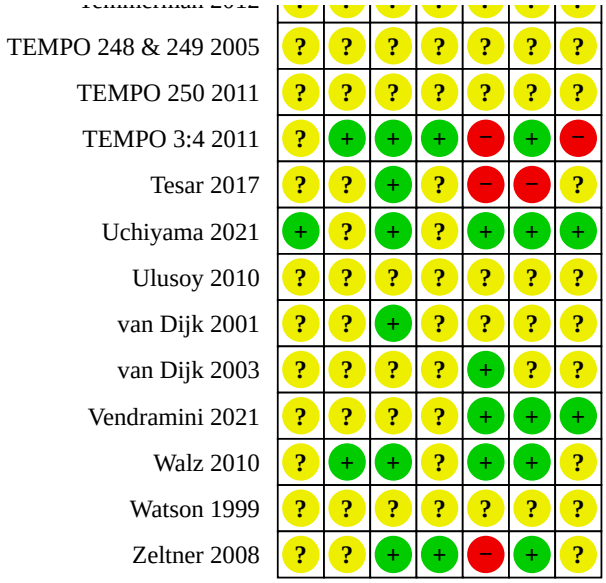
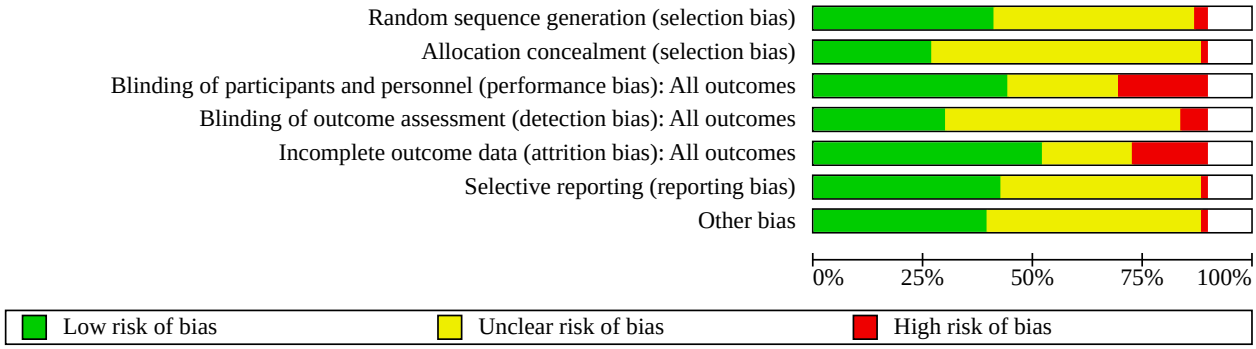


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies



In some cases, authors were contacted for additional information, but only four investigators responded to our queries (LOCKCYST 2009; Soliman 2009; Temmerman 2012; Walz 2010).

Allocation

Random sequence generation

Random sequence generation was low risk in 26 studies (ALADIN 2013; ALADIN 2 2019; Amro 2016; Blazer-Yost 2021; Brosnahan 2022; Cadnapaphornchai 2005; Cadnapaphornchai 2011; DIPAK 1 2014; DRINK 2018; ELATE 2011; El Ters 2020; Nowak 2020; Fassett 2010; HALT-PKD Study A 2014; HALT-PKD Study B 2014; Kramers 2020; LOCKCYST 2009; Nowak 2019; PREVENT-ADPKD 2018; RAPYD 2012; Ruggenenti 2005; Schaefer 2019; SIRENA 2010; SUISSE ADPKD 2007; TAME-PKD 2018; Uchiyama 2021), high risk in two studies (Higashihara 2008; Nutahara 2005); and there were insufficient data to inform assessment in the remaining 29 studies.

Allocation concealment

Allocation concealment was low risk in 17 studies (Amro 2016; Blazer-Yost 2021; Cadnapaphornchai 2005; Cadnapaphornchai 2011; DRINK 2018; ELATE 2011; Fassett 2010; LOCKCYST 2009; RAPYD 2012; PREVENT-ADPKD 2018; Ruggenenti 2005; Schaefer 2019; SIRENA 2 2016; SUISSE ADPKD 2007; TAME-PKD 2018; TEMPO 3:4 2011; Walz 2010), high in one study (Braun 2014) and unclear in the remaining 39 studies.

Blinding

The overall blinding was variable. Blinding of investigators and outcome assessors was often not specified.

Performance bias

Participants and investigators were blinded in 28 studies (AIPRI 1996; ALADIN 2 2019; Al Therwani 2017; Blazer-Yost 2021; Brosnahan 2022; Cadnapaphornchai 2011; El Ters 2020; Nowak 2020; HALT-PKD Study A 2014; HALT-PKD Study B 2014; Hogan

2010; Kramers 2020; LOCKCYST 2009; Nakamura 2001d; Nakamura 2012a; NOCTURNE 2020; Nowak 2019; Perrone 2020; REPRISE 2017; Ruggenenti 2005; Schaefer 2019; TAME-PKD 2018; TEMPO 3:4 2011; Tesar 2017; Uchiyama 2021; van Dijk 2001; Walz 2010; Zeltner 2008) and not blinded in thirteen studies (Amro 2016; Braun 2014; Chaudhary 2021; DIPAK 1 2014; DRINK 2018; ELATE 2011; Fassett 2010; Melemadathil 2013; PREVENT-ADPKD 2018; RAPYD 2012; SIRENA 2010; Soliman 2009; SUISSE ADPKD 2007). In ALADIN 2013, participants were blinded to the treatment while investigators were aware of the allocated group. Blinding was not specified in the remaining 15 studies.

Detection bias

Outcome assessors were blinded in 19 studies (ALADIN 2013; ALADIN 2 2019; Amro 2016; Blazer-Yost 2021; Cadnapaphornchai 2011; DIPAK 1 2014; El Ters 2020; Nowak 2020; LOCKCYST 2009; Nowak 2019; PREVENT-ADPKD 2018; Ruggenenti 2005; Schaefer 2019; SIRENA 2 2016; SIRENA 2010; Soliman 2009; SUISSE ADPKD 2007; TEMPO 3:4 2011; Zeltner 2008) whereas in four studies (ELATE 2011; Fassett 2010; Melemadathil 2013; RAPYD 2012) assessors were aware of treatment allocation. Outcome assessor blinding was unclear in the remaining 34 studies.

Incomplete outcome data

Attrition bias overall was variable; the overall drop-out rate ranged from 1.6% to 44%. In nine studies, the drop-out rate was greater than 20%, either across the study population or in any arm, all of which were deemed high risk of attrition bias (AIPRI 1996; Cadnapaphornchai 2005; Melemadathil 2013; Nutahara 2005; Pasari 2019; SIRENA 2010; TEMPO 3:4 2011; Tesar 2017; Zeltner 2008). In two studies (ALADIN 2 2019; Hogan 2010) > 20% of participants were not included in kidney outcomes, and these were also judged to be at high risk of attrition bias. Thirty-three studies were judged to be at low risk of bias and unclear in the remaining 13 studies.

Selective reporting

There were no concerns for selective reporting bias in 27 studies (ALADIN 2013; ALADIN 2 2019; Al Therwani 2017; Blazer-Yost 2021; Braun 2014; Brosnahan 2022; DIPAK 1 2014; DRINK 2018; El Ters 2020; Nowak 2020; HALT-PKD Study A 2014; HALT-PKD Study B 2014; Hogan 2010; NOCTURNE 2020; Nowak 2019; Perrone 2020; PREVENT-ADPKD 2018; REPRISE 2017; Schaefer 2019; SIRENA 2 2016; SUISSE ADPKD 2007; TAME-PKD 2018; TEMPO 3:4 2011; Uchiyama 2021; Vendramini 2021; Walz 2010; Zeltner 2008). Tesar 2017 was deemed to be at high risk of selective reporting, due to concerns regarding the changing of endpoints and the influence on findings. Selective reporting was unclear in the remaining 29 studies.

Other potential sources of bias

Overall, 25 studies were judged to be at low risk of other biases, one study was at high risk of bias due to the involvement of the sponsor (TEMPO 3:4 2011), and the remaining 31 studies were judged unclear.

Eighteen studies reported receiving funding from industry (ALADIN 2013; Al Therwani 2017; ELATE 2011; Higashihara 2008; Hogan 2010; LOCKCYST 2009; NOCTURNE 2020; Perrone 2020; RAPYD 2012; REPRISE 2017; Schaefer 2019; SIRENA 2010; SIRENA 2 2016; TEMPO 248 & 249 2005; TEMPO 250 2011; TEMPO 3:4 2011; Tesar 2017; van Dijk 2003; Walz 2010). In seven of these studies (ALADIN 2013; ELATE 2011; Hogan 2010; LOCKCYST 2009; RAPYD 2012; REPRISE 2017; SIRENA 2 2016), the authors specified the sponsor's involvement in the study design, data collection, data analysis, interpretation of results, and writing the manuscript, and therefore these were judged as low risk of bias. In the remaining 18 studies, the role of the sponsor was unclear.

Effects of interventions

See: **Summary of findings 1** Summary of findings table - V2R antagonists compared to placebo for autosomal dominant polycystic kidney disease; **Summary of findings 2** Summary of findings table - Somatostatin analogues compared to control for autosomal dominant polycystic kidney disease; **Summary of findings 3** Summary of findings table - Low blood pressure targets compared to standard blood pressure targets for autosomal dominant polycystic kidney disease

Overall, outcomes reported were mostly confined to eGFR, SCr and kidney structure (kidney and cyst volumes), while patient-important outcomes were rarely reported.

Disease-progression modifying agents

V2R antagonists

All studies included in these comparisons used the V2R antagonist tolvaptan (NOCTURNE 2020; Perrone 2020; REPRISE 2017; Schaefer 2019; TEMPO 248 & 249 2005; TEMPO 250 2011; TEMPO 3:4 2011; Uchiyama 2021).

Primary outcomes

Kidney function

- TEMPO 3:4 2011 reported tolvaptan may have little or no effect on SCr over three years of follow-up compared to placebo (Analysis 1.1, 1154 participants: MD -0.01 mg/dL, 95% CI -0.08 to 0.06; low certainty evidence).
- TEMPO 250 2011 reported the effects of high versus low dose tolvaptan on SCr were unclear due to very low certainty evidence (Analysis 2.1, 46 participants: MD -0.12 mg/dL, 95% CI -0.36 to 0.12).
- TEMPO 3:4 2011 reported there may be little or no difference in doubling of SCr with tolvaptan compared to placebo (Analysis 1.2, 1444 participants: RR 0.96, 95% CI 0.73 to 1.25; low certainty evidence).
- Tolvaptan probably improves change in eGFR compared to placebo (Analysis 1.3 (3 studies, 2758 participants): MD 1.26 mL/min/1.73 m^2, 95% CI 0.73 to 1.78; I^2 = 0%; moderate certainty evidence).
  - Subgroup analysis by time frame (one year or less, or greater than one year) did not demonstrate any effect modification.
- Uchiyama 2021 reported the diuretic trichlormethiazide combined with tolvaptan versus tolvaptan alone may make little difference to the change in eGFR per month (Analysis 4.1, 10 participants: MD 1.02 mL/min/ 1.73 m^2, 95% CI -1.07 to 3.11; low certainty evidence).

No other primary outcomes were reported.

Secondary outcomes

Death

- REPRISE 2017 reported too few events to determine the effect of tolvaptan versus placebo on death (Analysis 1.5, 1370 participants: RR 0.34, 95% CI 0.01 to 8.22; very low certainty evidence).

Pain

- Tolvaptan probably slightly decreases kidney pain compared to placebo (Analysis 1.6.1 (4 studies, 3076 participants): RR 0.53, 95% CI 0.28 to 1.00, I^2 = 83%; moderate certainty evidence).
- Tolvaptan may slightly decrease back pain compared to placebo (Analysis 1.6.2 (2 studies, 1457 participants): RR 0.56, 95% CI 0.35 to 0.90; I^2 = 0%; low certainty evidence).
- Schaefer 2019 reported tolvaptan may decrease pain in the extremities; however, the evidence is very uncertain (Analysis 1.6.3, 91 participants: RR 0.07, 95% CI 0.00 to 1.19).

Quality of life

- Uchiyama 2021 reported that the diuretic trichlormethiazide combined with tolvaptan versus tolvaptan alone has uncertain effects on QoL, as measured using the KDQoL overall kidney disease component summary (Analysis 4.4.1, 10 participants: MD 3.70, 95% CI -10.46 to 17.86), the SF-36 physical component summary (Analysis 4.4.2, 10 participants: MD 0.50, 95% CI -11.84 to 12.84) and the SF-36 mental component summary (Analysis 4.4.3, 10 participants: MD 2.40, 95% CI -7.12 to 11.92) (all very low certainty evidence).
- Perrone 2020 reported patient burden due to nocturia using the Nocturia Quality-of-Life Questionnaire. During treatment, reported patient burden due to nocturia increased by 1.5 points for 20 mg modified release tolvaptan, 6.9 points for 20.20 mg modified release tolvaptan, 5.1 points for 60 mg modified release tolvaptan, 15.0 points for 120 mg modified release tolvaptan, and 13.1 points for 90.30 mg immediate release tolvaptan (low certainty evidence).

Blood pressure

- TEMPO 3:4 2011 reported tolvaptan may reduce SBP (Analysis 1.7, 1422 participants: MD -3.00 mm Hg, 95% CI -4.50 to -1.50) and DBP (Analysis 1.8, 1422 participants: MD -1.40 mm Hg, 95% CI -2.48 to -0.32 (all low certainty evidence).
- TEMPO 250 2011 reported high-dose tolvaptan compared to low-dose tolvaptan may reduce SBP (Analysis 2.2, 46 participants: MD -9.00 mm Hg, 95% CI -16.98 to -1.02) and DBP (Analysis 2.3, 46 participants: MD -6.00 mm Hg, 95% CI -11.21 to -0.79) (all low certainty evidence).
- Uchiyama 2021 reported the diuretic trichlormethiazide combined with tolvaptan versus tolvaptan alone had uncertain effects on SBP (Analysis 4.2, 10 participants: MD -4.10 mm Hg, 95% CI -15.26 to 7.06) and DBP (Analysis 4.3, 10 participants: MD -1.00 mm Hg, 95% CI -8.93 to 6.93) (all very low certainty evidence).

Total kidney volume

- TEMPO 3:4 2011 reported that tolvaptan, compared to placebo, probably reduces TKV (Analysis 1.9, 1317 participants: -2.70 mL/cm, 95% CI -3.24 to -2.16; moderate certainty evidence).
- Schaefer 2019 reported that tolvaptan, compared to placebo, had uncertain effects on height-adjusted TKV in children less than 17 years of age (Analysis 1.10, 113 participants: MD 0.09 mL/cm, 95% CI -0.40 to 0.59; very low certainty evidence)
- NOCTURNE 2020 reported that the pooled tolvaptan treatment groups (modified release (MR) + immediate release (IR) –2.07%, P = 0.0127), the tolvaptan MR 80 mg group (–2.55%, P = 0.0108), and the tolvaptan MR 50 mg group (–2.46%, P = 0.0155) each exhibited a greater mean per cent decrease in TKV from baseline to week three versus the placebo group (0.09%).

Urinary protein excretion

- TEMPO 3:4 2011 reported that tolvaptan, compared to placebo, may have little or no effect on albuminuria (Analysis 1.12, 1157 participants: MD -1.60 mg/mmol, 95% CI -3.95 to 0.75; low certainty evidence).
- Uchiyama 2021 reported that the combination of trichlormethiazide with tolvaptan versus tolvaptan alone had uncertain effects on UACR (Analysis 4.5, 10 participants: MD -4.60 mg/g, 95% CI -110.95 to 101.75; very low certainty evidence).

Urine osmolality and specific gravity

- Schaefer 2019 reported that tolvaptan, compared to placebo, may decrease urine osmolality at one week (Analysis 1.13.1, 91 participants: -303.00 mOsm/kg, 95% CI -383.66 to -222.35) and one month (Analysis 1.13.2, 91 participants: -323.00 mOsm/kg, 95% CI -426.47 to -219.53) (all low certainty evidence).
- Schaefer 2019 reported that tolvaptan, compared to placebo, may decrease urine specific gravity at one week (Analysis 1.14.1, 91 participants: -0.01 mOsm/kg, 95% CI -0.01 to -0.00) and one month (Analysis 1.14.2, 91 participants: -0.01 mOsm/kg, 95% CI -0.01 to -0.01) (all low certainty evidence).

Adverse events

- Compared to placebo, tolvaptan may make little or no difference to the incidence of serious adverse events (Analysis 1.15 (4 studies, 3076 participants): RR 1.06, 95% CI 0.68 to 1.66; I^2 = 63%; low certainty evidence).
- Compared to placebo, tolvaptan may increase thirst (Analysis 1.16.8 (4 studies, 3076 participants): RR 5.30, 95% CI 1.05 to 26.70, I^2 = 97%), dry mouth (Analysis 1.16.4 (4 studies, 2996 participants): RR 5.13, 95% CI 0.63 to 41.71; I^2 = 94%), and nocturia (Analysis 1.16.7 (2 studies, 1457 participants): RR 7.81, 95% CI 0.64 to 95.51; I^2 = 92%) (all low certainty evidence).
- Compared to placebo, tolvaptan probably increases polyuria (Analysis 1.16.6 (2 studies, 1457 participants): RR 17.63, 95% CI 2.41 to 128.96; I^2 = 85%), liver enzyme elevation (Analysis 1.16.9 (3 studies, 2901 participants): RR 2.08, 95% CI 1.43 to 3.02; I^2 = 0%), and fatigue (Analysis 1.16.15 (3 studies, 1632 participants): RR 2.53, 95% CI 1.65 to 3.87; I^2 = 0%) (all moderate certainty evidence).
- Compared to placebo, tolvaptan may decrease hypertension (Analysis 1.16.10 (2 studies, 1541 participants): RR 0.50, 95% CI 0.21 to 1.17; I^2 = 38%), and urinary tract infection (UTI) (Analysis 1.16.12 (REPRISE 2017, 1366 participants): RR 0.15, 95% CI 0.07 to 0.30) (all low certainty evidence).
- Compared to placebo, tolvaptan probably makes little or no difference to headache (Analysis 1.16.1 (4 studies, 2996 participants): RR 1.05, 95% CI 0.89 to 1.24; I^2 = 0%), diarrhoea

(Analysis 1.16.2 (4 studies, 3076 participants): RR 1.02, 95% CI 0.66 to 1.55; I^2 = 35%), dizziness (Analysis 1.16.3 (3 studies, 1710 participants): RR 1.24, 95% CI 0.90 to 1.72; I^2 = 0%), nausea (Analysis 1.16.5 (3 studies, 1710 participants): RR 0.69, 95% CI 0.40 to 1.16; I^2 = 25%), or upper respiratory tract infection (Analysis 1.16.11 (2 studies, 1557 participants) RR 0.66, 95% CI 0.15 to 2.99; I^2 = 70%) (all moderate certainty evidence).

- Perrone 2020 reported that compared to MR tolvaptan, IR tolvaptan shows little or no difference in any adverse event, polyuria, thirst, or nocturia (Analysis 3.1).
- Compared to placebo, there are probably more withdrawals due to adverse events with tolvaptan (Analysis 1.17 (3 studies, 1632 participants): RR 3.94, 95% CI 2.34 to 6.65; I^2 = 0%; moderate certainty evidence).

No other secondary outcomes were reported.

Somatostatin analogues versus placebo

Primary outcomes

Kidney function

- Somatostatin analogues compared to placebo may slightly reduce SCr (Analysis 5.1 (2 studies, 91 participants): MD -0.43 mg/dL, 95% CI -0.86 to -0.01; I^2 = 0%; low certainty evidence) but probably have little or no effect on eGFR (Analysis 5.2 (4 studies, 180 participants): MD 4.11 mL/min/1.73 m^2, 95% CI -3.19 to 11.41; I^2 = 0%; moderate certainty evidence) or change in eGFR (Analysis 5.3 (3 studies, 404 participants): MD -0.10 mL/min/1.73 m^2, 95% CI -0.70 to 0.50; I^2 = 0%; moderate certainty evidence). Descriptive findings from Temmerman 2012, which could not be included in the meta-analysis, also reported no significant difference in GFR between treatment groups and placebo (Analysis 5.4).
  - Subgroup analysis by time frame (one year or less, or greater than one year) did not demonstrate any effect modification.
- Somatostatin analogues compared to placebo may have little or no effect on kidney failure (Analysis 5.5 (2 studies, 405 participants): RR 0.64, 95% CI 0.16 to 2.49; I^2 = 39%; low certainty evidence).
- ALADIN 2 2019 reported the combined outcome of kidney failure and doubling of SCr may be decreased in those treated with somatostatin analogues compared to placebo (Analysis 5.6, 100 participants: RR 0.41, 95% CI 0.21 to 0.81; low certainty evidence); however, DIPAK 1 2014 reported there was no difference in the combined outcome of doubling of SCr and < 30% GFR loss (Analysis 5.7, 305 participants: RR 0.72, 95% CI 0.43 to 1.20; low certainty evidence). No studies reported doubling of SCr separately.
- ALADIN 2 2019 reported no difference in the incidence of acute kidney injury (AKI) between somatostatin analogues and placebo (Analysis 5.8, 100 participants: RR 0.77, 95% CI 0.22 to 2.70).

Secondary outcomes

Death

- DIPAK 1 2014 reported the effects of somatostatin analogues compared to placebo on death were uncertain (Analysis 5.9, 309 participants: RR 3.02, 95% CI 0.12 to 73.55; very low certainty evidence).

Pain

- ALADIN 2 2019 reported there may be little or no difference in back or flank pain between somatostatin analogues and placebo (Analysis 5.10, 100 participants: RR 0.77, 95% CI 0.33 to 1.79; low certainty evidence).

Quality of life

- DIPAK 1 2014 reported there may be no difference between somatostatin analogue and placebo on health-related QoL (Analysis 5.11, 305 participants: MD -0.02, 95% CI -0.12 to 0.08; low certainty evidence).
- ALADIN 2 2019 reported somatostatin analogue had uncertain effects on depression and anxiety compared to placebo (Analysis 5.12, 100 participants: RR 0.19, 95% CI 0.01 to 3.91; very low certainty evidence).

Blood pressure

- Somatostatin analogues may have little or no effect on BP; however, the evidence is very uncertain.
  - SBP: Analysis 5.13 (2 studies, 91 participants: MD 0.79 mm Hg, 95% CI -3.54 to 5.13; I^2 = 0%)
  - DBPL Analysis 5.14 (2 studies, 91 participants: MD -0.38 mm Hg, 95% CI -3.68 to 2.92; I^2 = 0%)
  - MAP: Analysis 5.15 (ALADIN 2013, 79 participants: MD -0.10 mm Hg, 95% CI -3.66 to 3.46).

Total kidney volume

- Somatostatin analogues may decrease TKV volume compared to placebo (Analysis 5.16 (3 studies, 114 participants): MD -0.62 L, 95% CI -1.22 to -0.01; I^2 = 11%; low certainty evidence).
- In a pooled analysis using SMD including TKV or height-adjusted (ht) TKV as per cent change, absolute change or final measure, somatostatin analogues probably decrease TKV volume compared to placebo (Analysis 5.17 (6 studies, 500 participants): SMD -0.33, 95% CI -0.51 to -0.16; I^2 = 0%; moderate certainty evidence).
- Somatostatin analogues may have little or no effect on cyst volume compared to placebo (Analysis 5.18 (2 studies, 82 participants): MD -0.50 L, 95% CI -1.18 to 0.18; I^2 = 37%; low certainty evidence).
- Somatostatin analogues had uncertain effects on total parenchymal volume compared to placebo (Analysis 5.19 (2 studies, 82 participants): MD -67.67 mL, 95% CI -249.45 to 114.12; I^2 = 78%; very low certainty evidence).

Urinary protein excretion

- ALADIN 2013 reported somatostatin analogues versus placebo may have little or no effect on proteinuria (Analysis 5.20, 91 participants: MD -0.05 g/24 hours, 95% CI -0.17 to 0.07; low certainty evidence)
- Somatostatin analogues versus placebo may have little or no effect on albuminuria (Analysis 5.21 (2 studies, 101 participants): MD -17.71 g/24 hours, 95% CI -86.96 to 51.55; I^2 = 0%; low certainty evidence).

Adverse events

- Compared to placebo, somatostatin analogues may increase serious adverse events (Analysis 5.22 (2 studies, 405

participants): RR 1.81, 95% CI 1.01 to 3.25; low certainty evidence).

- Compared to placebo, somatostatin analogues probably increase alopecia (3 studies, 484 participants: RR 8.58, 95% CI 1.53 to 48.03; I^2 = 0%), diarrhoea or abnormal faeces (4 studies, 496 participants: RR 5.59, 95% CI 2.05 to 15.23; I^2 = 72%), dizziness (3 studies, 484 participants: RR 2.24, 95% CI 1.25 to 4.02; I^2 = 0%), and fatigue (2 studies, 405 participants: RR 1.79 95% CI 1.21 to 2.67; I^2 = 14%) (all moderate certainty evidence) (Analysis 5.23).
- DIPAK 1 2014 reported increased chest pain with somatostatin analogues (Analysis 5.23.3, 305 participants: RR 5.96, 95% CI 1.36 to 26.19).
- Compared to placebo, somatostatin analogues may have little to no effect on anaemia (3 studies, 484 participants: RR 1.65, 95% CI 0.28 to 9.72; I^2 = 86%) or infection (3 studies, 484 participants: RR 0.86, 95% CI 0.59 to 1.24; I^2 = 28%) (all low certainty evidence) (Analysis 5.23).
- Somatostatin analogues had uncertain effects on epigastric pain, gastrointestinal symptoms, fever, headache, renal cyst infection, and UTI (Analysis 5.23).
- DIPAK 1 2014 reported those treated with somatostatin analogues were withdrawn from the study due to adverse events more often than placebo (Analysis 5.24, 305 participants: RR 32.79, 95% CI 1.98 to 541.63; low certainty evidence).

No other secondary outcomes were reported.

mTOR inhibitors

Primary outcomes

Kidney function

mTOR inhibitors versus placebo

- mTOR inhibitors versus placebo or no treatment probably makes little or no difference to eGFR (Analysis 6.1 (4 studies, 165 participants): MD 0.32 mL/min/1.73 m^2, 95% CI -5.98 to 6.62; I^2 = 34%; moderate certainty evidence).
  - Subgroup analysis by time frame (one year or less, or greater than one year) did not demonstrate any effect modification.
- mTOR inhibitors versus placebo or no treatment may make little or no difference to kidney failure (need for KRT) (Analysis 6.3 (2 studies, 472 participants): RR 3.87, 95% CI 0.44 to 34.18; I^2 = 0%; low certainty evidence) or the need for transplantation (Analysis 6.4 (Walz 2010, 431 participants): RR 1.01, 95% CI 0.06 to 16.11; low certainty evidence).

mTOR inhibitors plus renin-angiotensin-aldosterone system (RAAS) inhibitors versus RAAS inhibitors alone

- Soliman 2009 reported that mTOR inhibitors plus ARB versus ARB alone had uncertain effects on the doubling of SCr (Analysis 8.1, 16 participants: RR 0.33, 95% CI 0.04 to 2.56; very low certainty evidence).
- RAPYD 2012 reported both high-dose and low-dose mTOR inhibitors plus RAAS inhibitors versus RAAS inhibitors alone had uncertain effects on GFR (Analysis 8.2.1, Analysis 8.2.2).
- Soliman 2009 reported that mTOR inhibitors plus ARB versus ARB alone had uncertain effects on GFR (Analysis 8.2.3).

Secondary outcomes

Death

mTOR inhibitors versus placebo

- Walz 2010 reported no difference in death could be determined due to very few events (Analysis 6.5).

Blood pressure

mTOR inhibitors versus placebo

- mTOR inhibitors had uncertain effects on BP (Analysis 6.6; Analysis 6.7; Analysis 6.8) (very low certainty evidence).

mTOR inhibitors plus RAAS inhibitors versus RAAS inhibitors alone

- mTOR inhibitors plus RAAS inhibitors had uncertain effects on BP (Analysis 8.3; Analysis 8.4) (very low certainty evidence).

Total kidney volume

mTOR inhibitors versus placebo

- mTOR inhibitors probably make little or no difference to TKV (Analysis 6.9 (4 studies 151 participants): MD -0.07 L, 95% CI -0.59 to 0.45; I^2 = 0%; moderate certainty evidence). Studies that could not be included in the meta-analysis (Analysis 6.11) demonstrated variability, with some studies indicating a decrease in TKV (Melemadathil 2013; Mora 2013).
- The effects of mTOR inhibitors on other measures of kidney volume are unclear (all very low certainty evidence).
  - Per cent change in TKV (Analysis 6.10 (Braun 2014, 17 participants): -3.00%, 95% CI -7.83 to 1.83).
  - Cyst volume (Analysis 6.12 (SIRENA 2010, 15 participants): MD -55.00 mL, 95% CI -862.98 to 752.98).
  - Total parenchymal volume (Analysis 6.14 (SIRENA 2010, 15 participants): MD 15.00 mL, 95% CI -75.44 to 105.44).
  - Studies that could not be included in the meta-analyses also demonstrated inconsistency (total parenchymal volume: Analysis 6.15; cyst volume: Analysis 6.13).

mTOR inhibitors plus RAAS inhibitors versus RAAS inhibitors alone

- mTOR inhibitors plus RAAS inhibitors may make little or no difference to TKV (Analysis 8.5) and cyst volume (Analysis 8.6) across different doses of mTOR inhibitors and types of RAAS inhibitors (all low certainty evidence).

mTOR inhibitors plus somatostatin analogues versus somatostatin analogues alone

- ELATE 2011 reported that mTOR inhibitors plus somatostatin analogues may make little or no difference to TKV (Analysis 7.1: descriptive data only).

Urinary protein excretion

mTOR inhibitors versus placebo

- mTOR inhibitors may make little or no difference to proteinuria (Analysis 6.16 (3 studies, 479 participants): SMD 0.00, 95% CI -0.83 to 0.83; I^2 = 80%; low certainty evidence). Melemadathil

2013, which could not be combined in the meta-analysis, reported that proteinuria was higher with mTOR inhibitors (Analysis 6.17), and SIRENA 2 2016 reported proteinuria may double with mTOR inhibitors (Analysis 6.18).
- mTOR inhibitors may make little or no difference to albuminuria (Analysis 6.19 (3 studies, 148 participants): SMD 0.01, 95% CI -0.64 to 0.67; I^2 = 64%; low certainty evidence).

mTOR inhibitors plus RAAS inhibitors versus RAAS inhibitors alone

- RAPYD 2012 reported high-dose mTOR inhibitors combined with RAAS inhibitors may increase proteinuria (Analysis 8.7.1, 35 participants: MD 0.50 g/24 hours, 95% CI 0.09 to 0.91; low certainty evidence) but not with low-dose mTOR inhibitors (Analysis 8.7.2, 37 participants: MD -0.10 g/24 hours, 95% CI -0.29 to 0.09; low certainty evidence).

Adverse events

mTOR inhibitors versus placebo

- mTOR inhibitors may make little or no difference to serious adverse events (Analysis 6.20 (2 studies, 71 participants): RR 1.03, 95% CI 0.43 to 2.45; I^2 = 0%; low certainty evidence).
- mTOR inhibitors probably increase angioedema (3 studies, 560 participants: RR 13.39, 95% CI 2.56 to 70.00; I^2 = 0%), diarrhoea (4 studies, 601 participants: RR 1.73, 95% CI 1.28 to 2.33; I^2 = 0%) and oral ulcers (4 studies, 590 participants: RR 6.82, 95% CI 4.47 to 10.39; I^2 = 0%) (all moderate certainty evidence) (Analysis 6.21).
- mTOR inhibitors may increase anaemia (Walz 2010, 431 participants: RR 3.41, 95% CI 1.79 to 6.51), hyperlipidaemia (Walz 2010, 431 participants: RR 5.68, 95% CI 2.23 to 14.43), and infection (5 studies, 631 participants: RR 1.15, 95% CI 1.02 to 1.31; I^2 = 20%) (low certainty evidence) (Analysis 6.21).
- mTOR inhibitors may make little or no difference to arrhythmias (SIRENA 2 2016, 41 participants: RR 0.95, 95% CI 0.27 to 3.30), dermatitis (2 studies, 71 participants: RR 2.77, 95% CI 0.48 to 15.98; I^2 = 0%), nausea (Walz 2010, 431 participants: RR 1.69, 95% CI 0.85 to 3.37) or peripheral oedema (2 studies, 71 participants: RR 0.86, 95% CI 0.15 to 5.05; I^2 = 62%) (all low certainty evidence) (Analysis 6.21).

mTOR inhibitors plus RAAS inhibitors versus RAAS inhibitors alone

- The effect of mTOR inhibitors plus RAAS inhibitors on adverse events is unclear (Analysis 8.8; very low certainty evidence).

No other secondary outcomes were reported.

Metformin

Primary outcomes

Kidney function

Metformin versus placebo

- Metformin may make little or no difference to change in eGFR (Analysis 9.1 (2 studies, 142 participants): MD 2.87 mL/min/1.73 m^2, 95% CI -0.29 to 5.92; I^2 = 0%), rate of eGFR decline (Analysis 9.2), or annual rate of eGFR decline (Analysis 9.3) (low certainty evidence).
- No events of kidney failure were recorded (Analysis 9.4).

No other primary outcomes were reported.

Secondary outcomes

Death

Metformin versus placebo

- TAME-PKD 2018 reported one death in the metformin group and none in the placebo group; hence, there is insufficient data to determine an effect (Analysis 9.5).

Pain

Metformin versus placebo

- There were too few events to determine metformin's impact across the spectrum of pain outcomes compared to placebo (Analysis 9.6).

Quality of life

Metformin versus placebo

- TAME-PKD 2018 reported metformin may have little or no effect on SF-36 physical component summary (Analysis 9.7.1, 84 participants: MD -1.90, 95% CI -4.93 to 1.13) and SF-36 mental component summary (Analysis 9.7.2, 84 participants: MD 0.30, 95% CI -2.67 to 3.27) and (all low certainty evidence).

Metformin versus hydrochlorothiazide versus placebo (cross-over study)

- Kramers 2020 reported that hydrochlorothiazide treatment in people who had received tolvaptan improved the QoL in seven of 13 participants. QoL was not significantly different from baseline during metformin (P = 0.90) or placebo treatment (P = 0.50) (low certainty evidence) (Analysis 10.1: descriptive data only).

Total kidney volume

Metformin versus placebo

- Metformin may make little or no difference to the per cent change in htTKV (Analysis 9.8 (2 studies, 140 participants): MD 1.05%, 95% CI -1.73 to 3.83; I^2 = 0%; low certainty evidence). Two studies were not reported in sufficient detail to be included in the meta-analysis.
- Chaudhary 2021 reported that at month 12, TKV increased by 0.11% in metformin-treated participants compared to 1.01% in the control group.
- Pasari 2019 reported metformin treatment resulted in significantly lower TKV, 4.26% and 9.51% in the metformin and placebo groups, respectively.
- TAME-PKD 2018 reported metformin may have little or no effect on the mean annual per cent change in htTKV (Analysis 9.9) and absolute change in htTKV (Analysis 9.10) but may increase height-adjusted liver volume (Analysis 9.11).

Adverse events

Metformin versus placebo

- Metformin may make little or no difference to serious adverse events (Analysis 9.12 (2 studies, 148 participants): RR 1.16, 95% CI 0.26 to 5.18; I^2 = 20%; low certainty evidence).
- Metformin may increase diarrhoea (2 studies, 148 participants: RR 1.80, 95% CI 1.16 to 2.80; I^2 = 0%) and nausea (2 studies, 148 participants: RR 1.92, 95% CI 1.10 to 3.36; I^2 = 0%) (Analysis 9.13) (all low certainty evidence).
- Metformin had uncertain effects on gastrointestinal tract symptoms, infection, hypoglycaemia, sustained oedema refractory to diuretics, UTI or cyst rupture (Analysis 9.13).

Bosutinib at different dosages and versus placebo

Primary outcomes

- Tesar 2017 reported that, compared to placebo, "bosutinib increased mean serum creatinine in all groups at day 15; these remained stable over the 24-month initial treatment period and then returned close to baseline after a 30-day washout at the end of the treatment period" (low certainty evidence).
- The effect on the per cent change in eGFR was unclear across all dosages of bosutinib due to the very low certainty evidence (Analysis 11.2).

No other primary outcomes were reported.

Secondary outcomes

- Tesar 2017 reported TKV was lower with all doses of bosutinib (200 mg, 400 mg and 600 mg) than placebo (Analysis 11.4: descriptive data only).
- There were too few events to determine a difference between placebo and bosutinib for serious adverse events (Analysis 11.5).
- There were more treatment-adverse events in the 400 mg and 400/200 mg bosutinib groups compared to the 200 mg bosutinib and placebo groups. The most commonly reported adverse events were gastrointestinal, primarily diarrhoea and liver-related (Analysis 11.6: descriptive data only) (low certainty evidence).

No other secondary outcomes were reported.

Pioglitazone versus placebo

Primary outcome

Blazer-Yost 2021 did not report any of our primary outcomes.

Secondary outcomes

- Blazer-Yost 2021 reported that in 15 participants, the mean per cent change in TKV with pioglitazone versus placebo was 4.3 ± 6.3% versus 7.85 ± 7.68%, respectively. The MD between the two 12-month periods was −3.5% (95% CI −8.4 to –1.4, P = 0.146).

No other secondary outcomes were reported.

Antihypertensive therapies

Angiotensin-converting-enzyme inhibitors

Primary outcomes

Kidney function

ACEi versus placebo

- Cadnapaphornchai 2005 reported that ACEi may make little or no difference to SCr (Analysis 13.1, 42 participants: MD -0.02 mg/dL, 95% CI -0.14 to 0.09; I^2 = 23%; low certainty evidence).
- The effect of ACEi on eGFR was unclear due to very low certainty evidence (Analysis 13.2 (2 studies, 103 participants): MD -3.41 mL/min/1.73 m^2, 95% CI -15.83 to 9.01; I^2 = 46%).
- AIPRI 1996 reported that ACEi may make little or no difference to the doubling of SCr (Analysis 13.3, 64 participants: RR 1.01, 95% CI 0.45 to 2.28; low certainty evidence).
- Kidney failure was not reported.

ACEi versus CCB

- Ecder 1999 reported that compared to CCB, the effect of ACEi was unclear on SCr due to very low certainty evidence (Analysis 14.1, 24 participants: MD 0.01 mg/dL, 95% CI -0.10 to 0.12).
- Ecder 1999 reported that ACEi may decrease eGFR (Analysis 14.2, 24 participants: MD -13.00 mL/min/1.73 m^2, 95% CI -17.56 to -8.44; low certainty evidence).
- Doubling SCr and kidney failure were not reported.

ACEi versus ARB

- Compared to ARB, ACEI may make little or no difference to SCr (Analysis 15.1 (2 studies, 52 participants): MD 0.00 mg/dL, 95% CI -0.09 to 0.10; I^2 = 0%: low certainty evidence).
- Ulusoy 2010 reported that ACEI may make little or no difference to eGFR (Analysis 15.2, 32 participants: MD -3.40 mL/min/1.73 m^2, 95% CI -22.69 to 15.89; low certainty evidence).
- Doubling SCr and kidney failure were not reported.

ACEi plus ARB versus ACEi alone

- Compared to ACEi alone, ACEi plus ARB may have little or no effect on the mean annual change in eGFR (Analysis 16.2, (2 studies, 1043 participants): MD -0.02 mL/min/1.73 m^2, 95% CI -0.30 to 0.26; I^2 = 0%; low certainty evidence).
- SCr, doubling SCr and kidney failure were not reported.

ACEi versus beta-blockers

- Zeltner 2008 reported that compared to beta-blockers, ACEi may make little or no difference to SCr (Analysis 17.1, 37 participants: MD 0.18 mg/dL, 95% CI -0.12 to 0.48; low certainty evidence).
- The effect of ACEi on eGFR was unclear (Analysis 17.2 (2 studies, 65 participants): MD -8.06 mL/min/1.73 m^2, 95% CI -29.62 to 13.50; I^2 = 95%; very low certainty evidence).
- Zeltner 2008 reported that the effect of ACEi on the need for KRT was very unclear due to the small number of events reported (Analysis 17.4, 37 participants: RR 0.39, 95% CI 0.02 to 8.97; very low certainty evidence).
- Doubling of SCr was not reported.

Secondary outcomes

Death

ACEi plus ARB versus ACEi alone

- Compared to ACEi alone, ACEI plus ARB may make little or no difference to death (Analysis 16.3 (2 studies, 1043 participants): RR 0.84, 95% CI 0.26 to 2.72; I^2 = 0%; low certainty evidence).

Pain

ACEi plus ARB versus ACEi alone

- Compared to ACEi alone, ACEi plus ARB probably makes little or no difference to back or flank pain (Analysis 16.4 (2 studies, 1044 participants): RR 0.36, 95% CI 0.05 to 2.33; I^2 = 0%; moderate certainty evidence).

Quality of life

ACEi plus ARB versus ACEi alone

- Compared to ACEi alone, ACEi plus ARB probably makes little or no difference to QoL SF-36 physical component summary (Analysis 16.5.1 (2 studies, 1043 participants): MD -0.02, 95% CI -0.16 to 0.12) and SF-36 mental component summary (Analysis 16.5.2 (2 studies, 1043 participants): MD 0.10, 95% CI -0.19 to 0.39) (all moderate certainty evidence).

Cardiovascular events

ACEi plus ARB versus ACEi alone

- Compared to ACEi alone, ACEi plus ARB probably makes little or no difference to cardiovascular events (Analysis 16.6 (2 studies, 1044 participants): RR 0.94, 95% CI 0.41 to 2.15; I^2 = 46%; moderate certainty evidence).

ACEi versus beta-blockers

- Zeltner 2008 reported that the effect of ACEi compared to beta-blockers on cardiovascular events is unclear (Analysis 17.5, 37 participants: RR 1.18, 95% CI 0.08 to 17.42; very low certainty evidence).

Blood pressure

ACEi versus placebo

- Cadnapaphornchai 2005 reported that the effect of ACEi on SBP was unclear (Analysis 13.4, 42 participants: MD -5.44 mm Hg, 95% CI -14.26 to 3.38; very low certainty evidence).
- Cadnapaphornchai 2005 reported that compared to no treatment, ACEi may lower DBP (Analysis 13.5, 42 participants: MD -4.96 mm Hg, 95% CI -8.88 to -1.04; low certainty evidence).
- van Dijk 2003 reported that compared to no treatment, ACEi may lower MAP (Analysis 13.6, 61 participants: MD -5.00 mm Hg, 95% CI -6.29 to -3.71) (low certainty evidence).

ACEi versus CCB

- Ecder 1999 reported that compared to CCB, ACEi may decrease SBP (Analysis 14.3, 24 participants: MD -5.00 mm Hg, 95% CI -8.62 to -1.38), DBP (Analysis 14.4, 24 participants: MD -3.00 mm Hg, 95% CI -5.40 to -0.60) and MAP (Analysis 14.5, 24 participants: MD -3.00 mm Hg, 95% CI -5.40 to -0.60) (all low certainty evidence).

ACEi versus ARB

- Ulusoy 2010 reported that compared to ARB, ACEi may make little or no difference to SBP (Analysis 15.3, 32 participants: MD -3.50 mm Hg, 95% CI -9.75 to 2.75), DBP (Analysis 15.4, 32 participants: MD -1.80 mm Hg, 95% CI -5.23 to 1.63) or MAP (Analysis 15.5, 32 participants: MD -2.20 mm Hg, 95% CI -6.41 to 2.01) (low certainty evidence).

ACEi versus beta-blockers

- Zeltner 2008 reported that compared to beta-blockers, ACEi may have little or no effect on SBP (Analysis 17.6, 37 participants: MD -1.00 mm Hg, 95% CI -2.29 to 0.29; low certainty evidence).
- Zeltner 2008 reported ACEi may increase DBP (Analysis 17.7, 37 participants: MD 1.00 mm Hg, 95% CI 0.35 to 1.65; low certainty evidence).
- van Dijk 2003 reported ACEi may decrease MAP (Analysis 17.8, 28 participants: MD -3.00 mm Hg, 95% CI -4.92 to -1.08; low certainty evidence).

Total kidney volume

ACEi versus placebo

- Cadnapaphornchai 2005 reported that compared to no treatment, ACEi may make little or no difference to TKV (Analysis 13.7, 42 participants: MD -42.50 mL, 95% CI -115.68 to 30.67; low certainty evidence).

ACEi plus ARB versus ACEi alone

- HALT-PKD Study B 2014 reported that compared to ACEi alone, ACEi plus ARB probably makes little or no difference to change in TKV (Analysis 16.7, 553 participants: MD -0.20%, 95% CI -0.87 to 0.47; moderate certainty evidence).

Hospital admissions

ACEi plus ARB versus ACEi alone

- HALT-PKD Study B 2014 reported that compared to ACEi alone, hospital admissions may be lower with ACEi plus ARB (Analysis 16.8, 485 participants: RR 0.78, 95% CI 0.68 to 0.90; low certainty evidence).

Urinary protein excretion

ACEi versus placebo

- Compared to placebo, ACEI may make little or no difference to albuminuria (Analysis 13.8 (2 studies, 103 participants): SMD -0.12, 95% CI -0.51 to 0.26; I^2 = 0%; low certainty evidence).

ACEi versus CCB

- Ecder 1999 reported that compared to CCB, ACEi may decrease albuminuria (Analysis 14.6, 24 participants: MD -134.00 mg/g, 95% CI -176.01 to -91.99; low certainty evidence).

ACEi plus ARB versus ACEi alone

- Compared to ACEi alone, ACEi plus ARB may makes little or no difference to albuminuria (Analysis 16.9 (2 studies, 1042 participants): SMD -0.04, 95% CI -0.16 to 0.08; I^2 = 0%; low certainty evidence).

ACEi versus beta-blockers

- Compared to beta-blockers, the effect of ACEi on albuminuria was unclear (Analysis 17.10 (2 studies, 65 participants) SMD -0.19, 95% CI -1.77 to 1.39; I^2 = 89%; very low certainty evidence).

Adverse events

ACEi plus ARB versus ACEi alone

- HALT-PKD Study B 2014 reported that compared to ACEi alone, ACEi plus ARB may make little or no difference to adverse events (Analysis 16.10).

Angiotensin receptor blockers versus calcium channel blockers

Primary outcomes

- Nutahara 2005 reported that compared to CCB, ARB may slightly decrease SCr (Analysis 18.1, 40 participants: MD -0.45 mg/dL, 95% CI -0.90 to 0.00; low certainty evidence).
- Nutahara 2005 reported that compared to CCB, the effects of ARB on eGFR (Analysis 18.2, 31 participants: MD 6.30 mL/min/1.73 m^2, 95% CI -8.49 to 21.09) and doubling of SCr (Analysis 18.3, 49 participants: RR 0.17, 95% CI 0.02 to 1.34) was unclear (all very low certainty evidence).

No other primary outcomes were reported.

Secondary outcomes

- Nutahara 2005 reported that compared to CCB, ARB may decrease proteinuria (Analysis 18.4, 24 participants: MD -304.00 mg/day, 95% CI -578.54 to -29.46) and albuminuria (Analysis 18.5, 25 participants: MD -238.00 mg/day, 95% CI -394.61 to -81.39) (all low certainty evidence).

No other secondary outcomes were reported.

Spironolactone versus placebo

- Nowak 2019 reported that compared to placebo, spironolactone may make little or no difference to change in eGFR (Analysis 19.1, 60 participants: MD -2.00 mL/min/1.73 m^2, 95% CI -7.90 to 3.90; low certainty evidence).

No other primary outcomes were reported.

Secondary outcomes

- Nowak 2019 reported spironolactone may reduce brachial SBP (median change -6 mm Hg, interquartile range (IQR) -15 to 1) compared to placebo (median change -2 mm Hg, IQR -7 to 10), P = 0.04, but there may be little or no effect on brachial DBP (median change -4 mm Hg, IQR -10 to 3) compared to placebo (median change -1 mm Hg, IQR -7 to 9) (P = 0.2) (low certainty evidence).
- Nowak 2019 reported too few events to determine an effect on dizziness, muscle cramping or soreness, vision changes, increased urination, hyperkalaemia, fatigue, increased thirst, nausea and elevated AST/ALT (Analysis 19.4).

No other secondary outcomes were reported.

Low versus standard blood pressure targets

Low SBP/DBP targets were defined as 95/60 to 110/75 mm Hg, and standard targets as 120/70 to 130/80 mm Hg.

Primary outcomes

- HALT-PKD Study A 2014 reported that compared to standard BP targets, low BP targets probably had little or no effect on change in eGFR (Analysis 20.1, 557 participants: MD 0.10 mL/min/1.73 m^2, 95% CI -0.32 to 0.52; moderate certainty evidence).
- HALT-PKD Study A 2014 reported that low BP targets may make little or no difference to the incidence of AKI (Analysis 20.2, 558 participants: RR 1.04, 95% CI 0.54 to 1.99; low certainty evidence).

No other primary outcomes were reported.

Secondary outcomes

Death

- HALT-PKD Study A 2014 reported that compared to standard BP targets, the impact of low BP targets on death was uncertain (Analysis 20.3, 558 participants: RR 0.21, 95% CI 0.01 to 4.30; very low certainty evidence).

Quality of life

- HALT-PKD Study A 2014 reported that compared to standard BP targets, low BP targets may make little or no difference to the SF-36 physical component summary (Analysis 20.4.1, 558 participants: MD 0.13, 95% CI -0.06 to 0.32) but may improve the SF-36 mental component summary (Analysis 20.4.2, 558 participants: MD -0.23, 95% CI -0.45 to -0.01) (all low certainty evidence)

Total kidney volume

- HALT-PKD Study A 2014 reported that compared to standard BP targets, the per cent annual increase in TKV was probably lower in the low BP target group (Analysis 20.5, 558 participants: MD -1.00%, 95% CI -1.67 to -0.33; moderate certainty evidence).

Hospital admissions

- HALT-PKD Study A 2014 reported that compared to standard BP targets, low BP targets may slightly decrease hospital admission (Analysis 20.6, 558 participants: RR 0.80, 95% CI 0.65 to 0.99; low certainty evidence).

Urinary protein excretion

- HALT-PKD Study A 2014 reported that low BP targets probably decrease albuminuria compared to standard BP targets (Analysis 20.7, 557 participants: MD -6.20 mg/day, 95% CI -8.95 to -3.45; moderate certainty evidence)

Adverse events

- HALT-PKD Study A 2014 reported that compared to standard BP targets, low BP targets probably make little or no difference to serious adverse events (Analysis 20.8, 558 participants: RR 0.91, 95% CI 0.69 to 1.19; moderate certainty evidence).

Other symptom management therapies

Antiplatelet agents versus placebo

Primary outcomes

- Nakamura 2001d reported antiplatelet agents may have little or no effect on SCr (Analysis 21.1, 22 participants: MD -0.13 mg/dL, 95% CI -0.52 to 0.26; I^2 = 69%; low certainty evidence).
- Nakamura 2001d reported antiplatelet agents may have little or no effect on GFR (Analysis 21.2, 22 participants: MD 2.24 mL/min/1.73 m^2, 95% CI -8.05 to 12.53; I^2 = 0%; low certainty evidence).

No other primary outcomes were reported.

Secondary outcomes

- Nakamura 2001d reported antiplatelet agents may have little or no effect on SBP (Analysis 21.3, 22 participants: MD 5.04 mm Hg, 95% CI -7.43 to 17.43; low certainty evidence).
- Nakamura 2001d reported antiplatelet agents may have little or no effect on DBP (Analysis 21.4, 22 participants: MD 6.24 mm Hg, 95% CI-3.27 to 15.74; low certainty evidence).
- Nakamura 2001d reported antiplatelet agents had uncertain effects on albuminuria (Analysis 21.5, 22 participants: MD -60.53 µg/min, 95% CI -129.06 to 8.01; very low certainty evidence).

Statins versus placebo

Primary outcomes

- Compared to placebo, statin therapy had uncertain effects on change in eGFR (Analysis 22.1 (2 studies, 140 participants): SMD -1.28, 95% CI -3.96 to 1.40; I^2 = 98%; very low certainty evidence).
- Fassett 2010 and AIPRI 1996 reported no significant differences in eGFR between statin and placebo-treated participants.
- Cadnapaphornchai 2011 reported statin therapy may have no effect on 24-hour CrCl in a paediatric population (Analysis 22.3, 81 participants: MD 0.00 mL/min/1.73 m^2; 95% CI -10.12 to 10.12; low certainty evidence).
- van Dijk 2001 reported statins increased eGFR in the first cross-over period (Analysis 22.3).

No other primary outcomes were reported.

Secondary outcomes

Blood pressure

- Compared to placebo, statins may have little or no effect on SBP (Analysis 22.4 (2 studies, 140 participants): MD 0.32 mm Hg, 95% CI -3.20 to 3.84; I^2 = 0%; low certainty evidence).
- Compared to placebo, statins may have little or no effect on DBP (Analysis 22.5 (2 studies, 140 participants): MD -1.17 mm Hg, 95% CI -3.84 to 1.50; I^2 = 0%; low certainty evidence).

Total kidney volume

- Cadnapaphornchai 2011 reported that in a paediatric population, pravastatin therapy may decrease htTKV compared to placebo (Analysis 22.6, 91 participants: MD -8.00, 95% CI -9.24 to -6.76; low certainty evidence).

Urinary protein excretion

- Cadnapaphornchai 2011 reported that in a paediatric population, pravastatin therapy may have little to no effect on a > 20% increase in urine microalbuminuria excretion (Analysis 22.8, 91 participants: RR 1.21, 95% CI 0.76 to 1.93; low certainty evidence).

Adverse events

- Adverse events of statin therapy were poorly reported, and the certainty of the evidence was very low. Data were only available regarding elevated liver enzymes (aspartate aminotransferase) in Cadnapaphornchai 2011 (Analysis 22.9, 91 participants: RR 0.86, 95% CI 0.06 to 13.29).

Eicosapentaenoic acid versus standard therapy

Primary outcomes

- Higashihara 2008 reported that eicosapentaenoic acid versus standard therapy may have little or no effect on SCr (Analysis 23.1, 41 participants: RR 0.16 mg/dL, 95% CI -0.55 to 0.87; low certainty evidence).
- Higashihara 2008 reported that eicosapentaenoic acid versus standard therapy may have little or no effect on eGFR (Analysis 23.2, 41 participants: MD 6.10 mL/min/1.73 m^2, 95% CI -11.16 to 23.36; low certainty evidence).

No other primary outcomes were reported.

Secondary outcomes

- Higashihara 2008 reported that eicosapentaenoic acid versus standard therapy may have little or no effect on TKV (Analysis 23.3, 41 participants: -209.00 mL, 95% CI -729.06 to 311.00; low certainty evidence).
- Higashihara 2008 reported that eicosapentaenoic acid versus standard therapy may have little or no effect on albuminuria (Analysis 23.4, 41 participants: MD 82.40 mg/day, 95% CI -162.09 to 326.89; low certainty evidence).

Dietary interventions and supplements

Prescribed water intake versus standard water intake

Primary outcomes

Kidney function

- DRINK 2018 reported that compared to ad libitum water intake, prescribed water intake may increase SCr: ad libitum water increased SCr by 6 mmol/L and prescribed water decreased SCr by 9 mmol/L (P = 0.65).
- PREVENT-ADPKD 2018 reported that compared to ad libitum water intake, prescribed water intake probably makes little or no difference to doubling of SCr (Analysis 24.2, 184 participants: RR 1.33, 95% CI 0.31 to 5.97; moderate certainty evidence).
- Compared to ad libitum water intake, prescribed water intake probably makes little or no difference in change in eGFR (Analysis 24.3 (2 studies, 226 participants): MD 0.07 mL/min/1.73 m^2, 95% CI -0.96 to 1.10; I^2 = 0 %; moderate certainty evidence).
- PREVENT-ADPKD 2018 reported that compared to ad libitum water intake, prescribed water intake may make little or no difference to those experiencing a > 25% decrease in eGFR (Analysis 24.5, 184 participants: RR 0.75, 95% CI 0.27 to 2.08; low certainty evidence).
- PREVENT-ADPKD 2018 reported that compared to ad libitum water intake, prescribed water intake may have little or no effect on kidney failure (Analysis 24.6, 184 participants: RR 1.00, 95% CI 0.14 to 6.95; low certainty evidence).
  - Subgroup analysis of study duration (one year or less, or greater than one year) did not demonstrate effect modification.
- For a composite ADPKD disease progression outcome (including the rate of eGFR decline, MAP, UACR and kidney pain), PREVENT-ADPKD 2018 reported that compared to ad libitum water intake, prescribed water intake may have little or no effect (Analysis 24.7: HR 0.91, 95% CI 0.73 to 1.13; low certainty evidence).

Secondary outcomes

Pain

- PREVENT-ADPKD 2018 reported that compared to ad libitum water intake, prescribed water intake may make little or no difference to pain (Analysis 24.8, 184 participants: RR 0.98, 95% CI 0.81 to 1.19; low certainty evidence).

Blood pressure

- PREVENT-ADPKD 2018 reported that compared to ad libitum water intake, prescribed water intake may have little or no effect on SBP (Analysis 24.9), DBP (Analysis 24.10), or MAP (Analysis 24.11: descriptive data only).

Total kidney volume

- PREVENT-ADPKD 2018 reported that compared to ad libitum water intake, prescribed water intake probably has little or no effect on htTKV (Analysis 24.12, 184 participants: MD -16.00 mL, 95% CI -60.71 to 28.71; moderate certainty evidence) and annual per cent change in htTKV (Analysis 24.13, 184 participants: MD -1.00%, 95% CI -2.51 to 0.51; moderate certainty evidence).

Urinary protein excretion

- PREVENT-ADPKD 2018 reported that compared to ad libitum water intake, prescribed water intake may have little or no effect on UACR (Analysis 24.14; low certainty evidence).

Urine volume and urine osmolality

- PREVENT-ADPKD 2018 reported that compared to ad libitum water intake, prescribed water intake probably increases urine volume (Analysis 24.15, 184 participants: MD 633.00 mL, 95% CI 369.00 to 897.00; moderate certainty evidence) and urine osmolality (Analysis 24.16, 185 participants: MD -129.23 mOsmol/kg, 95% CI -220.20 to -38.26; moderate certainty evidence).

Adverse events

- PREVENT-ADPKD 2018 reported that compared to ad libitum water intake, prescribed water intake may increase serious adverse events (Analysis 24.17, 184 participants: RR 1.61, 95% CI 1.04 to 2.48; low certainty evidence).
- Prescribed water intake probably increases hyponatraemia (Analysis 24.18.2 (2 studies, 226 participants): RR 4.19, 95% CI 1.08 to 16.25; moderate certainty evidence).
- Prescribed water intake may have little or no effect on UTI (Analysis 24.18.1 (2 studies, 226 participants): RR 1.08, 95% CI 0.55 to 2.15; I^2 = 0%; low certainty evidence).
- The effect of prescribed water intake is unclear for cyst rupture (Analysis 24.18.3), cyst infection (Analysis 24.18.4), nephrolithiasis (Analysis 24.18.5) and dysuria (Analysis 24.18.6) due to very few reported events.

Low osmolar diet

No primary outcomes were reported.

Secondary outcomes

- Amro 2016 reported that compared to a normal diet, a low osmolar diet may decrease urine osmolality (Analysis 25.1, 32 participants: MD -187.00 mOsm/kg, 95% CI -331.57 to -42.43; low certainty evidence).

No other secondary outcomes were reported.

Curcumin versus placebo

Primary outcomes

- Nowak 2020 reported no difference in change in eGFR between curcumin and placebo-treated participants after 12 months (Analysis 26.1: descriptive data only).

No other primary outcomes were reported.

Secondary outcomes

- Nowak 2020 reported there may be little or no difference in TKV between curcumin and placebo (Analysis 26.2, 57 participants: MD 66 mL/m, 95% CI -141.35 to 273.55; low certainty evidence).
- Nowak 2020 reported that compared to placebo, curcumin therapy may result in no difference in adverse events (Analysis 26.3, 68 participants: RR 0.89, 95% CI 0.39 to 2.03; low certainty evidence). Serious adverse events were not reported.

No other secondary outcomes were reported.

Vitamin D versus placebo

Primary outcomes

- Vendramini 2021 reported that the effects of vitamin D on eGFR were unclear due to very low certainty evidence (Analysis 27.1).

No other primary outcomes were reported.

Secondary outcomes

- Vendramini 2021 reported that the effects of vitamin D on BP were unclear due to very low certainty evidence (Analysis 27.2; Analysis 27.3)

No other secondary outcomes were reported.

Vitamin D versus traditional Chinese herbal medicine

Primary outcomes

- Biao 1997 reported that compared to traditional Chinese medicine, vitamin D may decrease SCr (Analysis 28.1, 34 participants: MD -64 µmol/L, 95% CI -116.09 to -11.91) and may result in higher GFR (Analysis 28.2, 34 participants: MD 22.60 mL/min, 95% CI 0.92 to 44.28 (all low certainty evidence).

No other primary or secondary outcomes were reported.

Niacinamide versus placebo

Primary outcomes

- El Ters 2020 reported that compared to placebo, niacinamide may make little or no difference to eGFR (Analysis 29.1; descriptive data only).

No other primary outcomes were reported.

Secondary outcomes

- El Ters 2020 reported that compared to placebo, niacinamide may have little or no effect on back or abdominal pain (Analysis 29.2, 36 participants: MD -0.20, 95% CI -1.38 to 0.98; low certainty evidence).

- El Ters 2020 reported that compared to placebo, niacinamide may have little or no effect on the per cent change in TKV (Analysis 29.4, 36 participants: MD -1.50%, 95% CI -6.05 to 3.05; low certainty evidence).
- El Ters 2020 reported that the effects of niacinamide compared to placebo on adverse effects (Analysis 29.5) and QoL (Analysis 29.3) were unclear (very low certainty evidence).

No other secondary outcomes were reported.

DISCUSSION

Summary of main results

In this updated Cochrane review, 57 RCTs (8016 randomised participants) evaluating 18 therapeutic interventions in ADPKD were included.

No intervention had high certainty evidence for clinically important effects on death, kidney failure or patient-important outcome measures such as QoL or pain. The V2R antagonist, tolvaptan, probably slows both the decline in eGFR (mean follow-up of 20 months) and the increase of TKV (mean follow-up of 36 months) in moderate certainty evidence. However, there was little or no evidence of benefit in preventing kidney failure or death from any cause. Tolvaptan therapy was also associated with adverse events, such as nocturia. Adherence to tolvaptan treatment was lower when compared to placebo, and a higher percentage of patients in the intervention arm discontinued studies due to adverse events.

Low BP targets (mean follow-up of 60 months) and somatostatin analogues (mean follow-up of 20 months) probably result in a smaller increase of TKV; however, there was no evidence of benefit in preserving kidney function, preventing kidney failure, or reducing death. Somatostatin analogues probably increase the risk of alopecia, diarrhoea or abnormal faeces, dizziness and fatigue. There was limited data for children.

Little evidence or inconclusive results were found for the impact of antihypertensive agents (ACEi, ARB, CCB, beta-blockers), eicosapentaenoic acids, mTOR inhibitors, vitamin D compounds, prescribed water intake, low osmolar diets, metformin, niacinamide, curcumin, pioglitazone, spironolactone, bosutinib or antiplatelet agents on disease progression and patient outcomes. These treatments may be associated with undefined benefits in terms of kidney function and other secondary endpoints, such as BP or proteinuria.

Overall completeness and applicability of evidence

The completeness and applicability of the evidence varied largely depending on the therapeutic intervention. The majority of studies reported the progression of ADPKD through surrogate endpoints (e.g. change in kidney volume, BP control, change in eGFR). Hard clinical outcomes such as death or kidney failure were only marginally addressed and had insufficient data to draw definitive conclusions. Surrogate outcomes are useful proxies for clinical outcomes, particularly in slow-progressing diseases such as ADPKD. However, the main disadvantage of using surrogate outcomes is that the favourable effects of interventions do not always translate into clear benefits for hard endpoints.

While eGFR is a useful outcome measure for treatment effectiveness, this parameter remains relatively stable in the early stages of ADPKD. Therefore, its utility as an outcome measure is diminished in populations of younger ADPKD patients with preserved eGFR. The Consortium for Radiologic Imaging for the Study of Polycystic Kidney Disease (Rule 2006) demonstrated that baseline kidney volume predicted the rate of TKV increase in ADPKD. Therefore, kidney volume was proposed as a surrogate endpoint of disease progression and has since been extensively used in studies. Despite this, the benefits of some interventions (e.g. mTOR inhibitors and somatostatin analogues) on kidney volumes have not corresponded with the benefits of slowing kidney function decline. This raises the question of whether these biomarkers are appropriate as outcomes for assessing the effectiveness of novel interventions in ADPKD when used in isolation.

Outcomes such as cyst pain and cardiovascular diseases have been identified as core outcomes for both clinicians and patients with ADPKD (Cho 2017). However, these outcomes have been poorly reported in clinical trials. Likewise, data on major patient-centred outcomes, such as QoL, was also sparse.

Quality of the evidence

The quality of the evidence on interventions for slowing the progression of ADPKD was highly varied. Tolvaptan therapy has been evaluated in two large RCTs (REPRISE 2017; TEMPO 3:4 2011) and showed moderate certainty evidence of benefits for kidney function and volume preservation.

Some studies included in this review were of lower quality. Nine studies were published only as abstracts (Biao 1997; Chaudhary 2021; Melemadathil 2013; Mora 2013; Pasari 2019; Temmerman 2012; TEMPO 248 & 249 2005; TEMPO 250 2011; Watson 1999), and important information regarding methodology and patient outcomes was not reported. Eight of the included studies were cross-over studies often conducted on very small populations (Al Therwani 2017; Blazer-Yost 2021; Kramers 2020; Perrone 2020; Ruggenenti 2005; SIRENA 2010; Uchiyama 2021; van Dijk 2001), and it was not always possible to ascertain the results of each intervention.

Many studies focused on small cohorts and were not powered to observe significance in patient-centred outcomes. These results are inconclusive and probably more useful for hypothesis-setting for larger confirmation studies than for providing definite indications for clinical practice.

Furthermore, numerous studies did not provide adequate reporting or information on the blinding of patients, investigators, or both to allow us to properly assess the risks of bias. Limitations in study reporting and design markedly reduced confidence in the results.

The extreme heterogeneity in study length (ranging from single-day interventions to 60 months) also should be addressed. Many studies were indeed designed to assess treatment effects in a very short time, as per their exploratory nature. Short-term studies preclude interpretations of hard outcomes (death, kidney failure), particularly in slowly progressing conditions such as ADPKD. Performing cumulative outcome analyses with such study heterogeneity in the duration of follow-up is potentially unreliable. Subgroup analyses were performed for primary outcomes based

on follow-up duration; however, these were limited by the small number of studies contributing to each outcome.

The applicability of findings is also limited by participant attrition in many studies. Although the overall drop-out rate varied widely across the studies (1.6% to 33%), this rate was greater than 10% in 17 studies, which included many of the largest studies conducted on ADPKD patients. Furthermore, in many cases, drop-outs were unbalanced among the study groups, being more frequently observed in the active rather than in the control arm. High dropout rates may introduce important attrition bias and limit the internal validity of findings. Per-protocol analyses can be useful to bypass limitations related to high dropout rates. However, such approaches convey a high risk of bias due to the selection of patients and may provide clinically dubious information as they may overestimate the benefit or underestimate the harm of an intervention.

Potential biases in the review process

Despite using a systematic search of electronic databases, including the Cochrane Kidney and Transplant Group's specialised register of studies and applying a standardised procedure for data extraction and analysis incorporating assessment of study methodology, the findings of our review should be interpreted with caution. The lack of studies pertaining to several interventions represents the key limitation. In many instances, the effect of a given intervention was addressed only in single studies, or results were reported in such a way as to prevent meta-analyses. Furthermore, data on hard outcomes such as kidney failure and death were scarce.

Agreements and disagreements with other studies or reviews

After decades of symptomatic treatment for ADPKD, we now have several therapeutic interventions targeting ADPKD biology, arising from a wealth of experimental and non-randomised studies (Chang 2012). Many of these have not demonstrated meaningful clinical benefit. Indeed, tolvaptan is the only agent to have gained international registration for use in ADPKD and to have demonstrated clear therapeutic benefits on kidney volume and function with large RCTs. International uptake and acceptance of tolvaptan has been widespread following its registration, first in Japan in 2014, Canada and Europe in 2015, and the USA and Australia in 2018. We have seen the number of prescriptions for tolvaptan increasing internationally. In Japan, tablet prescribing increased by more than three times from 2015 to 2017 (Inoue 2020). While somatostatin analogues have been registered for use in Italy since 2018, other countries have not followed suit based on the current available evidence.

A recent systematic review and network meta-analysis of RCTs of therapeutic interventions for ADPKD patients reported similar results to those presented here (Tsukamoto 2022). They also found tolvaptan to be the only therapeutic agent to demonstrate a statistically significant benefit to change in kidney function while also reducing the growth of TKV. Metformin may preserve kidney function; however, this effect was not statistically significant. TKV was significantly reduced by somatostatin analogues, tyrosine kinase inhibitors, and mTOR inhibitors, although none of these agents preserved kidney function. An additional narrative review of current ADPKD therapies considered both tolvaptan and somatostatin to be current therapeutic treatments (Capuano 2022). However, they also concluded that the evidence for somatostatins was gathered from smaller populations, and results between trials were not as strong.

AUTHORS' CONCLUSIONS

Implications for practice

Tolvaptan was the only therapeutic agent to demonstrate a therapeutic benefit on kidney function and kidney volume. However, there is still insufficient evidence to determine tolvaptan's impact on death and kidney failure, and therapy was associated with adverse events. The appropriateness of therapy should be assessed at an individual patient level and consider the risks and benefits of therapy.

Likewise, while blood pressure control with RAAS inhibitors and somatostatin analogues slowed the growth of kidney volume, they have not demonstrated meaningful benefits on important outcomes such as kidney function, kidney failure or death, and somatostatin analogues were associated with adverse events.

Implications for research

Further research is needed to confirm the role of certain interventions in the management of ADPKD. Other interventions, such as metformin, require evaluation in larger clinical trials with sufficient sample sizes to determine efficacy. More conclusive data on the safety profiles of some agents and long-term effects are needed. Future clinical research should also focus on core outcomes important to clinicians and consumers, such as those identified in the SONG-PKD project (Cho 2017). Twenty-three ongoing studies were identified in our search, including large RCTs with long-term follow-up, which may clarify the role of specific interventions in ADPKD management.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

AIPRI 1996

Study characteristics	
Methods	Study design • Parallel, double-blind RCT • Duration of study: January 1989 to December 1990 • Follow-up: 3 years • ADPKD assessment: unclear • Countries: Italy, France, Germany • Setting: international multicentre study (49 centres)
Participants	Study characteristics • Inclusion criteria: men and women between the ages of 18 and 70 years who had chronic renal insufficiency caused by various diseases; SCr 1.5 to 4.0 mg/dL (133 to 354 mmol/L); 24-hour estimated CrCl 30 to 60 mL/min with variations > 30% in at least 3 measurements • Exclusion criteria: therapy-resistant oedema; treatment with corticosteroids, NSAIDs, or immunosuppressive drugs; UPE > 10 g/24 h; serum albumin < 25 g/L; renovascular hypertension; malignant hypertension or MI or CVA in the 6 months preceding the study; CHF (NYHA class III or IV); insulin-dependent DM; elevated serum AST concentration; collagen disease; obstructive uropathy; cancer; chronic cough; history of ACEi allergy; drug or alcohol abuse; pregnancy Baseline characteristics • Number: intervention group (300); control group (283) (64 diagnosed with ADPKD) • Mean age ± SD (years): intervention group (51± 13); control group (51 ± 12) • Sex (M/F): intervention group (220/80); control group (201/82)
Interventions	Intervention group • Benazepril: 10 mg/d Control group • Placebo Duration of intervention • 3 years
Outcomes	Reported outcomes • Doubling SCr • SCr • UPE • DBP
Notes	Additional information • Separate data on ADPKD patients were not provided • Funding: not reported
Risk of bias	

AIPRI 1996 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Sixty-eight patients in the benazepril group and 61 in the placebo group did not complete the study be cause of death, other adverse events, lack of cooperation, or protocol violations"
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Al Therwani 2017

Study characteristics	
Methods	Study design • Double-blind placebo-controlled cross-over RCT • Duration of study: not reported • Follow-up: 2 days • ADPKD assessment: genetic testing or Ravine criteria • Country: Denmark • Setting: single centre (Outpatient Nephrology Clinic of the Department of Medicine at Holstebro Hospital, Denmark)
Participants	Study characteristics • Inclusion criteria: Caucasian men and women; 18 to 65 years; BMI 18.5 to 35.5 kg/m2; ADPKD diagnosed by genetic testing for PKD1 (> 85%) and PKD2 mutations, or presence of one of the following ultrasonographic findings in accordance to the classical Ravine criteria: negative family history of ADPKD with more than 10 cysts in each kidney, and exclusion of other causes of extra-renal or renal cyst formations; a family history of ADPKD (15 to 39 years and 3 cysts or more unilaterally or bilaterally; 40 to 59 years and 2 or more cysts in each kidney; 60+ years and at least 4 cysts in each kidney); kidney function corresponding to CKD stages 1–3 (eGFR > 30 mL/min/1,73 m^2) • Exclusion criteria: clinical signs of diseases in the heart, lungs, endocrine organs, brain or neoplastic disease; clinically significant abnormalities in blood or urine sample at the inclusion; previous cerebrovascular insults; previous clinical evidence of aneurysm; alcohol or drug abuse; smoking; pregnancy or breastfeeding; clinically significant changes in the electrocardiogram; medication except antihypertensive agents and oral contraceptives; BP > 170/105 mm Hg despite treatment with metoprolol and/or amlodipine

Al Therwani 2017 *(Continued)*

	Baseline characteristics • Number (randomised/analysed: 21/18 • Mean age (range): 47 years (21 to 62) • Gender (M/F): 6 /12 • Mean BP ± SD (mm Hg): SBP (137 ± 13); DBP (88 ± 7) • Diagnosis of CKD: CKD 1-3 • Ethnicity: 100% Caucasian • Mean weight ± SD: 85.2 ± 12.7 Kg • BMI: 28 ± 5 kgm^2
Interventions	Intervention group • Tolvptan: 60 mg/d • Oral administered at 8:00 am Control group • Placebo: identical gelatine capsules • Oral administered at 8:00 am Co-interventions • Antihypertensive medications, including diuretics, ACEi, and ARB were discontinued or substituted with metoprolol 50 mg and/or amlodipine 5 mg 14 days prior to each examination day • BP >170/105 mm Hg: metoprolol 50 mg and/or amlodipine 5 mg was given and increased up to metoprolol 150 mg and/or amlodipine 10 mg. Continued BP > 170/105 mm Hg despite treatment with metoprolol 150 mg and/or amlodipine 10 mg led to withdrawal from the study. The usual antihypertensive treatment was resumed immediately after the end of the examination day • Prior to each examination day, ADPKD patients consumed a 4-day standardised diet of 11,000 KJ/d. The diet was delivered from our facilities, and in conformity with general dietary guidelines, it was composed of 15% proteins, 55% carbohydrates and 30% fat. The sodium content was 150 mmol/day. No additional sodium or other spices were allowed. The daily fluid intake was also standardised to 2.5 L, including a maximum of two cups of coffee or tea. No alcohol or soft drinks were allowed during the diet period
Outcomes	Reported outcomes • CH20 • Kidney function: 51Cr-EDTA clearance, UO, u-AQP2, u-ENaC, FE_{na}, u-nitrate • Haemodynamics: bBP, cBP, PWV, AI • Vasoactive hormones: PRC, p-ANG II, p-Aldo, p-AVP
Notes	Additional information • Protocol registration/published: not reported • Ethics: "This study was approved by The Central Denmark Region Committees on Health Research Ethics" • Declaration of interest/disclosures: "The authors declare that they have no competing interests." • Funding declared: "The study was supported by grants from The Research Foundation of Central Denmark Region and Otsuka."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement

Al Therwani 2017 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "placebo were coated in identical gelatine capsules" Comment: double-blind placebo controlled RCT
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No other concerns identified
Selective reporting (reporting bias)	Low risk	No other concerns identified
Other bias	Unclear risk	Pharmaceutical funder, no statement confirming its role or evidence of its involvement in the study design

ALADIN 2013

Study characteristics	
Methods	Study design • Single-blind, placebo-controlled RCT • Duration of study: 27 April 2006 to 12 May 2008 • Follow-up: 3 years • ADPKD assessment: NMR • Country: Italy • Setting: multicentre (5 sites)
Participants	Study characteristics • Inclusion criteria: > 18 years; clinical and ultrasound diagnosis of ADPKD; GFR > 40 mL/min/1.73 m^2 (estimated by the 4 variable MDRD equation); written informed consent • Exclusion criteria: DM; overt proteinuria (UPE > 1 g/24 h) or abnormal urinalysis suggestive of concomitant, clinically significant glomerular disease; urinary tract lithiasis, infection or obstruction; cancer; psychiatric disorders and any condition that might prevent full comprehension of the purposes and risks of the study; pregnancy, lactation or childbearing potential and ineffective contraception (oestrogen therapy in postmenopausal women not stopped) Baseline characteristics • Number: intervention group (40); control group (39) • Mean age ± SD (years): intervention group (36 ± 8); control group (38 ± 8) • Sex (M/F): intervention group (17/23); control group (20/190
Interventions	Intervention group • Long-acting somatostatin: 40 mg every 28 days Control group

ALADIN 2013 *(Continued)*

	• Placebo: saline solution Duration of intervention • 3 years
Outcomes	Reported outcomes • Change over baseline of the total kidney volume at 1 and 3 years follow-up • Change in total cyst volume • Change in non-cystic (parenchymal) volume • eGFR and mGFR • Clinical laboratory tests • Adverse events
Notes	Additional information • Funding: "This research was partly funded by PKD Foundation, Kansas City, MO, USA (grant number 01TRN07a). Novartis Italia (Origgio, Varese, Italy) freely supplied Octreotide-LAR, but did not fund the study."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation according to a computer-generated randomisation list
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants were blinded to treatment but study physicians and nurses were aware of the allocated group
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded to allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	6/79 (7.5%) patients did not complete the study. Data were analysed on a modified ITT basis
Selective reporting (reporting bias)	Low risk	All defined outcomes were reported
Other bias	Low risk	The study was partly funded by Novartis; however, the authors state that "....the sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication"

ALADIN 2 2019

Study characteristics

ALADIN 2 2019 *(Continued)*

Methods	Study design • Parallel-group double-blind, placebo-controlled phase III RCT • Duration of study: 11 October 2011 to 20 March 2014 • Follow-up: 3 years • ADPKD assessment: Ravine criteria • Country: Italy • Setting: multicentre (4 sites, co-ordinated by Istituto di Ricerche Farmacologiche Mario Negri IRCCS)
Participants	Study characteristics • Inclusion criteria: > 18 years; men and women with ADPKD and eGFR between 15 and 40 m:/min/1.73 m^2 • Exclusion criteria: confounding factors that could affect kidney function loss independently of kidney growth and treatment allocation (HbA1c > 8%, BP > 180/110 mm Hg, UPE > 3 g/24 h); abnormal urinalysis suggestive of concomitant, clinically significant glomerular disease; urinary tract lithiasis or infection; symptomatic gallstones, cancer, or major systemic disease; unable to provide informed consent; and pregnant, lactating, or potentially childbearing women without adequate contraception Baseline characteristics • Number: intervention group (51); control group (49) • Mean age ± SD (years): intervention group (48.7 ± 8.9); control group (50 ± 9.3) • Gender (M/F): intervention group (31/20); control group (26/23) • Mean SBP/DBP ± SD (mm Hg): intervention group (134.9 ± 15.4/81.8 ± 9.3); control group (132.3 ± 13.2/83.1 ± 8.4) • Mean weight ± SD (kg): intervention group (77.2 ± 14.6); control group (76.4 ± 14.1) • Median proteinuria, IQR (mg/24 h): intervention group (268, 135 to 805); control group (260, 130 to 460) • Median albuminuria, IQR (µg/mL): intervention group (50.7, 21.0 to 118.1); control group (28.3, 12.8 to 96.2) • Median eGFR, IQR (mL/min/1.73 m^2): intervention group (27.9, 23.5 to 32.2); control group (25.8, 19.5 to 33.2) • Median UACR, IQR (mg/g): intervention group (77.3, 35.9 to 225.9); control group (45.5, 25.5 to 181.9) • ADPKD imaging classification: intervention group (1A: 2, 1B: 2, 1C: 16, 1D: 13, 1E: 15, not evaluable: 3); control group (1A: 1, 1B: 6, 1C: 13, 1D: 13, 1E: 14, not evaluable: 2) • Median TKV, IQR (mL): intervention group (2338, 1967 to 3807); control group (2591, 1959 to 3835)
Interventions	Intervention group • Octreotide-LAR: 2 x 20-mg IM injections every 28 days Control group • Placebo: 2 MI injections of 0.9% sodium chloride solution every 28 days Duration of intervention • 3 years Co-interventions or additional treatments • Not reported
Outcomes	Reported outcomes • Change in TKV: 12 months follow-up • Long-term outcome: decline in GFR at 6 months to 3 years • Total liver volume • Total cyst volume

ALADIN 2 2019 *(Continued)*

- Doubling SCr or kidney failure
- BP: measured in the dominant arm after a 10-minute rest in the sitting position. The mean of 3 measurements, taken 2 minutes apart, was recorded for statistical analysis
- Scr
- eGFR
- Urinary proteinuria
- Urinary albumin
- UACR
- Urinary sodium
- CrCl
- Urinary urea
- Urinary glucose
- Urinary phosphorus excretion
- Urinary osmolality assessment

Notes	Additional information • Protocol registration/published: Protocol provided as an appendix • Ethics: "The study protocol was approved by each site's institutional review board: the Comitato di Bioetica of the Local Health Authority of the Province of Bergamo, the Comitato Bioetico of the Local Health Authority of the Province of Agrigento, the Comitato Etico of the University of Naples Federico II, and the Comitato Etico per la Sperimentazione of the Province of Treviso. The Comitato Etico of the Local Health Authority of Lecce and the Comitato Etico of the Fondazione IRCCS Cà Granda Ospedale Maggiore di Milano also approved the protocol, but the centers of Lecce and Milan did not include patients. Written informed consent was obtained from all participants in compliance with the Declaration of Helsinki" • Declaration of interest/disclosures: "The authors have declared that no competing interests exist."Funding declared: "The costs of the ALADIN 2 study were covered internally by the participating Centers. Novartis Farma (Origgio, Varese, Italy), freely supplied Octreotide-LAR, but did not fund the study and had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Participants were randomly assigned to treatment groups 1:1 by an independent investigator (G. A. Giuliano see: ALADIN 2 Study Organization in S1 Appendix), using a web-based, computer-generated randomization list created using SAS (version 9.2), stratified by center and the presence or absence of risk factors with a random block size of 4 or 8.)"
Allocation concealment (selection bias)	Unclear risk	The appendix mentions randomisation paragraph 1 in the methods, but this provides no details about allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The appendix mentions randomisation paragraph 1 in the methods, but this provides no details about allocation concealment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All of the operators were blinded to patient treatment allocation" Comment: Blinding of outcome assessors for short-term primary outcome
Incomplete outcome data (attrition bias) All outcomes	High risk	1/3 of participants did not have a evaluable CT scan at 1 year

ALADIN 2 2019 *(Continued)*

Selective reporting (reporting bias)	Low risk	No other concerns identified
Other bias	Low risk	Internal funding with drug provided by pharma with no influence in the trial

Amro 2016

Study characteristics	
Methods	Study design • Parallel RCT • Duration of study: not reported • Follow-up: 2 weeks • ADPKD assessment: Ravine criteria • Country: USA • Setting: single setting (Tufts Medical Center)
Participants	Study characteristics • Inclusion criteria: 8 to 60 years; ADPKD; eGFR ≥ 60 mL/min/1.73 m^2 • Exclusion criteria: long-term use of medications known to affect AVP secretion; hyponatremia; presence of physical or cognitive impairments that prevent participation or consent; pregnancy Baseline characteristics • Number: intervention group (17); control group (17) • Mean age ± SD (years): intervention group(43.1 ± 13); control group (44.4 ± 9.8) • Sex (M/F): intervention group (3/14); control group (3/14)
Interventions	Intervention group • Low-osmolar: low-sodium (1500 mg/d), low-protein (0.8 g/kg body weight) diet and adjusted water prescription Control group • No intervention
Outcomes	Reported outcomes • Plasma copeptin levels • Total daily urinary solute reduction • 24-hour urine osmolality reduction
Notes	Additional information • Support: "Dr Amro was supported by a National Institutes of Health (NIH) institutional training grant (5T32DK007777). Performance of this project and Dr Perrone were supported in part by the National Center for Advancing Translational Sciences, NIH (grant UL1 TR001064). Funders of this study had no role in study design; collection, analysis, and interpretation of data; writing the report; and the decision to submit the report for publication." • Financial Disclosure: "Dr Perrone has received research funding from Otsuka and is a consultant for Otsuka, Sanofi–Genzyme, Novartis, Mitsubishi Tanabe Pharma Development America, and Vertex. The other authors declare that they have no other relevant financial interests."

Amro 2016 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation completed using R statistical software version 1.14.4 package "blockrand,"
Allocation concealment (selection bias)	Low risk	Allocation using printed cards in envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	It was not possible to blind participants because the intervention group received specific water pre-scriptions and counseling for sodium and protein reduction.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Technician was blinded to treatment assignments and the visit timeline
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only one participant lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Protocol paper not published
Other bias	Low risk	No other concerns identified

Biao 1997

Study characteristics

Methods	Study design • Parallel RCT • Duration of study: not reported • Follow-up: 3 months • ADPKD assessment: Echo • Country: China • Setting: not reported
Participants	Study characteristics • Inclusion criteria: not reported • Exclusion criteria: not reported Baseline characteristics • Number: intervention group (18); control group (16) • Mean age ± SD (years): intervention group (36 ± 8); control group (38 ± 8) • Sex (M/F): not reported
Interventions	Intervention group • Calcitriol: 0.25 to 1.0 µg/d

Biao 1997 *(Continued)*

	Control group • Qijudihuang mix: 10 mL/d Duration of intervention • 3 months
Outcomes	Reported outcomes • Creatinine • GFR
Notes	Additional information • Abstract-only publication • Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Blazer-Yost 2021

Study characteristics

Methods	Study design • Phase 1b, double-blind placebo-controlled, cross-over RCT • Duration of study: 21 January 2016 to 20 August 2019 • Follow-up: 12 months • ADPKD assessment: MRI • Country: USA

Blazer-Yost 2021 *(Continued)*

- Setting: single-centre

Participants	Study characteristics • Inclusion criteria: male or female ADPKD patients aged 18 to 55 years; eGFR ≥ 50 mL/min/1.73 m^2 by 4 parameter MDRD-CKD-Epi formula, or any other eGFR formula orCrCl; normal liver enzymes (ALT/AST); fasting blood glucose between 70 and 120; for female patients, a willingness to use double contraception to avoid pregnancy while in study; able to give informed consent; in the opinion of the investigator, high likelihood of progressive kidney disease • Exclusion criteria: diabetes (fasting blood sugar > 130 twice, HgbA1C > 7%, on any blood sugar lowering medication, or past diagnosis of diabetes not occurring during pregnancy); uncontrolled hypertension as determined by the examining physician; history of impaired systolic function (ejection fraction < 50%) by previous ECHO or known ischaemic CVD; findings suggestive of a kidney disease other than ADPKD; systemic illness requiring immunosuppressive or anti-inflammatory agents; congenital absence of a kidney or history of a total nephrectomy; history of cyst reduction or partial nephrectomy; history of renal cyst aspiration within the previous year; history of bladder cancer, or gross haematuria; inability to undergo MRI due to implantable devices or foreign objects that preclude MRI; active kidney transplant; allergy or sensitivity to any of the components of the test materials; institutionalised; currently pregnant or plans to become pregnant during the study Baseline characteristics • Number: 18 • Mean age ± SD: 34+.21 ± 7.54 years • Gender (M/F): 7/11 • Mean BP ± SD (mm Hg): SBP (133.83 ± 13.29); DBP (87.72 ± 6.74) • Ethnicity: White (13); non-white (5) • Mean total protein ± SD: 7.24 ± 0.21 mmol/L • Mean albuminuria ± SD: 4.38 ± 0.23 g/dL • Mean eGFR ± SD: 86.29 ± 26.51 mL/min/m^2 • Mean SCr ± SD: 1.03 ± 0.36 mg/dL
Interventions	Intervention group • Pioglitazone: 15 mg once/d • Washout period: 2 to 4 weeks Control group • Placebo • Washout period: 2 to 4 weeks Duration of intervention • 1 year Co-interventions or additional treatments • Not reported
Outcomes	Reported outcomes • Safety outcomes • Per cent change in TKV • The net change (decrease) in resistance (which converts to an increase in total body water (TBW)) was assessed by bioimpedance analysis (BIA) over the course of each arm ○ Episodes of CHF: new onset of pulmonary symptoms together with either increased interstitial oedema on chest X-ray or changes by an ECG (increase in end-diastolic ventricular volume or new/increased pericardial effusion)

Blazer-Yost 2021 *(Continued)*

- Oedema: number of episodes of oedema, classified as either 1) sustained > 1 week of oedema despite adjustment of diet or 2) unresponsive to diuretic therapy
- Change in ECG parameters consistent with coronary artery disease (reduction in systolic ejection fraction and/or wall motion abnormalities)
- Any doctor's visit or hospitalisation for new cardiac symptoms, ventricular volume or new increase in pericardial effusion

- Hypoglycaemia: number of episodes of hypoglycaemia (defined as blood glucose < 70 mg/dL)
- Liver function: number of episodes of elevated ALT or AST to > 2 times ULN
- Measures of kidney function
  - Change in eGFR by CKDepi formula
  - Change in micro-UACR
  - Average MAP from both BP readings taken at each visit over the 12 months
- Other PKD parameters
  - Percent change in liver size by MRI
  - Cumulative pain score (0 to 10 scale) as the average area under the concentration-time curve between baseline and last trial visit or last visit before requirement of surgical or medical therapy for pain

Notes

Additional information

- Protocol registration/published: Published as protocol
- Ethics: "The study was approved by the US Food and Drug Administration (IND 117464) and the Indiana University Institutional Review Board (1308084213)."
- Declaration of interest/disclosures: "B.L.B.-Y. is the inventor of a published (23 April 2020) patent application entitled 'PPAR Gamma Modulators for Treating Cystic Disease'. R.L.B. is the founder and chief scientific officer of Rene Medical and Apoptocyst and serves on the Scientific Review Panel of Otsuka. K.M.P.-S. is currently an employee of Eli Lilly, Indianapolis, IN, USA. V.E.T. reports grants and/or other fees from Acceleron Pharma, Blueprint Medicines, Mironid, Otsuka Pharmaceuticals, Palladio Biosciences, Sanofi Genzyme, Regulus Therapeutics and Vertex Pharmaceuticals, all outside the submitted work."
- Funding declared: "The work was supported by a grant from the US Food and Drug Administration (RO1 FD004826). The Polycystic Kidney Disease Foundation provided funding for the pioglitazone and placebo formulations. An Indiana National Institute of Health (NIH) Clinical Translational Science Award (UL1TR002529-01) provided preclinical support, regulatory guidance, study monitoring, database support and statistical support. Measurements of kidney and liver volumes were supported in part by the Mayo Clinic Robert M. and Billie Kelley Pirnie Translational PKD Center and NIH Diabetes and Digestive and Kidney Diseases grant P30DK090728. S.M.M. is also supported by NIH grants AR072581, DK110871 and ULTR002529-01 and receives consulting fees from Amgen, Sanifit, Ardeylx and Novo Nordisk and grants from Chugai and Keryx. B.L.B.-Y. is supported by a Department of Defense Peer Reviewed Medical Research Program grant (W81XWH16-PRMRP-IIRA). R.N.M. is funded by an NIH award (NIHK23DK102824). The funding sources had no role in the study design, data collection/interpretation or writing of the manuscript."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were block randomized by an investigational pharmacist to placebo or pioglitazone" Comment: appropriate methods with no concerns
Allocation concealment (selection bias)	Low risk	Quote: "The investigational pharmacist distributed the medication to patients and performed pill counts upon return to ensure blinding of the patients and investigators, and both the pioglitazone and placebo were over encapsulated in an identical manner" Comment: appropriate methods

Blazer-Yost 2021 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Ultrasound images were analyzed by a single-blind analyst" for MRI ". No contrast agents were utilized. Individuals involved in the acquisition and analysis of images were blinded regarding group assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar number of participants lost across groups and intention to treat analysis undertaken
Selective reporting (reporting bias)	Low risk	No obvious concerns with outcomes reported as indicated in the trial registration and protocol publication
Other bias	Low risk	No other concerns identified

Braun 2014

Study characteristics	
Methods	Study design • Open-label pilot RCT • Duration of study: December 2006 to July 2009 • Follow-up: 12 months • ADPKD assessment: MRI • Country: USA • Setting: single centre
Participants	Study characteristics • Inclusion criteria: 21 to 66 years with ADPKD; eGFR ≥ 25 mL/min/1.73 m^2 • Exclusion criteria: DM; hospitalisation for acute illness in the previous 2 months; life expectancy < 2 years; pregnancy; history of non-adherence or drug or alcohol dependency; serious psychiatric illness; proteinuria > 500 mg/24 h; fasting hypertriglyceridemia > 400 mg/dL or LDL cholesterolemia > 190 mg/dL despite treatment, thrombocytopenia < 100,000 platelets/mL; use of systemic immunosuppressive drugs; participation in another interventional study Baseline characteristics • Number: intervention group 1 (10); intervention group 2 (10); control group (10) • Mean age ± SD (years): intervention group 1 (44.9 ± 8.6); intervention group 2 (53.2 ± 15); control group (49.4 ± 11) • Gender (M/F): intervention group 1 (10/0); intervention group 2 (10/0); control group (9/1) • Diagnosis of ADPKD (Kidney failure from ADPKD before age 56 years): intervention group 1 (8/10); intervention group 2 (4/10); control group (7/10) • Hypertension (≥ 140/90 mm Hg before age 35 years): intervention group 1 (3/10); intervention group 2 (3/10); control group (5/10) • eGFR (25 to 59 mL/min/1.73 m^2): intervention group 1 (4/10); intervention group 2 (3/10); control group (2/10) • Mean eGFR ± SD (mL/min/1.73 m^2): intervention group 1 (70.4 ± 33); intervention group 2 (65.1 ± 33.5); control group (69.9 ± 18.8)

Braun 2014 *(Continued)*

- MAP ± SD (mm Hg): intervention group 1 (93.8 ± 7.6); intervention group 2 (100 ± 9.1); control group (90.1 ± 7.5)
- Ethnicity (white/other): intervention group 1 (10/0); intervention group 2 (10/0); control group (9/1)
- Initial total kidney volume (>1500 mL): intervention group 1 (7/10); intervention group 2 (6/10); control group (6/10)
- Mean baseline TKV ± SD (mL): intervention group 1 (1919.1 ± 903.6); intervention group 2 (1454.1 ± 801.5); control group (1907.1 ± 1126.8)

Interventions	Intervention group 1 • Low-dose rapamycin: rapamycin was provided as a 1 mg Rapamune (Pfizer, Inc., New York, NY) tablet, with doses to achieve the desired trough blood levels (24 hours after the previous day's morning dose at weeks 1, 2, 4, and 6 and months 3, 6, 9, and 12) • Trough blood levels: 2 to 5 ng/mL Intervention group 2 • Standard-dose rapamycin: rapamycin was provided as a 1 mg Rapamune (Pfizer, Inc., New York, NY) tablet, with doses to achieve the desired trough blood levels (24 hours after the previous day's morning dose at weeks 1, 2, 4, and 6 and months 3, 6, 9, and 12) • Trough blood levels: > 5 ng/mL Control group • Standard care Duration of intervention • 12 months Co-interventions or additional treatments • Fluid intake of 2500 to 3000 mL/24 hours, primarily water; a low-sodium diet of 2300 mg/24 h; and caffeine avoidance were recommended to all patients, along with control of hypertension
Outcomes	Reported outcomes • Change in GFR: 125I-iothalamate and urinary clearances (coefficient of variation, 9.2%) • eGFR data (CKD-EPI equation) • Rapamycin blood levels: chromatography-mass spectrometry • Liver volume
Notes	Additional information • Protocol registration/published: not reported • Ethics: the study was approved by the institutional review board • Declaration of interest/disclosures: B.H. reports having received grant funding from Siemens Healthcare for research in CT dose reduction; he has no personal financial disclosures. • Funding declared: "This investigator-initiated research study was supported by a $250,000 research grant from Wyeth Pharmaceuticals, now Pfizer/ Wyeth. No one from either of those companies has had any role whatsoever in the study design, data handling or evaluation, or any aspect of preparing or writing this manuscript."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly assigned in this pilot study to one of three groups"

Braun 2014 *(Continued)*

		Comment: unclear methods about sequence generation
Allocation concealment (selection bias)	High risk	Open-label allocation of treatment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label allocation of treatment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	> 80% completed the study and had data for the primary outcome
Selective reporting (reporting bias)	Low risk	No other concerns identified
Other bias	Low risk	No other concerns identified

Brosnahan 2022

Study characteristics	
Methods	Study design • Double-blind placebo-controlled RCT • Duration of study: November 2016 to September 2019 • Follow-up: 12 months • ADPKD assessment: Ravine criteria • Country: USA • Setting: single centre (University of Colorado Anschutz Medical Campus)
Participants	Study design • Inclusion criteria: aged 30 to 60 years; diagnosis of ADPKD; eGFR 50 to 80 ml/min/1.73 m^2; BP < 130/80 mm Hg; if on antihypertensive medications, steel doses for at least 4 weeks; free for alcohol or drug dependence; able to give informed consent • Exclusion criteria: DM; current or history of smoking in last 12 months; hospitalisation within last 3 months; severe comorbidities; pregnancy, or inability for females to use contraception; BMI < 21 kg/m^2 Baseline characteristics • Number (randomised/analysed): intervention group (26/22); control group (25/23) • Mean age ± SD (years): intervention group (48 ± 8); control group (48 ± 7) • Gender (M/F): intervention group (11/15); control group (8/17)
Interventions	Intervention group • Metformin: starting dose 500 mg twice/d with meals and up-titrated if well tolerated every 2 weeks by 500 mg to a maximal dose of 1000 mg twice/d Control group

Brosnahan 2022 *(Continued)*

	• Placebo: twice/d with meals Duration of intervention • 12 months
Outcomes	Reported outcomes • Full randomised dose • At least 50% of the randomised dose • Height-adjusted TKV • eGFR • Adverse events
Notes	Additional information • Support: "This study was supported by grants from the NIH National Institute of Diabetes and Digestive and Kidney Diseases (R21 DK107969-01A1, to GMB and MBC) and the Zell Foundation. The funders had no role in study design, data collection, analysis, reporting, or the decision to submit the manuscript for publication." • Financial Disclosure: "Dr Chonchol reports grants from the Department of Defense and from Otsuka, Sanofi, and Corvidia, all outside the submitted work. Dr Gitomer reports grant funding from NIDDK and the Department of Defense, also funding from Sanofi, Kadmon, and Otsuka, all outside the submitted work. Dr Wang reports grants from NIDDK and Department of Defense. Dr Klawitter reports grants from NIDDK independent of the submitted work. Dr Nowak reports grants from NIDDK and the PKD Foundation outside the submitted work. Taylor Struemph reports grants from NIDDK, grants from the VA, and grants from Sanofi outside the submitted work. The other authors declare that they have no relevant financial interests."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The patients were categorized based on a block randomization scheme (ie, in block of 2 participants) and then a random number generator was used to assign the participants to either metformin or placebo"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "To ensure consistency, the volumetric measurements of TKV were performed on deidentified images by 1 reader (WW) who was blinded to the patients' study assignments" Comment: independent data monitoring was involved but no information on other outcome monitoring, including co-primary outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Small drop out rate that is consistent across study arms
Selective reporting (reporting bias)	Low risk	Justification of primary outcomes is provided

Brosnahan 2022 *(Continued)*

Other bias	Low risk	No other concerns identified

Cadnapaphornchai 2005

Study characteristics

Methods	Study design • Parallel RCT • Duration of study: commenced 1998 • Follow-up: 60 months • ADPKD assessment: Echo • Country: USA • Setting: single centre, national recruitment
Participants	Study characteristics • Inclusion criteria: aged 4 to 21 years; normal kidney function (CrCl > 80 mL/min/1.73 m^2) • Exclusion criteria: past history of allergy to study medication or inability to comply with the study protocol Baseline characteristics • Number: intervention group (45); control group (40) • Mean age ± SD (years): intervention group (11 ± 5); control group (12 ± 5) • Sex (M/F): intervention group (29/16); control group (17/23)
Interventions	Intervention group • Enalapril: 0.6 to 40 mg/kg/d Control group • Standard therapy Duration of intervention • 60 months
Outcomes	Reported outcomes • BP • Kidney volume • eGFR • LVMI • Albuminuria
Notes	Additional information • Three study groups ○ Hypertensive, borderline and severe PKD; hypertensive and borderline have been analysed as 2 separate studies • Funding: "This clinical trial was supported by National Institutes of Health (NIH) National Institute of Diabetes and Digestive and Kidney Diseases Grant R01 DK058793, NIH National Center for Research Resources Grant MO1 RR00069, and the Zell Family Foundation"

Cadnapaphornchai 2005 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised random number generator
Allocation concealment (selection bias)	Low risk	Block randomisation using a sealed, numbered envelope
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	22/85 (26%) patients withdrew. Data were not analysed on ITT basis
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Cadnapaphornchai 2005 borderline

Study characteristics

Methods	Study design • Parallel RCT • Duration of study: commenced 1998 • Follow-up: 60 months • ADPKD assessment: Echo • Country: USA • Setting: single centre, national recruitment
Participants	Study characteristics • Inclusion criteria: aged 4 to 21 years; normal kidney function; borderline hypertension (more than 50% of either systolic or diastolic BP measurements (at least 12 determinations in the dominant arm with appropriate cuff) above the 75th percentile for age-, sex-, and height-matched healthy subjects) • Exclusion criteria: past history of allergy to study medications or inability to comply with the study protocol Baseline characteristics • Number: intervention group (15); control group (12) • Mean age ± SD (years): intervention group (11 ± 5); control group (12 ± 3) • Sex (M/F): intervention group (10/5); control group (5/7)
Interventions	Intervention group

Cadnapaphornchai 2005 borderline *(Continued)*

	• Enalapril: 0.6 to 40 mg/kg/d Control group • Standard therapy Duration of intervention • 60 months
Outcomes	Reported outcomes • BP • Kidney volume • eGFR • LVMI • Albuminuria
Notes	Additional information • Funding: "This clinical trial was supported by National Institutes of Health (NIH) National Institute of Diabetes and Digestive and Kidney Diseases Grant R01 DK058793, NIH National centre for Research Resources Grant MO1 RR00069, and the Zell Family Foundation"

Cadnapaphornchai 2005 normotensive

Study characteristics	
Methods	Study design • Parallel RCT • Duration of study: commenced 1998 • Follow-up: 60 months • ADPKD assessment: Echo • Country: USA • Setting: single centre, national recruitment
Participants	Study characteristics • Inclusion criteria: aged 4 to 21 years; normal kidney function; normal BP (SBP and DBP measurements (at least 12 determinations in the dominant arm with appropriate cuff) between the 25th and 75th percentile for age-, sex-, and height-matched healthy subjects); severe ADPKD • Exclusion criteria: past history of allergy to study medications or inability to comply with the study protocol Baseline characteristics • Number: intervention group (16); control group (15) • Mean age ± SD (years): intervention group (12 ± 5); control group (12 ± 5) • Sex (M/F): intervention group (9/7); control group (5/10)
Interventions	Intervention group • Enalapril: 0.6 to 40 mg/kg/d Control group • Standard therapy

Cadnapaphornchai 2005 normotensive *(Continued)*

	Duration of intervention • 60 months
Outcomes	Reported outcomes • BP • Kidney volume • eGFR • LVMI • Albuminuria
Notes	Additional information • Funding: "This clinical trial was supported by National Institutes of Health (NIH) National Institute of Diabetes and Digestive and Kidney Diseases Grant R01 DK058793, NIH National Center for Research Resources Grant MO1 RR00069, and the Zell Family Foundation"

Cadnapaphornchai 2011

Study characteristics	
Methods	Study design • Parallel, double-blind, placebo-controlled, phase III RCT • Duration of study: July 2007 to October 2009 • Follow-up: 5 years • ADPKD assessment: MRI • Country: USA • Setting: single centre; recruited nationally
Participants	Study characteristics • Inclusion criteria: ADPKD; aged 8 to 22 years; eGFR > 80 mL/min/m^2 • Exclusion criteria: past allergic history to medications used in the study; history of liver or muscle disease; pregnancy or lactation; inability to cooperate with or clinical contraindication for magnetic nuclear imaging; identified difficulties interfering with the ability to adhere to the study regimen Baseline characteristics • Number: intervention group (56); control group (54) • Mean age ± SD (years): intervention group (16 ± 4); control group (16 ± 4) • Gender (F): intervention group (61%); control group (63%)
Interventions	Intervention group • Pravastatin: 20 to 40 mg/d Control group • Placebo Duration of intervention • 3 years Co-interventions

Cadnapaphornchai 2011 *(Continued)*

	• ACEi (lisinopril)
Outcomes	Combined endpoint of 20% or greater change • Total kidney volume • LVMI • UAE Overall change • Total kidney volume • LVMI • UAE
Notes	Additional information • Funding: "This research was supported by the National Institutes of Health, the National Center for Research Resources, and the Zell Family Foundation."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised in a double-blind manner using randomisation codes
Allocation concealment (selection bias)	Low risk	Treatments labelled A or B, one being statin treatment and the other placebo. The research pharmacist chose which letter represented the statin treatment and placed the code in a sealed envelope
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind using placebo control
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The images were de-identified and TKV was measured by stereology by a single analyst who had no knowledge of the participant's status
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall completion rate of 83%
Selective reporting (reporting bias)	Unclear risk	A priori protocol paper not located
Other bias	Low risk	No other concerns identified

Chaudhary 2021

Study characteristics

Methods	Study design • Parallel RCT • Duration of study: not reported • Follow up: 12 months

Chaudhary 2021 *(Continued)*

- ADPKD assessment: not reported
- Country: India
- Setting: not reported

Participants	Study characteristics • Inclusion criteria: ADPKD; eGFR > 45 mL/min • Exclusion criteria: diabetics; pregnant; breastfeeding; liver disease Baseline characteristics • Number: intervention group (35); control group (35) • Mean age ± SD (years): not reported • Sex (M/F): not reported
Interventions	Intervention group • Metformin: up to 200 mg/d Control group • Placebo
Outcomes	Reported outcomes • Change in total kidney volume • Change in eGFR • Change in proteinuria
Notes	Additional information • Abstract-only publications • Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information provided within abstract about randomisation methods
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Abstact-only publications; 70 participants recruited, results of 60 reported with explanation of withdrawals provided
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make a judgement

Chaudhary 2021 *(Continued)*

Other bias	Unclear risk	Insufficient information to make a judgement

DIPAK 1 2014

Study characteristics

Methods

Study design

- Parallel-group open-label RCT
- Duration of study: July 2012 to August 2017
- Follow-up: 132 weeks (mean duration was 104 weeks)
- ADPKD assessment: Ravine criteria
- Country: the Netherlands
- Setting: multicentre (66 sites)

Participants

Study characteristics

- Inclusion criteria: aged 18 to 60 years who had later stage ADPKD; eGFR 30 to 60 mL/min/1.73 m^2
- Exclusion criteria: bradycardia; a history of gallstones or pancreatitis; and diseases or medication use that could confound end point assessment (e.g. DM, use of NSAIDs, use of lithium or tolvaptan)

Baseline characteristics

- Number (randomised/analysed): intervention group (154/153); control group (155/152)
- Mean age ± (years): intervention group (48.2 ± 7.4); control group (48.5 ± 7.2)
- Gender (M/F): intervention group (71/82); control group (71/81)
- Mean BP ± SD (SBP/DBP): intervention group (132.3 ± 12.6/82.3 ± 9.0); control group (133.4 ± 14.0/82.1 ± 10)
- Ethnicity. (white/Asian/missing): intervention group (147/2/4); control group (148/3/1)
- Mean weight ± SD (kg): intervention group (84.5 ± 16.5); control group (83.6 ± 17.3)
- Mean height ± SD (m): intervention group (1.77 ± 0.1); control group (1.76 ± 0.1)
- Mean BMI ± SD: intervention group (26.9 ± 4.5); control group (27.1 ± 4.8)
- Median TKV, IQR (mL): intervention group (2046, 1383 to 2964); control group (1874, 1245 to 2868)
- CKD stages (2/3a/3b/4): intervention group (41/55/57/0); control group (41/62/47/2)
- Mean eGFR ± SD (mL/min/1.73 m^2): intervention group (51.0 ± 11.5); control group (51.4 ± 11.2)
- ADPKD imaging classification: intervention group (1A: 2, 1B: 2, 1C: 16, 1D: 13, 1E: 15, not evaluable 3); control group (1A: 1, 1B: 6, 1C: 13, 1D: 13, 1E: 14, not evaluable: 2)

Interventions

Intervention group

- Lanreotide: 120 mg SC once every 4 weeks, down-titrated to 90 mg if eGFR decreased to < 30 mL/min/1.73 m^2 during the trial. If patients did not tolerate 120 mg, lanreotide was down-titrated to 90 mg, 60 mg, or stopped

Control group

- Standard of care

Duration of intervention

- 120 weeks

Co-interventions or additional treatments

DIPAK 1 2014 *(Continued)*

	• BP < 140/90 mm Hg to be reached with a sodium-restricted diet and, as a first-choice BP–lowering agent, an ACEi or ARB. The choice of additional antihypertensive medication and dietary advice was left to the discretion of the treating physician
Outcomes	Reported outcomes • Change in kidney function (slope of eGFR over time): 12 weeks to end of treatment phase • Change in eGFR between pretreatment and post-treatment visits • Incidence of worsening kidney function: 2 consecutive measurements ≥ 30% decrease from pretreatment eGFR or need for KRT • Change in htTKV • Change in health-related QoL • Adverse events • Tolerability of lanreotide
Notes	Additional information • Protocol registration/published: Protocol provided as an appendix and published • Ethics: "The study protocol was approved by each site's institutional review board: the Comitato di Bioetica of the Local Health Authority of the Province of Bergamo, the Comitato Bioetico of the Local Health Authority of the Province of Agrigento, the Comitato Etico of the University of Naples Federico II, and the Comitato Etico per la Sperimentazione of the Province of Treviso. The Comitato Etico of the Local Health Authority of Lecce and the Comitato Etico of the Fondazione IRCCS Cà Granda Ospedale Maggiore di Milano also approved the protocol, but the centers of Lecce and Milan did not include patients. Written informed consent was obtained from all participants in compliance with the Declaration of Helsinki" • Declaration of interest/disclosures: "Dr Gansevoort received grant support and fees for serving on advisory boards and steering committees from IPSEN, Otsuka Pharmaceuticals and Sanofi- Genzyme. In addition, Dr Gansevoort holds the Orphan Medicinal Product Designation status at the European Medicines Agency for lanreotide as treatment for ADPKD (EMA/OD/027/15). Dr Drenth has received grant support and fees for serving on advisory boards and consultancy from IPSEN and Novartis. All money is paid to their employers. No other potential conflict of interest relevant to this article was reported." • Funding declared: "No funding party had any role in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomly assigned (1:1) to the lanreotide group, which received lanreotide and standard care, or to the control group, which received standard care alone. Randomization with a block size of 6 was performed centrally with the use of an interactive voice response system, with stratification according to sex, age (≤45 years or >45 years), and eGFR (≤45 mL/min/1.73m2 or >45 mL/min/1.73m2)." Comment: appropriate methods
Allocation concealment (selection bias)	Unclear risk	The appendix mentions randomisation paragraph 1 in the methods, but this provides no deals about allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Because lanreotide is a gel, administration of this drug results in temporary injection infiltrates. Manufacturing a placebo that has a similar effect has not been possible from a technical point of view, which precluded execution of this trial as a double-blinded randomized trial" Comment: open-label trial but not possible to placebo-controlled

DIPAK 1 2014 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "To minimize bias, efficacy end points will be assessed in a blinded fashion (eGFR and MRI kidney and liver volume measurements will be done centrally by personnel blinded for treatment allocation)." Comment: appropriate reporting identified in the protocol
Incomplete outcome data (attrition bias) All outcomes	Low risk	15% of the trial participants didn't complete the trial, with more in the intervention group. However, ITT analysis undertaken in 153 for both primary efficacy and safety analyses
Selective reporting (reporting bias)	Low risk	All appropriate reporting of outcomes has occurred
Other bias	Low risk	No other concerns identified

DRINK 2018

Study characteristics	
Methods	Study design • Parallel open-label phase 2 RCT • Duration of study: January 2017 and January 2018 • Follow-up: 2 months • ADPKD assessment: radiological and or genetic evidence of PKD1 or PKD2 mutations • Country: UK • Setting: single centre
Participants	Study characteristics • Inclusion criteria: aged 16 years or older; ability to provide informed consent eGFR ≥ 20 mL/min/1.73 m^2; able to self-monitor urine specific gravity • Exclusion criteria: fluid overload states (e.g. heart failure, cirrhosis or requirement for fluid restriction); confounding illness impacting on kidney disease (e.g. concomitant diabetes or glomerulonephritis); treatment with diuretics for fluid overload (those on diuretics for hypertension may participate in the trial after a run-in period of 2 weeks); treatment with tolvaptan in the last 4 weeks; pregnancy or breastfeeding Baseline characteristics • Number: intervention group (21); control group (21) • Mean age ± SD (years): intervention group (32 ± 15); control group (31 ± 14) • Gender (M/F): intervention group (9/12); control group (9/12)
Interventions	Intervention group • Prescribed water intake: daily fluid prescription derived from the free-water clearance formula Control group • Ad libitum water intake: advised to drink to thirst with a target UOsm 300 mOsm/Kg Duration of intervention • 2 months Co-interventions or additional treatments

DRINK 2018 *(Continued)*

	• Both groups were guided through trial smartphone application installation and given secure login details. They were provided with Siemens Multistix GP indicator strips and shown how to test their urine and read the USG. Both groups advised to maintain a urine-specific gravity ≤ 1.010
Outcomes	Reported outcomes • Recruitment rate • Achievement of urinary osmolality ≤ 270 mOsm/kg at week 8 • Proportion of participants able to self-monitor • Change in copeptin • Determine acute changes in mGFR and eGFR • Adverse events • UTI • Hyponatremia
Notes	Additional information • Protocol registration/published: Published and cited • Ethics: "The study was approved by the East of England Essex Research Committee (16/ EE/0026)..." • Declaration of interest/disclosures: none declared • Funding declared: British Renal Society and Kidney Care UK Joint Grants Programme (15-004), PKD Charity, Addenbrooke's Charitable Trust (24/15 A) and Kidney Research UK (TF_009_20161125)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants will be randomly assigned (1:1) to HW or AW water intake using a manual sealed envelope system
Allocation concealment (selection bias)	Low risk	Manual sealed envelope system prepared by the Cambridge Clinical Trials Unit statistician and to which the trial team will be blinded
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label, unblinded study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT all randomised participants included and low number of withdrawals
Selective reporting (reporting bias)	Low risk	Pre-published protocol paper available. However, some secondary outcomes such as QoL not reported
Other bias	Low risk	No other concerns identified

Ecder 1999

Study characteristics

Ecder 1999 *(Continued)*

Methods	Study design • Parallel RCT • Duration of study: 1991 to 1994 • Follow-up: 7 years • ADPKD assessment: Echo • Country: USA • Setting: single centre
Participants	Study characteristics • ADPKD with hypertension (BP > 140/90 mm Hg in a sitting position or taking antihypertensive drugs); GFR > 50 mL/min/1.73 m^2 • Exclusion criteria: not reported Baseline characteristics • Number: intervention group (12); control group (12) • Mean age ± SD (years): intervention group (41 ± 2); control group (42 ± 3) • Sex (M/F): intervention group (5/7); control group (8/4)
Interventions	Intervention group • Enalapril: mean dose 17 mg/d Control group • Amlodipine: mean dose 9 mg/d Duration of intervention • 60 months
Outcomes	Reported outcomes • Mean BP • GFR • Albuminuria
Notes	Additional information • Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement

Ecder 1999 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

El Ters 2020

Study characteristics	
Methods	Study design • Parallel double-blind placebo-controlled, RCT • Duration of study: September 2015 to November 2016 • Follow-up: 12 months • ADPKD assessment: Ravine criteria • Country: USA • Setting: single centre
Participants	Study characteristics • Inclusion criteria: 18 to 60 years of age; eGFR > 55 mL/min/1.73 m^2 • Exclusion criteria: history of liver disease, abnormal liver function test; heavy alcohol usage; chronic diarrhoea; thrombocytopenia; hypophosphatemia; pregnancy or lactation; treatment with tolvaptan within the prior 2 months; concomitant use of antiepileptic drugs; and partial nephrectomy, total nephrectomy, or renal cyst reduction within a year before screening Baseline characteristics • Number: intervention group (18); control group (18) • Mean age ± SD (years): intervention group (40.1 ± 10.90); control group (44.7 ± 9.1) • Gender (M/F): intervention group (10/8); control group (6/12) • Diagnosis of ADPKD: intervention group (1A: 0, 1B: 3, 1C: 5, 1D: 5, 1E: 5, 2: 0); control group (1A: 0, 1B: 1, 1C: 10, 1D: 6, 1E: 1, 2: 0) • Hypertension: intervention group (18/18); control group (14/18) • Mean eGFR ± SD (mL/min/1.72 m^2): intervention group (78.1 ± 18.6); control group (68.1 ± 12) • Mean hfTKV ± SD (mL/m): intervention group (1210 ± 772); control group (1021 ± 434) • Ethnicity (Caucasian, non-Hispanic/Hispanic): intervention group (18/0/0); control group (18/0)
Interventions	Intervention group • Tolvaptan: 30 mg/kg/d oral in 2 divided doses Control group • Placebo: matching placebo as split dose regimens with the first dose taken upon waking and the second taken 8–9 h later. After 1 week, subjects who tolerate their initial dose will up-titrate once Duration of intervention

El Ters 2020 *(Continued)*

	• 12 months Co-interventions or additional treatments • Subjects are additionally encouraged to drink plain water per thirst throughout the day and one to two glasses of water before bedtime to help maintain proper hydration status
Outcomes	Reported outcomes • Ratio of acetylated p53 (at K382) to total p53 protein abundance in PBMCs • htTKV: 3 investigators independently measured the same set of images. Raters were blinded to the intervention group and also the time point to mitigate observer bias • Overall pain (PKD 8 questionnaire) • QoL (PKD 8 questionnaire) • eGFR • C-reactive protein • UPCR • Urine monocyte chemoattractant protein-1 concentration • Enzyme-linked immunosorbent assay • Adverse events: aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, serum phosphorus, and platelet count
Notes	Additional information • Protocol registration/published: not published • Ethics: "Both studies were approved by the University of Kansas Medical Center Institutional Review Board. All participants provided written informed consent before participating in the study." • Declaration of interest/disclosures: "FS has received fees for serving on Otsuka advisory boards. DM has received a research grant from Otsuka and serves on an Otsuka advisory board. FE has received fees as a member of the Otsuka Safety Committee for pediatric studies. RDG has nothing to disclose. DB has received consultation fees from Otsuka. MAC has served as a consultant to Otsuka. LS, AD, KS, and SES are employees of Otsuka." • Funding: "This research is sponsored by Otsuka Pharmaceutical Development & Commercialization, Inc. (Rockville, MD, USA)."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "blocked randomization schedule that was generated by a statistician and shared only with the research pharmacy." Comment: appropriate methods with no concerns
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement about how therapies were assigned following randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Three investigators independently measured the same set of images. Raters were blinded to intervention group and also timepoint, to mitigate observer bias." Comment: appropriate methods

El Ters 2020 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar number of participants lost across groups and intention to treat analysis undertaken
Selective reporting (reporting bias)	Low risk	No obvious concerns with outcomes reported as indicated in the trial registration and protocol publication
Other bias	Low risk	No other concerns identified

ELATE 2011

Study characteristics	
Methods	Study design • Parallel, open-label RCT • Duration of study: June 2010 to July 2012 • Follow-up: 48 weeks • ADPKD assessment: CT scan • Country: the Netherlands • Setting: single centre
Participants	Study characteristics • Inclusion criteria: symptomatic PLD due to ADPKD or autosomal dominant PLD; aged 18 to 70 years; severe PLD (liver volume > 2500 mL); written informed consent • Exclusion criteria: surgical intervention or somatostatin analogue treatment within 3 months before baseline; kidney transplantation; symptomatic chole(cysto)lithiasis; hypercholesterolaemia or hypertriglyceridaemia, not controlled by lipid-lowering therapy; granulocytopenia or thrombocytopenia; infection with hepatitis B or C, HIV, TBC or severe comorbidities Baseline characteristics • Number: intervention group (21); control group (23) ◦ Patients affected by ADPKD: 15/44 (34%) • Mean age ± SD (years): intervention group (11 ± 5); control group (12 ± 5) • Sex (M/F): intervention group (2/19); control group (3/20)
Interventions	Intervention group • Octreotide: 40 mg (IM) every 4 weeks • Everolimus: 2.5 mg/d Control group • Octreotide: 40 mg (IM) every 4 weeks Duration of intervention • 48 weeks
Outcomes	Reported outcomes • Total liver volume • Kidney volume • QoL (EuroQoL EQ-5D questionnaire)

ELATE 2011 *(Continued)*

	• Adverse events
Notes	Additional information • Separate data on ADPKD patients were available only for kidney volumes • Funding: Novartis provided the drug everolimus and partially funded the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised generated randomisation list
Allocation concealment (selection bias)	Low risk	Quote: "A computer generated randomisation list is made by an independent biostatistics unit using a permuted block design with a random block size of 4 to guarantee a balanced allocation"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	Low risk	5/39 (11%) patients dropped from the study. Unclear how many were ADPKD. The authors performed both ITT and per-protocol analyses on the primary outcome measure
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Low risk	Quote: "Novartis provided the drug everolimus and partially funded the study. They did not have any influence on the execution of the trial or the preparation of the manuscript, since this was an investigator-initiated trial"

Fassett 2010

Study characteristics

Methods	Study design • Parallel, open-label RCT • Duration of study: not reported • Follow-up: 24 months • ADPKD assessment: Echo • Country: Australia • Setting: multicentre (number of sites not reported)
Participants	Study characteristics • Patients with Echo diagnosis of ADPKD • Exclusion criteria: participation in other studies

Fassett 2010 *(Continued)*

	Baseline characteristics • Number: intervention group (29); control group (20) • Mean age ± SD (years): intervention group (53 ± 15); control group (49 ± 12) • Sex (M/F): intervention group (12/17); control group (8/12)
Interventions	Intervention group • Pravastatin: 20 mg/d Control group • Standard therapy Duration of intervention • 24 months
Outcomes	Reported outcomes • eGFR • UPE
Notes	Additional information • Funding source: "This project was supported by a grant from the Clifford Craig Medical Research Trust"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random number list
Allocation concealment (selection bias)	Low risk	Repeating blocks of 10
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	11 of 60 (18%) were lost to follow-up and their results were not included in analysis
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

HALT-PKD Study A 2014

Study characteristics

Methods	Study design • Parallel, double-blind, placebo-controlled RCT • Duration of study: February 2006 to June 2014 • Follow-up: 4 to 8 years • ADPKD assessment: MRI • Country: USA • Setting: multicentre (7 sites)

Participants	Study characteristics
	• Inclusion criteria: 15 to 49 years; GFR > 60 mL/min/1.73 m^2; hypertension or high-normal BP; informed consent
	• Exclusion criteria: documented kidney vascular disease; UACR ≥ 0.5; kidney disease other than ADPKD; currently pregnant or intention of becoming pregnant throughout; serum potassium > 5.5 mEq/L for participants currently on ACEi or ARB therapy; > 5.0 mEq/L for participants not currently on ACEi or ARB therapy; history of angioneurotic oedema; contraindication to ACEi or ARB; angina, past MI, arrhythmia; systemic illness necessitating NSAIDs, immunosuppressant or immunomodulatory medications; hospitalisation for an acute illness in past 2 months; life expectancy < 2 years; history of noncompliance, drug or alcohol dependence within the past year; unclipped cerebral aneurysm 7 mm in diameter; treatment within the past 30 days on an interventional study; creatinine supplements within 3 months before the screening visit; congenital absence of a kidney or history of a total nephrectomy
	Baseline characteristics
	• Number: intervention group (273); control group (285)
	  ◦ Standard BP group: intervention group (140); control group (144)
	  ◦ Low BP group: intervention group (133); control group (141)
	• Mean age ± SD (years): intervention group (37.0 ± 8.3); control group (36.3 ± 8.3)
	  ◦ Standard BP group (36.3 ± 8.4); low BP group (36.9 ± 8.2)
	• Gender (M/F): intervention group (141/132); control group (142/143)
	  ◦ Standard BP group (143/141); low BP group (140/134)

Interventions	Intervention group • Lisinopril: 5 to 40 mg stepwise for 4 weeks (5 mg, 10 mg, 20 mg, 40 mg) • Telmisartan: 40 to 80 mg stepwise for 4 weeks (2 weeks 40 mg, 2 weeks 80 mg) Control group • Lisinopril: 5 to 40 mg stepwise for 4 weeks (5 mg, 10 mg, 20 mg, 40 mg) • Placebo Co-interventions • Other antihypertensive treatments
Outcomes	Reported outcomes • Per cent change in kidney volume as assessed by NMR at baseline 24 and 48 months • Rate of change of albuminuria and 24-h urinary excretion of aldosterone • Frequency of all-cause hospitalisations • Hospitalisations because of cardiovascular events • QoL • Pain • Frequency of PKD-related symptoms

HALT-PKD Study A 2014 *(Continued)*

- Adverse effects of study medications
- Rate of change in GFR
- Kidney blood flow
- Left ventricular mass by NMR

Notes	Additional information • Two studies reported (A and B)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation by the data coordinating centre using random permuted blocks
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind with placebo control
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Details of blinding of outcome assessment not provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low number of withdrawals and utilisation of ITT analysis
Selective reporting (reporting bias)	Low risk	All outcomes specified in a priori protocol paper reported
Other bias	Low risk	Funded by the National Institute of Diabetes and Digestive and Kidney Diseases

HALT-PKD Study B 2014

Study characteristics

Methods	Study design • Parallel double-blind, placebo-controlled RCT • Duration of study: February 2006 through June 2014 • Follow-up (mean): 5.2 years • Assessment of ADPKD: Ravine's criteria • Country: USA • Setting: multicentre
Participants	Study characteristics • Inclusion criteria: 18 to 64 years; ADPKD; GFR 25 to 60 mL/min/1.73m^2; elevated BP • Exclusion criteria: renal vascular disease; elevated UACR; kidney disease other than ADPKD; diabetes; pregnancy; elevated serum potassium, contraindication for ACEi or ARB; indication (other than hy-

HALT-PKD Study B 2014 *(Continued)*

	pertension) for beta-blocker or calcium channel blocker therapy; certain systemic illness or illness requiring hospitalisation within 2 months; reduced life expectancy; history of noncompliance, drug, or alcohol dependence within the past year; unclipped cerebral aneurysm ≥ 7 mm in diameter Baseline characteristics • Number: intervention group (244); control group (242) • Mean age ± SD (years): intervention group (48.6 ± 8.5); control group (48.9 ± 8.1) • Sex (M/F): intervention group (115/129); control group (120/122)
Interventions	Intervention group • Lisinopril: 5 to 40 mg stepwise for 4 weeks (5 mg, 10 mg, 20 mg, 40 mg) • Telmisartan: 40 to 80 mg stepwise for 4 weeks (2 weeks 40 mg, 2 weeks 80 mg) Control group • Lisinopril: 5 to 40 mg stepwise for 4 weeks (5 mg, 10 mg, 20 mg, 40 mg) • Placebo Co-interventions • Other antihypertensive treatments for BP control of 120 to 130/70 to 80 mm Hg
Outcomes	Reported outcomes • Composite endpoint of time to either 50% reduction of baseline eGFR, ESKD (initiation of dialysis or pre-emptive transplant), or death • Rate of change of albuminuria and 24-h urinary excretion of aldosterone • Rate of change of albuminuria and 24-h urinary excretion of aldosterone • Frequency of all-cause hospitalisations • Hospitalisations because of cardiovascular events • QoL • Pain • Frequency of PKD-related symptoms • Adverse effects of study medications
Notes	Additional information • Funding: "Supported by grants from the National Institute of Diabetes and Digestive and Kidney Diseases (DK62410 to Dr. Torres, DK62408 to Dr. Chapman, DK62402 to Dr. Schrier, DK082230 to Dr. Moore, DK62411 to Dr. Perrone, and DK62401 to Washington University at St. Louis) and the National Center for Research Resources General Clinical Research Centers (RR000039 to Emory University, RR000585 to the Mayo Clinic, RR000054 to Tufts Medical Center, RR000051 to the University of Colorado, RR023940 to the University of Kansas Medical Center, and RR001032 to Beth Israel Deaconess Medical Center), National Center for Advancing Translational Sciences Clinical and Translational Science Awards (RR025008 and TR000454 to Emory University, RR024150 and TR00135 to the Mayo Clinic, RR025752 and TR001064 to Tufts University, RR025780 and TR001082 to the University of Colorado, RR025758 and TR001102 to Beth Israel Deaconess Medical Center, RR033179 and TR000001 to the University of Kansas Medical Center, and RR024989 and TR000439 to Cleveland Clinic), by funding from the Zell Family Foundation (to the University of Colorado), and by a grant from the PKD Foundation."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation by the data coordinating center using random permuted blocks

HALT-PKD Study B 2014 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind with placebo controlled
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind design, unclear on blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low number of drop-outs, ITT analysis used
Selective reporting (reporting bias)	Low risk	All outcomes reported per a priori protocol paper
Other bias	Low risk	*S*tudy drugs were donated by Boehringer Ingelheim Pharmaceuticals and Merck. Neither company had any role in the design of the study, accrual or analysis of data, the preparation of the manuscript, or the decision to submit the manuscript for publication

Higashihara 2008

Study characteristics	
Methods	Study design • Parallel, open-label RCT • Duration of study: not reported • Follow-up: 24 months • ADPKD assessment: CT scan • Country: Japan • Setting: multicentre (number of sites not reported)
Participants	Study characteristics • Inclusion criteria: 18 to 60 years; clinical and image diagnosis of ADPKD • Exclusion criteria: ESKD; haemorrhagic lesions such as gastric ulcer; intracranial aneurysm and past history of central nervous vascular disease; any condition that could prevent completion of the planned follow-up; pregnant or lactating women or fertile women without effective contraception Baseline characteristics • Number: intervention group (21); control group (20) • Mean age ± SD (years): intervention group (47 ± 11); control group (47 ± 12) • Sex (M/F): intervention group (15/6); control group (14/6)
Interventions	Intervention group • Eicosapentaenoic acid-ethyl ester: 2.4 g/d Control group • Standard therapy

Higashihara 2008 *(Continued)*

	Duration of intervention • 24 months
Outcomes	Reported outcomes • Kidney volumes • Fatty acid composition of the total phospholipid fraction of erythrocytes • Plasma cholesterol • Triglycerides • CrCl • UAE
Notes	Additional information • Funding source: "This study was supported by a grant from the Ministry of Health, Labor and Welfare of Japan". "EPA ethyl ester capsules (Epadel-S®) and research funds were provided by Mochida Pharmaceutical Co. Ltd (Tokyo, Japan) to each participating institute."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "...using the dynamic balancing method to ensure equal distributions"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement, presumably open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement, presumably open-label study
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants withdrew from study
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Funding: Sponsored by Mochida Pharmaceutical Co. Ltd, unclear of their role in the trial

Hogan 2010

Study characteristics

Methods	Study design • Parallel, double-blind RCT • Duration of study: not reported

Hogan 2010 *(Continued)*

- Follow-up: 1 year (plus 1-year open-label extension with all patients switched to octreotide)
- ADPKD assessment: CT scan or magnetic nuclear imaging
- Country: USA
- Setting: single centre

Participants	Study characteristics • Inclusion criteria: men and women aged 18 years or older; diagnosis of ADPKD or ADPLD; severe PLD defined as liver volume > 4000 mL or symptomatic disease due to mass effects from hepatic cysts; not candidates for or declined surgical intervention ○ Genetic details: PKD1 (25), 6 patients PKD2 (6); no PKD mutations (3) • Exclusion criteria: inability to provide informed consent; women of childbearing potential unwilling to employ adequate contraception; SCr > 3 mg/dL or dialysis dependency; symptomatic gallstones or biliary sludge; uncontrolled hypertension (SBP > 160 mm Hg; DBP >100 mm Hg); DM; cancer or major systemic diseases that could prevent completion of the planned follow-up or interfere with data collection or interpretation; current or prior use of somatostatin analogue within 6 months of enrolment or history of significant adverse reaction from a somatostatin analogue Baseline characteristics • Number: intervention group (28); control group (14) • Mean age ± SD (years): intervention group (50 ± 9); control group (50 ± 7) • Sex (M/F): intervention group (5/23); control group (1/13)
Interventions	Intervention group • Octreotide: 40 mg every 28 ± 5 days Control group • Placebo Duration of intervention • 1 year
Outcomes	Reported outcomes • Kidney volume • Kidney function • QoL • Safety
Notes	Additional information • 34 patients (24 in the intervention and 10 in the control group) had ADPKD and 8 had ADPLD • No separate data in the two populations were provided with respect to change in QoL and safety • Funding: "M.C.H. received partial funding support for this study from Novartis USA. N.F.L. and T.V.M. are named inventors on pending patent applications filed by Mayo Clinic claiming methods for using somatostatin analogs to treat polycystic liver disease."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization assignment to octreotide or matching placebo treatment was independently managed by the research pharmacy"

Hogan 2010 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	All patients completed the study but 13 were excluded from kidney outcomes (volume and function) assessment
Selective reporting (reporting bias)	Low risk	All defined outcomes were reported
Other bias	Low risk	Funding: Novartis supported the study. The sponsor was not involved in the study design, patient enrolment, data collection, interpretation, or manuscript preparation. The manuscript was prepared by the authors and reviewed by the sponsor

Kramers 2020

Study characteristics	
Methods	Study design • Triple parallel placebo-controlled, double-blind cross-over RCT • Duration of study: October 2018 to September 2019 • Follow-up: 8 weeks • ADPKD assessment: ultrasound • Country: the Netherlands • Setting: single centre, University Medical Center Groningen
Participants	Study characteristics • Inclusion criteria: 18 to 50 years; diagnosis of ADPKD; eGFR ≥ 45 mL/min/1.73 m^2; treated with tolvaptan (indication on the basis of criteria by the ERA-EDTA workgroup, the highest tolerated dose); provided informed consent • Exclusion criteria: potential safety risk in the opinion of the investigators; unlikeliness to adequately comply with the trials' procedures; concomitant use of medication or illnesses likely to confound end point assessments; pregnancy or breastfeeding; known contraindications or allergies to the study medication Baseline characteristics • Number: 13 • Mean age ± SD: 45 ± 8 years • Gender (M/F): 6/7 • Mayo risk class: 1A/1B (4); 1C/1D (9); 2 (0) • Mean total protein ± SD: 7.24 ± 0.21 mmol/L • Mean albuminuria ± SD: 4.38 ± 0.23 mmol/L

Kramers 2020 *(Continued)*

- Mean GFR ± SD: 55 ± 11 mL/min/1.73 m^2
- Mean BP ± SD (mm Hg): SBP (125 ± 13); DBP (77 ± 7)
- Mean weight ± SD: 91 ± 11 kg
- Co-morbidities: Not reported

Interventions	Intervention 1 • Hydrochlorothiazide: in the morning, 12.5 mg in week 1 and 25 mg in week 2 • Placebo: in the evening Intervention 2 • Metformin: 500 mg twice/d in week 1 and 1000 mg twice/d in week 2 Control • Placebo: double-blind placebo treatment (in the morning and evening) Duration of intervention • 2 weeks Co-interventions or additional treatments • Not reported
Outcomes	Reported outcomes • Absolute urine volume (L/24 h) • Copeptin (pmol/L) • Measured GFR • Adverse events • Serious adverse events • Urine creatinine excretion
Notes	Additional information • The inclusion criteria age and baseline eGFR were broadened (age 18 to 55 years, amended October 10, 2018; eGFR ≥ 30 ml/min/1.73 m^2, amended June 3, 2019) to be able to include the projected number of participants • Protocol registration/published: protocol provided in supplement file • Ethics: "The clinical trial was in accordance with the Declaration of Helsinki and approved by the medical ethical committee of UMCG. All participants provided written informed consent before entry into the trial." • Declaration of interest/disclosures: "R.T. Gansevoort reports consultancy agreements with AstraZeneca, Bayer, Galapagos, Otsuka Pharmaceuticals, and SanofiGenzyme; received consultancy fees from Otsuka Pharmaceuticals, the manufacturer of tolvaptan (paid to the institution); research funding from AstraZeneca, Bayer, Galapagos, Otsuka Pharmaceuticals, and Sanofi-Genzyme; honoraria from Bayer, Galapagos, Mironid, Otsuka Pharmaceuticals, and anofi-Genzyme; serving in an advisory or leadership role for American Journal of Kidney Diseases, CJASN, Journal of Nephrology, Kidney360, Nephrology Dialysis Transplantation, and Nephron Clinical Practice; and serving as a member of the steering committee of the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and its Outcomes (TEMPO) 3:4 and Replicating Evidence of Preserved Renal Function: Investigation of Tolvaptan Safety and Efficacy (REPRISE) trials that studied tolvaptan. K.R. Hallows reports consultancy agreements with Maze Therapeutics, Inc.; ownership interest in Bristol Myers Squibb; research funding from Esperion Therapeutics, Inc. and Otsuka Pharmaceutical Co., Ltd.; and serving on the editorial board of American Journal of Physiology Renal Physiology and as an associate editor of Frontiers in Renal and Epithelial Physiology. H.L. Heerspink reports ongoing consultancy agreements with AbbVie, AstraZeneca, Bayer, Boehringer Ingelheim, Chinook, CSL Behring, Dimerix, Fresenius, Gilead, Janssen, Merck, Mitsubishi Tanabe, Mundi Pharma, NovoNordisk,

Kramers 2020 *(Continued)*

and Travere Pharmaceuticals; research funding from AbbVie, AstraZeneca, Boehringer Ingelheim, and Janssen research support (grant funding directed to employer); and speakers bureau for AstraZeneca. E. Meijer reports research funding from the Dutch Kidney. Foundation, Ipsen, Otsuka Pharmaceuticals, and Sanofi (all money was paid directly to the institution); received consultancy fees from Otsuka Pharmaceuticals, the manufacturer of tolvaptan (paid to the institution); and other interests or relationships with the Dutch Kidney Foundation, Health Holland, Nieren.nl, NvN, and Werkgroep Erfelijke Nierziekten. D.J.M. Peters reports ownership interest in Bayer, BioCity Scotland, Innoser, and Mironid Ltd. J. Qiu reports research funding from International Graduate School 1874 (Diabetic Microvascular Complications—Diabetes Microvascular Complications [DIAMICOM]) of the German Research Foundation. D.J. Touw reports research funding from Astellas Pharma BV and Chiesi Pharmaceuticals BV, serving in an advisory or leadership role for Sanquin (Amsterdam, The Netherlands), and serving as a member of the Medical Advisory Board. All remaining authors have nothing to disclose."

- Funding declared: "The authors received unrestricted grants from Otsuka Pharmaceuticals (the manufacturer of a vasopressin V2 receptor antagonist). This study was sponsored by Dutch Kidney Foundation grant 18OKG04" (UL1TR002529-01) provided preclinical support, regulatory guidance, study monitoring, database support and statistical support. Measurements of kidney and liver volumes were supported in part by the Mayo Clinic Robert M. and Billie Kelley Pirnie Translational PKD Center and NIH Diabetes and Digestive and Kidney Diseases grant P30DK090728. S.M.M. is also supported by NIH grants AR072581, DK110871 and ULTR002529-01 and receives consulting fees from Amgen, Sanifit, Ardeylx and Novo Nordisk and grants from Chugai and Keryx. B.L.B.-Y. is supported by a Department of Defense Peer Reviewed Medical Research Program grant (W81XWH16-PRMRP-IIRA). R.N.M. is funded by an NIH award (NIHK23DK102824). The funding sources had no role in the study design, data collection/interpretation or writing of the manuscript."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "An independent pharmacist used a computer program to randomize participants in blocks of six, for the six possible treatment orders of the three treatments. The pharmacist was not involved in the further conduct of the study." Comment: appropriate methods with no concerns
Allocation concealment (selection bias)	Unclear risk	Quote:"The pharmacist was not involved in the further conduct of the study." Comment: while personnel was appropriate there is no reporting of the method used for allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All patients, investigators, and health care providers were blinded to treatment allocation.", "Double Blind" Comment: appropriate methods
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No numbers lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No trial registration and limited methods provided in the protocol
Other bias	Low risk	No other concerns identified

LOCKCYST 2009

Study characteristics	
Methods	Study design • Parallel, double-blind RCT • Duration of study: October 2007 to February 2008 • Follow-up: 24 weeks • ADPKD assessment: CT scan • Country: Netherlands and Belgium • Setting: multicentre (2 sites)
Participants	Study characteristics • Inclusion criteria: men and women aged 18 years and older; > 20 liver cysts revealed by CT scan; ADPKD was diagnosed where > 5 kidney cysts in either one or both kidneys were visible on CT; otherwise, the patient was diagnosed with other forms of PLD • Exclusion criteria: use of oral contraceptives or oestrogen supplementation; pregnancy or breastfeeding; symptomatic gallstones; HD; history of severe illnesses Baseline characteristics • Number: intervention group (27); control group (27) ◦ Affected by ADPKD: 32/54 (59%) • Mean age, range (years): intervention group (50, 34 to 65); control group (50, 33 to 68) • Sex (M/F): intervention group (3/24); control group (4/23)
Interventions	Intervention group • Lanreotide: 120 mg/d every 28 days Control group • Placebo Duration of intervention • 24 weeks
Outcomes	Reported outcomes • Liver volume • Kidney volume • Abdominal symptoms • Health-related QoL (SF-36) • Type and severity of gastrointestinal symptoms
Notes	Additional information • Data on kidney volumes in the subpopulation of ADPKD patients (32) were obtained courtesy of the authors • Funding source: "This study was funded in part by Ipsen, Boulogne Billancourt, France."

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

LOCKCYST 2009 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated random number list
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed by an un-blinded investigational pharmacist in blocks of 4, and the 2 treatment arms were allocated in a 1:1 ratio within each block"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All CT scans were blinded to patient identity and date of birth as well as date of scan"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analyses were performed on an ITT basis. Only 2 participants withdrew
Selective reporting (reporting bias)	Unclear risk	Computer-generated random number list
Other bias	Low risk	The study was sponsored by Ipsen. The authors state that "The sponsor of the study had no role in the study design, data collection, data analysis, interpretation of the study results, or writing of the manuscript"

Melemadathil 2013

Study characteristics	
Methods	Study design • Parallel, open-label RCT • Duration of study: not reported • Follow-up: 1 year • ADPKD assessment: magnetic nuclear imaging • Country: India • Setting: not reported
Participants	Study characteristics • ADPKD type 1 after genetic typing; 18 to 60 years; GFR > 40 mL/min/1.73 m^2; proteinuria < 0.5 g/24 h; informed consent • Exclusion criteria: proteinuria > 0.5 g/24 h or abnormal urinalysis; DM; malignancy; psychiatric disorder; hepatitis B, C; HIV; pregnancy and lactation; increased liver enzymes; dyslipidaemia; granulocytopenia or thrombocytopenia; co-medication with strong inhibitor of CYP3A4; hypersensitivity Baseline characteristics • Number: intervention group (40); control group (20) • Mean age ± SD (years): not reported • Sex (M/F): not reported
Interventions	Intervention group

Melemadathil 2013 *(Continued)*

	• Sirolimus: 2 mg/d Control group • Standard treatment Duration of intervention • 6 months extended to 1 year
Outcomes	Reported outcomes • Kidney volume • Cyst volume • Parenchymal volume • Proteinuria and other laboratory data • Adverse events
Notes	Additional information • Abstract-only publication • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised 2:1. Sequence generation not defined
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	High risk	6/40 (15%) patients in the mTOR group dropped or were lost to follow up. Unclear whether the study was analysed on ITT or PP basis
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Mora 2013

Study characteristics

Methods	Study design

Mora 2013 *(Continued)*

- Parallel RCT
- Duration of study: not reported
- Follow-up: 2 years
- ADPKD assessment: magnetic nuclear imaging
- Country: Argentina
- Setting: single centre

Participants	Study characteristics • Inclusion criteria: ADPKD diagnosis; eGFR > 60 mL/min/1.73 m^2; negative pregnancy test • Exclusion criteria: leukopenia (white cells/mm^3 < 4000); hepatic or systemic disease; coagulation disorders; malignancy Baseline characteristics • Number: intervention group (6); control group (6) • Mean age ± SD (years): not reported • Sex (M/F): not reported
Interventions	Intervention group • Rapamycin: 2 mg/m^2/d Control group • Standard therapy Duration of intervention • 24 months
Outcomes	Reported outcomes • Kidney volume • eGFR • Proteinuria
Notes	Additional information • Abstract-only publication • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information to permit judgement

Mora 2013 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Nakamura 2001d

Study characteristics	
Methods	Study design • Parallel, double-blind RCT • Duration of study: not reported • Follow-up: 6 months • ADPKD assessment: unclear • Country: Japan • Setting: single centre
Participants	Study characteristics • Inclusion criteria: normo- or hypertensive ADPKD patients with microalbuminuria • Exclusion criteria: creatinine > 1.5 mg/dL and/or eGFR < 70 mL/min Baseline characteristics • Number: intervention group (11); control group (11) • Mean age ± SD (years): not reported • Sex (M/F): not reported
Interventions	Intervention group • Dilazep dihydrochloride: 300 mg/d Control group • Placebo Duration of intervention • 6 months
Outcomes	Reported outcomes • UPE • BP • Kidney function
Notes	Additional information • Two subgroups of patients analysed as 2 studies • Funding source: not reported

Nakamura 2001d *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Nakamura 2001d hypertensive

Study characteristics

Methods	Study design • Parallel, double-blind RCT • Duration of study: not reported • Follow-up: 6 months • ADPKD assessment: unclear • Country: Japan • Setting: single centre
Participants	Study characteristics • Inclusion criteria: hypertensive ADPKD patients with microalbuminuria • Exclusion criteria: creatinine > 1.5 mg/dL and/or eGFR < 70 mL/min Baseline characteristics • Number: intervention group (5); control group (5) • Mean age: 52.2 years • Sex (M/F): 2/8
Interventions	Intervention group • Dilazep dihydrochloride: 300 mg/d

Nakamura 2001d hypertensive *(Continued)*

	Control group • Placebo Duration of intervention • 6 months
Outcomes	Reported outcomes • UPE • BP • Kidney function
Notes	Additional information • Funding source: not reported

Nakamura 2001d normotensive

Study characteristics	
Methods	Study design • Parallel, double-blind RCT • Duration of study: not reported • Follow-up: 6 months • ADPKD assessment: unclear • Country: Japan • Setting: single centre
Participants	Study characteristics • Inclusion criteria: normotensive ADPKD patients with microalbuminuria • Exclusion criteria: creatinine > 1.5 mg/dL and/or eGFR < 70 mL/min Baseline characteristics • Number: intervention group (6); control group (6) • Mean age: 46.6 years • Sex (M/F): 4/8
Interventions	Intervention group • Dilazep dihydrochloride: 300 mg/d Control group • Placebo Duration of intervention • 6 months
Outcomes	Reported outcomes • UPE • BP

Nakamura 2001d normotensive *(Continued)*

- Kidney function

Notes	Additional information • Funding source: not reported

Nakamura 2012a

Study characteristics	
Methods	Study design • Parallel, double-blind RCT • Duration of study: not reported • Follow-up: 12 months • ADPKD assessment: Echo • Country: Japan • Setting: single centre
Participants	Study characteristics • Inclusion criteria: ADPKD; good kidney function; microalbuminuria; hypertension (BP > 140/90 mm Hg) • Exclusion criteria: SCr > 1.0 mg/dL; eGFR < 60 mL/min; aged < 20 or > 80 years; current smoker ○ Additional exclusion criteria were 1 or more of the following: presence of another kidney disease; DM; CHF; IHD; PVD; liver disease; malignancy; collagen disease; CVA within the prior 6 months Baseline characteristics • Number: intervention group (10); control group (10) • Mean age ± SD (years): intervention group (57 ± 6); control group (58 ± 6) • Sex (M/F): intervention group (6/4); control group (5/5)
Interventions	Intervention group • Telmisartan: 80 mg/d Control group • Enalapril: 10 mg/d Duration of intervention • 12 months
Outcomes	Reported outcomes • BP • UAE • Inflammatory stress markers
Notes	Additional information • Funding source: not reported
Risk of bias	

Nakamura 2012a *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

NOCTURNE 2020

Study characteristics	
Methods	Study design • Phase 2, placebo-controlled, double-blind, placebo-masked, 4-arm parallel RCT • Duration of study: Enrolment commenced in October 2011, and the last subject visit was in July 2013 • Follow-up: 8 weeks; the primary endpoint was at 3 weeks • ADPKD assessment: Ravine criteria • Country: USA • Setting: multicentre (41 sites)
Participants	Study characteristics • Inclusion criteria: 18 to 50 years; BMI 19 and 35 kg/m^2; ADPKD; subjects not planning to become pregnant willing to comply with birth control requirements; in good health as determined by screening tests; providing informed consent and able to comply with all trial requirements • Exclusion criteria: using diuretics within 14 days prior to randomisation, or the requirement for intermittent or constant diuretic use for any reason; eGFR < 45 mL/min/1.73 m^2; incontinence, overactive bladder, or urinary retention; liver disease, liver function abnormalities, or serology other than that expected for ADPKD with cystic liver disease at baseline; history of renal surgery or cyst drainage within 6 months of randomisation; BP 150/95 mm Hg or < 90/40 mm Hg; heart rate outside the range of 40 to 90 bpm; advanced diabetes with a history of poor control; evidence of significant kidney disease renal cancer, single kidney, or recent kidney surgery; other significant medical history that may interfere with the study objectives; significant abnormalities in serum sodium concentration (< 135 or > 145 mEq/L); history of drug and/or alcohol abuse within 2 years prior to screening; clinically significant allergic reactions to tolvaptan or chemically related structures such as benzazepines; taken an investigational drug within 30 days preceding randomisation; taking medications or having concomitant illnesses likely to confound endpoint assessments, including taking approved therapies for the pur-

NOCTURNE 2020 *(Continued)*

	pose of affecting PKD cysts such as tolvaptan, somatostatin agonists, sirolimus, anti-sense RNA therapies, other vasopressin antagonists or agonists, and cyst reduction surgery; on antihypertensives that have not been on the same antihypertensive regimen for at least 30 days prior to the first dose of IMP; contraindications to, or interference with, MRI assessments; history of serious mental disorders that, in the opinion of the investigator, would exclude the subject from participating in this trial; previous exposure to tolvaptan Baseline characteristics • Number (randomised/completed): intervention group 1 (45/42); intervention group 2 (45/42); intervention group 3 (44/42); control group (43/39) • Mean age ± SD (years): intervention group 1 (34.1 ± 10.0); intervention group 2 (35.8 ± 7.9); intervention group 3 (32.2 ± 7.6); control group (33.9 ± 7.1) • Gender (M/F): intervention group 1 (27/18); intervention group 2 (22/23); intervention group 3 (24/20); control group (20/23) • Mean eGFR ± SD (mL/min/1.73m^2): intervention group 1 (86.9 ± 26.5); intervention group 2 (83.0 ± 25.3); intervention group 3 (86.4 ± 23.5); control group (85.1 ± 25.6) • Mean htTKV ± SD (mL/min): intervention group 1 (948.8 ± 504.4); intervention group 2 (1035.2 ± 457.3); intervention group 3 (866.2 ± 405.8); control group (992.0 ± 457.2) • Ethnicity: Hispanic-Latino/not Hispanic-Latino/unknown: intervention group 1 (2/43/0); intervention group 2 (4/40/1); intervention group 3 (5/39/0); control group (4/39/0) • Mean weight ± SD (kg): intervention group 1 (81.5 ± 14.5); intervention group 2 (79.4 ± 19.5); intervention group 3 (80.8± 16.1); control group (82.8 ± 20.3)
Interventions	Intervention group 1 • Tolvaptan: one MR 50 mg capsule in the morning • Placebo: one IR tablet in the morning and one in the evening Intervention group 2 • Tolvaptan: one MR 80 mg capsule in the morning • Placebo: one IR tablet in the morning and one in the evening Intervention group 3 • Tolvaptan: one IR 60 mg tablet in the morning and one IR 30 mg tablet in the evening • Placebo: one MR capsule in the morning Control group • Placebo: one MR capsule in the morning • Placebo: one IR tablet in the morning and one in the evening Co-interventions • Subjects were instructed to drink to thirst during their participation in the trial to maintain blinding and to avoid dehydration
Outcomes	Reported outcomes • Percent change in TKV at week 3 • Change in Total Score of the Autosomal Dominant Polycystic Kidney Disease Urinary Impact Scale (ADPKD-UIS) at 8 weeks
Notes	Additional information • Notes: “Subject baseline demographics and clinical characteristics were well balanced among treatment group” ◦ “Subjects had a mean eGFR of 85 ml/min per 1.73 m2, indicating relatively preserved kidney function and suggestive of earlier disease compared to the Tolvaptan Efficacy and Safety in Manage-

NOCTURNE 2020 *(Continued)*

ment of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes (TEMPO) 3:4 population, which had a mean baseline eGFR of w81 ml/min per 1.73 m^2. 13 Subjects in this study also had a mean TKV (w1.7 L) equivalent to that reported in the TEMPO 3:4 study, with a mean age of 34.0 years, which is approximately 5 years younger than the TEMPO 3:4 population, indicating a study population with the more aggressive disease with more rapid TKV growth for a given age."

- Protocol registration/published: The study protocol and informed consent form were reviewed and approved by the governing institutional review board or independent ethics committee for each investigational site prior to the trial start.
- Ethics: The study was conducted according to the International Conference on Harmonization Clinical Practice Consolidated Guideline and the applicable local laws and regulatory requirements of the sites at which the trial was performed. Written informed consent was obtained from all subjects (or their guardian or legal representative).
- Declaration of interest/disclosures: "RDP reports grants from Sanofi-Genzyme, personal fees from Palladio Biosciences, personal fees from Vertex Pharmaceuticals, personal fees from Goldfinch Bio Inc., grants from Otsuka Pharmaceutical, grants from Kadmon Holdings, personal fees from UpToDate Wolters Kluwer, and speaker fees from Otsuka SA. ABC reports paid consulting for Otsuka and Kadmon. DO, OS, JO, and SES are employees of Otsuka Pharmaceutical Development & Commercialization. FSC is a former employee of Otsuka Pharmaceutical and a current employee of Goldfinch Bio Inc"
- Funding declared: PHARMA funding - This study was funded by Otsuka Pharmaceutical Development & Commercialization (Rockville, MD). Andrew J. Horgan, PhD, of BioScience Communications, Inc. (New York, NY) assisted in drafting the manuscript, activity that was also funded by Otsuka

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "subjects were randomized in a 1:1:1:1 ratio" Comment: insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Study treatments were administered in a split regimen using a combination of MR capsules (tolvaptan or placebo) and IR tablets (tolvaptan or placebo) to achieve full blinding" Comment: double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar number of participants lost across groups and ITT analysis undertaken. Reasons for withdrawals explained
Selective reporting (reporting bias)	Low risk	No obvious concerns with outcomes reported as indicated in the trial registration and protocol publication. However, there was no statistical testing done on the week 8 data. This was prespecified in the protocol
Other bias	Unclear risk	Industry funding was declared and no evidence of their involvement in the analysis

Nowak 2019

Study characteristics	
Methods	Study design • Parallel, double-blind placebo-controlled RCT • Study duration: July 2014 to July 2016 • Follow-up: 6 months (± 2 weeks) • ADPKD assessment: Ravine criteria • Country: USA • Setting: single centre (University of Colorado Denver Anschutz Medical Campus)
Participants	Study characteristics • Inclusion criteria: ADPKD; 20 to 55 years; TKV 500 to 2500 mL; eGFR ≥ 60 mL/min/1.73 m^2; history of hypertension treated with stable ACEi or ARB • Exclusion criteria: serum potassium > 5.5 mEq/L or any single value > 6.0 mEq/L in the past 6 months; received an aldosterone antagonist in the past 6 months; using a potassium-sparing diuretic or other medication that could contribute to hyperkalaemia; BMI ≥ 40; smoking in past 12 months; history of severe congestive heart failure; hospitalised in the last 3 months; history of liver disease; received immunosuppressive therapy within the last year; used warfarin with an international normalised ratio > 2.5; an active infection or antibiotic use; alcohol dependence or abuse; pregnant, nursing, or planning to become pregnant; if using antioxidants and/or omega-3 fatty acids, their use was discontinued at least 4 weeks before study; if using cannabis, use was discontinued 2 weeks before vascular measurements Baseline characteristics • Number: intervention group (29); control group (32) • Mean age ± SD (years): intervention group (34 ± 10); control group (34 ± 9) • Gender (M): intervention group (55%); control group (38%) • Ethnicity (Non-Hispanic white): intervention group (79%); control group (88%)
Interventions	Intervention group • Spironolactone: 25 mg/d for 4 weeks, with dosing escalating to 50 mg/d for the rest of the study if tolerated Control group • Placebo Duration of intervention • 6 months Co-interventions or additional treatments • Not reported
Outcomes	Reported outcomes • Change in FMD_{BA} • BP • Pulse-wave velocity • Cellular markers of oxidative stress • Circulating markers of oxidative stress • Change in carotid artery compliance • Carotid artery β-stiffness index • Carotid SBP

Nowak 2019 *(Continued)*

- Carotid intimal medial thickness

Notes	Additional information • Protocol registration/published: Registered but no protocol • Ethics: "All procedures were approved by the Institutional Review Board of the University of Colorado Anschutz Medical Campus (13-1440) and adhere to the Declaration of Helsinki. The nature, benefits, and risks of the study were explained to the volunteers, and their written informed consent was obtained before participation" • Declaration of interest/disclosures: "The authors declare that they have no other relevant financial interests." • Funding declared: "This trial was supported by National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) R01DK097081. Dr Nowak is also supported by NIDDK K01DK103678. Additional support was provided by the National Institutes of Health (NIH) National Center for Advancing Translational Sciences Clinical and Translational Science Awards grant number UL1 TR002535. Additional funding was provided by the Zell Family Foundation. The funding agencies had no direct role in the conduct of the study; collection, management, analyses, and interpretation of the data; or preparation or approval of the manuscript"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation using computer generated procedure run and was kept by a statistician
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All investigators, coordinators, analysts, and participants were blinded to group assignment, with only the nursing staff not affiliated with the study and the statistician aware of the randomization."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All investigators, coordinators, analysts, and participants were blinded to group assignment, with only the nursing staff not affiliated with the study and the statistician aware of the randomization."
Incomplete outcome data (attrition bias) All outcomes	Low risk	98% of study participants randomised to the study completed study and included in the analysis
Selective reporting (reporting bias)	Low risk	No other concerns identified
Other bias	Low risk	No other concerns identified

Nowak 2020

Study characteristics

Methods	Study design • Parallel, double-blind, placebo-controlled RCT • Duration of study: November 2015 to December 2019 • Follow-up: 12 months

Nowak 2020 *(Continued)*

- ADPKD assessment: MRI
- Country: USA
- Setting: single centre (University of Colorado Anschutz Medical Campus)

Participants	Study characteristics • Inclusion criteria: 6 to 25 years; ADPKD, based on the presence of bilateral renal cysts in the setting of a family history of ADPKD; fairly preserved kidney function with an eGFR > 80 mL/min/1.73 m^2 • Exclusion criteria: currently taking a curcumin supplement; history of smoking within the past 12 months, or used cannabis within two weeks or antioxidants and/or omega-3 fatty acids within four weeks prior to baseline testing; alcohol dependence or abuse, history of hospitalisation within the last 3 months; active infection or receiving antibiotic therapy; pregnant, lactating, or unwilling to use adequate birth control; BMI ≥ 95th percentile in ages 6 to 17 or > 40 kg/m^2 in ages 18 to 25; inability to cooperate with study personnel and/or clinical contraindication for MRI, including severe claustrophobia, implants, devices, or non-removable body piercings Baseline characteristics • Number: intervention group (34); control group (34) • Mean age ± SD (years): intervention group (18 ± 6); control group (19 ± 5) • Gender (M/F): intervention group (15/19); control group (16/18) • Diagnosis of PKD: intervention group (1A: 0, 1B: 2, 1C: 7, 1D: 9, 1E: 7, not applicable: 9); control group (1A: 4, 1B: 5, 1C: 2, 1D: 6, 1E: 10, not applicable: 7) • Hypertension: intervention group (12); control group (17) • Diabetes: intervention group (1); control group (1) • Mean eGFR ± SD (mL/min/1.73 m^2): intervention group (115 ± 16); control group (118 ± 19) • Median htTKV, IQR (mL/min): intervention group (817, 331 to 1206); control group (718, 317 to 1094) • Mean SBP/DBP ± SD (mm Hg): intervention group (116 ± 12/71 ± 9); control group (118 ± 19/73 ± 10) • Ethnicity: Non-Hispanic White/Hispanic or other: intervention group (28/6); control group (28/6) • BMI (normal weight or underweight/overweight/obese): intervention group (23/6/5); control group (24/8/2)
Interventions	Intervention group • Cholecalciferol: single oral monthly dose (200,000 IU in the 1st and 2nd months and 50,000 UI in the 3rd month) • Duration: 3 months Control group • Placebo • Duration: 12 months Co-interventions or additional treatments • All patients were instructed to use sunscreen (SPF 30) during the study period
Outcomes	Reported outcomes • SBP and DBP • Inflammatory markers (IL-6, IL-10, TNG, FNK-B) • Vitamin D (25(OH)D) • Vitamin D regulatory enzymes (CYP27B1, CYP24A1)
Notes	Additional information • Protocol registration/published: Published • Ethics: "All procedures were approved by the institutional review board of the University of Colorado Anschutz Medical Campus and adhere to the Declaration of Helsinki. The nature, benefits, and risks of

Nowak 2020 *(Continued)*

the study were explained to the volunteers, and their written informed consent/assent was obtained prior to participation."

- Declaration of interest/disclosures: "M.A. Cadnapaphornchai reports consultancy agreements with Otsuka Pharmaceutical, honoraria from Otsuka Pharmaceutical, and serving as a scientific advisor or member of Otsuka tolvaptan pediatric steering committee. M. Chonchol reports consultancy agreements with Amgen, Corvidia, Otsuka, Reata, Tricidia, and Vifor; research funding from Corvidia, the National Institutes of Health, Otsuka, Reata, and Sanofi; honoraria from Amgen, Corvidia, Reata, Tricidia, and Vifor; and serving as a Deputy Editor of CJASN. B. Gitomer reports honoraria from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) for study section participation and from the Department of Defense urological diseases study section and reports serving as a CJASN editorial board member and a Polycystic Kidney Disease Foundation member of the Scientific Advisory Council. A. Jovanovich reports research funding as a site investigator for AstraZeneca; receiving study drug free of charge from Shire; and serving on the editorial board for CJASN, as a section editor for Clinical Nephrology, as an American Heart Association Council for Kidney in Cardiovascular Disease Leadership committee member, and as Chair of the Early Investigators Committee. J. Klawitter reports research funding from NIDDK and the PKD Foundation. K.L. Nowak reports research funding from Corvidia Therapeutics, Otsuka Pharmaceutical Development and Commercialization (data analysis), and Verdure Sciences and reports interacting with the PKD Foundation. D.E. Soranno reports consultancy agreements with Levin & Perconti Attorneys at Law. All remaining authors have nothing to disclose"
- Funding: "This trial was supported by National Institute of Diabetes and Digestive and Kidney Diseases grant K01DK103678. Additional support was provided by National Center for Advancing Translational Sciences Colorado Clinical and Translational Science award UL1TR002535 and National Institutes of Health high-end instrumentation grant S10OD018435. This work was also supported by the Zell Family Foundation. K.L. Nowak was also supported by the Baltimore PKD Research Clinical Core Center Pilot and Feasibility Program through National Institute of Diabetes and Digestive and Kidney Diseases grant P30DK090868. D.E. Soranno is supported by National Institute of Diabetes and Digestive and Kidney Diseases grant K08DK109226. C. Steele is supported by National Institute of Diabetes and Digestive and Kidney Diseases grant 5T32DK007135-4"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "After baseline measurements, randomization (curcumin or placebo) was performed by the statistician, using a computer-generated blocked randomization sequence, with stratification by age group" Comment: appropriate methods with no concerns
Allocation concealment (selection bias)	Unclear risk	Quote: "The placebo was selected to be carrot powder, based on a similar texture and color to active powder" Comment: insufficient information to permit judgement about how therapies were assigned following randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Ultrasound images were analyzed by a single-blind analyst" for MRI "No contrast agents were utilized. Individuals involved in the acquisition and analysis of images were blinded regarding group assignment" Comment: appropriate methods
Incomplete outcome data (attrition bias)	Low risk	Three participants lost to follow up (4%). ITT analysis with all participants included

Nowak 2020 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	No other concerns identified
Other bias	Low risk	No other concerns identified

Nutahara 2005

Study characteristics

Methods	Study design • Parallel RCT • Duration of study: not reported • Follow-up: 36 months • ADPKD assessment: unclear • Country: Japan • Setting: multicentre
Participants	Study characteristics • Inclusion criteria: ADPKD hypertensive patients aged 20 to 70 years • Exclusion criteria: pregnancy; creatinine > 2 mg/dL Baseline characteristics • Number: intervention group (25); control group (24) • Mean age (years): intervention group (48); control group (47) • Sex (M/F): intervention group (13/12); control group (13/11)
Interventions	Intervention group • Amlodipine: 2.5 to 10 mg/d Control group • Candesartan: 2 to 8 mg/d Duration of intervention • 36 months
Outcomes	Reported outcomes • Combined outcome of doubling SCr and/or decrease in eGFR to half of baseline • Albuminuria • Proteinuria • BP
Notes	Additional information • Funding source: "This study was supported by a grant from the Ministry of Health, Labor and Welfare of Japan"

Risk of bias

Nutahara 2005 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "...using the dynamic balancing method to ensure equal distributions"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	12/49 (24.4%) patients analysed on ITT basis
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Pasari 2019

Study characteristics	
Methods	Study design • Parallel, placebo-controlled RCT • Duration of study: not reported • Follow-up: 12 months; followed up at 3 monthly intervals; repeat CT scans were obtained at the end of 12 months • ADPKD assessment: not reported • Country: India • Setting: single centre (outpatient clinic)
Participants	Study characteristics • Inclusion criteria: ADPKD; eGFR > 60 mL/min/1.73m^2 • Exclusion criteria: not reported Baseline characteristics • Number: intervention group (20); control group (20) • Mean age ± SD (years): not reported • Gender (M/F): not reported
Interventions	Intervention group • Metformin: 1500 mg/d Control group

Pasari 2019 *(Continued)*

	• Placebo Duration of intervention • Not reported Co-interventions • Not reported
Outcomes	Reported outcomes • TKV • Flank pain • BP requiring antihypertensive therapy • Proteinuria • SCr • eGFR • Adverse events • Serious adverse events
Notes	Additional information • Trial registration: not reported • Protocol registration/published: not reported • Ethics: not reported • Declaration of interest/disclosures: not reported • Funding declared: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	50 participants enrolled but only 40 completed the study. No details provided about dropouts
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Perrone 2020

Study characteristics	
Methods	• Study design • Parallel, phase 2, double-blind placebo-controlled, cross-over RCT • Duration of study: October 2010 to June 2011 • Follow-up: 7 days • ADPKD assessment: Ravine criteria • Country: USA • Setting: multicentre (6 sites)
Participants	Study characteristics • Inclusion criteria: 18 to 50 years; ADPKD; eGFR > 60 mL/min/1.73 m^2 • Exclusion criteria: used diuretics within the past 14 days; cytochrome P450 3A4 inhibitors, except amiodarone, within 30 days; or cytochrome P450 3A4 inducers within 7 days of dosing; incontinence; overactive bladder; urinary retention (e.g. benign prostatic hypertrophy); significant nocturia/urgency; liver disease; liver function abnormalities; serology other than that expected for ADPKD with cystic liver disease (i.e. normal except for possible alterations in alkaline phosphatase and gamma-glutamyl transferase) Baseline characteristics • Number: intervention group 1 (12); intervention group 2 (13) • Mean age ± SD (years): intervention group 1 (39.4 ± 4.3); intervention group 2 (36.8 ± 9) • Gender (M/F): intervention group 1 (5/7); intervention group 2 (9/4) • Hypertension: intervention group 1 (7); intervention group 2 (9) • Proteinuria: intervention group 1 (5); intervention group 2 (2) • Mean eGFR ± SD (mL/min/1.73 m^2): intervention group 1 (76.7 ± 16.8); intervention group 2 (75.9 ± 14.5) • Mean time since diagnosis ± SD (years): intervention group 1 (26.1 ± 8), intervention group 2 (28 ± 7.1) • Mean weight ± SD (kg): intervention group 1 (80.4 ± 17.4), intervention group 2 (82.2 ± 18.9)

Interventions	Intervention group 1
	• Tolvaptan
	  ◦ IR: 90 + 30 mg split dose
	  ◦ MR: 120 mg/d
	  ◦ And either MR 20 mg/d, MR 60 mg, or MR 20 mg in a split dose (MR 20 + 20 mg)
	Intervention group 2
	• Tolvaptan
	  ◦ MR 20 mg/d
	  ◦ MR 60 mg/d
	  ◦ MR split dose 20 + 20 mg
	Duration of intervention
	• 7 days
	Co-interventions
	• Subjects were asked to drink to thirst during the outpatient dosing days and to limit dietary salt < 5 g/d, dietary protein < 1 g/kg/d and caffeinated drinks/foods to no more than 2 coffee equivalents/d

Outcomes	Reported outcomes • Pharmacokinetics

Perrone 2020 *(Continued)*

- Maximum (peak) plasma concentration
- Minimum (trough) plasma concentrations
- Average plasma concentration
- Time to maximum (peak) plasma concentration
- Area under the concentration-time curve from time 0 to 24 hours post-dose and, for daily regimens,
- Apparent total body clearance from plasma following extravascular administration

- Pharmacodynamics
  - Number of subjects with a spot urine osmolality concentration < 300 mOsm/kg at 23.5 hours post-dose
  - Duration that urine osmolality remained < 300 mOsm/kg
  - Urine osmolality
  - Urine volume and osmolality for the intervals of 0 to 4, 4 to 8, 8 to 12, 12 to 16, and 16 to 24 hours, and 0 to 24-hour urine volume
- Tolerability
  - Urine voids during daytime and nighttime
  - Impact of urinary symptoms on a subject's daily life using questionnaires on urinary urgency - ADPKD Nocturia Quality-of-Life Questionnaire, ADPKD Urinary Urgency Questionnaire, and ADPKD Urinary Frequency Questionnaire (not validated0
  - Urinary frequency
  - Nocturia
- Safety
  - Adverse events
  - Clinical laboratory parameters
  - Heart rate and blood pressure after subjects remained supine ≥ 3 minutes

Notes	Additional information

- Protocol registration/published: not reported
- Ethics: "The study protocol and informed consent form were reviewed and approved by the institutional review board or independent ethics committee for each investigational site before the commencement of the trial. Written informed consent was obtained from all subjects.."
- Declaration of interest/disclosures: "RDP reports grants from Sanofi-Genzyme, Reata, Otsuka Pharmaceutical, and Kadmon Holding; personal fees from Palladio Biosciences, Vertex Pharmaceuticals, Goldfinch Bio Inc., and UpToDate Wolters Kluwer; and speaker fees from Otsuka SA. ABC reports paid consultancy for Otsuka and Kadmon. DO, OS, JO, and SES are employees of Otsuka Pharmaceutical Development & Commercialization, Inc. FSC is a former employee of Otsuka Pharmaceutical and a current employee of Goldfinch Bio Inc"
- Funding declared: "funded by Otsuka Pharmaceutical Development & Commercialization, Rockville, MD. Alice G. Walton, PhD, of BioScience Communications, Inc. (New York, NY) assisted in drafting the manuscript, activity that was also funded by Otsuka."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Incomplete block randomization" Comment: insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study

Perrone 2020 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the trial
Selective reporting (reporting bias)	Low risk	No concerns with outcomes reported as indicated in the trial registration and protocol publication
Other bias	Unclear risk	No other concerns identified

PREVENT-ADPKD 2018

Study characteristics	
Methods	Study design • Parallel RCT • Duration of study: December 2015 to June 2021 • Follow-up: 36 months • ADPKD assessment: Pei-Ravine criteria • Country: Australia • Setting: multicentre (13 sites)
Participants	Study characteristics • Inclusion criteria: 18 to 67 years; ADPKD; eGFR ≥ 30 mL/min/1.73 m^2; htTKV in Mayo imaging subclass categories 1B to 1E; written informed consent • Exclusion criteria: potential safety risks for increased water intake; contraindication to undergoing MR; subjective risk of noncompliance with study procedures as determined by the lead investigator; presence of concomitant conditions that may have confounded end-point measures, and/or participation in other clinical trials Baseline characteristics • Number (randomised/reported/completed): intervention group (94/92/77); control group (93/92/81) • Mean age ± SD (years): intervention group (43.4 ± 10.9); control group (42.8 ± 11.2) • Gender (M/F): intervention group (50/42); control group (44/48) • Total with any PKD history: intervention group (91/92), control group (90/92) • Hypertension: intervention group (67/92); control group (72/92) • Mean eGFR ± SD (mL/min/1.73 m^2): intervention group (77.7 ± 24.8); control group (77.8 ± 25.3) • Median htTKVm IQR (mL/min): intervention group (629, 436.5 to 1124); control group (700.5, 485 to 1090) • Median 24-h urine volume, IQR (mL): intervention group (2228, 1548 to 3100); control group (2280, 1924 to 2998) • Mean 24-hour urine osmolality ± SD (mOsmol/Kg): intervention group (429 ± 181); control group (429 ± 147) • Mean SBP/DBP ± SD (mm Hg): intervention group (130 ± 12/80 ± 10); control group (131 ± 13/83 ± 11) • Ethnicity (Caucasian/Asian/other): intervention group (65/14/12); control group (69/12/11) • Mean BMI ± SD (kg/m^2): intervention group (26.6 ± 4.6); control group (27.5 ± 5.1)
Interventions	Intervention group

PREVENT-ADPKD 2018 *(Continued)*

- Prescribed water intake: the study dietitian calculated an individualised water prescription using the free water clearance formula, designed to determine the amount of water intake required to reduce urine osmolality to 270 mOsmol/kg or less using the mean baseline 24-hour urine osmolality. The study dietitian provided personalised counselling for consuming the water prescription, considering the patient's lifestyle, dietary solute intake, and preferences
- Patients self-monitored urine-specific gravity (daily for the first 2 weeks, twice-weekly for the first 6 months, and then as needed) to keep it below 1.010. The water prescription was recalculated during follow-up visits using 24-hour urine osmolality (3-monthly during the first year and then 6-monthly in the second and third years)

Control group

- Ad libitum water intake: at the second study visit, patients allocated to the ad libitum water intake group were advised to continue with their usual water intake and treatment

Duration of intervention

- 36 months

Co-interventions or additional treatments

- All patients were instructed to use sunscreen (SPF 30) during the study period

Outcomes

Reported outcomes

- Annual change (slope) in height-adjusted total kidney volume (18 and 36 months) normalised as a percentage
- Surrogate markers of systemic arginine vasopressin activity (24-hour urine osmolality and volume and serum copeptin)
- Kidney disease progression: slope of decline in eGFR from baseline and 3 months to 36 months, mean arterial pressure, spot UACR)
- Kidney pain: using a clinical outcome scale
- Composite outcome of kidney disease progression: ≥ 25% in eGFR reduction from baseline or week 12, worsening hypertension, worsening albuminuria, clinically significant kidney pain
- Physiological measure of treatment adherence: % of patients with 24-h urine osmolality < 300 mOsmol/Kg at each time point; and 24-hr urine osmolality < 300 mOsmol/Kg for > 50% of the time points
- Treatment acceptability: number of patients reporting water intake can be maintained lifelong and number of participants withdrawing from the study
- Adverse events: including hyponatremia (serum sodium ≤ 134 mmol/L or ADPKD-related medical events)

Notes

Additional information

- Protocol registration/published: Published and cited
- Ethics: "approved by the human research ethics committees at all study sites."
- Declaration of interest/disclosures: Some authors reported various funding from pharmaceutical companies, unlikely to have been conflicts
- Funding declared: "National Health and Medical Research Council of Australia and Danone Research, and neither had any decisional role in the trial design, data collection, data analysis, data interpretation, or the writing of the manuscript."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed centrally with a secure Web-based server in variable permuted blocks of four using a validated list provided by the trial statistician"

PREVENT-ADPKD 2018 *(Continued)*

		Comment: appropriate methods with no concerns
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation and concealed allocation will be performed with a secure, web-based randomisation service (Randomize. net)." Comment: appropriate methods with no concerns
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not possible for the intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "To assess total kidney volume, left and right kidney MRI-estimated volumes were quantified by blinded study personnel. Deidentified kidney images identified by MRI were encrypted and analyzed by the Imaging Core of the Mayo Translational PKD Center" Comment: appropriate methods for blinding outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Around 85% of completed the study with similar numbers in both arms. Intention to treat undertaken despite tolvaptan becoming available through public subsidy during the study (only 7 participants started during study)
Selective reporting (reporting bias)	Low risk	No obvious concerns with outcomes reported as indicated in the trial registration
Other bias	Low risk	No other concerns identified

RAPYD 2012

Study characteristics	
Methods	Study design • Parallel, open-label RCT • Duration of study: November 2007 to November 2008 • Follow-up: 24 months • ADPKD assessment: magnetic nuclear imaging • Country: Italy • Setting: multicentre (2 sites)
Participants	Study characteristics • Inclusion criteria: clinical, genetic and ultrasonographic diagnosis of type I ADPKD; 18 to 65 years; eGFR 40 to 80 mL/min/1.73 m^2 ○ Genetic details: All PKD1 • Exclusion criteria: evidence of active infection; evidence of infiltrate, cavitations or consolidation on chest X-ray; use of any investigational drug or treatment up to 4 weeks prior to the enrolment; known hypersensitivity to rapamycin and ramipril; screening/baseline total WCC < 3000/mm^3; platelet count < 100,000/mm^3; fasting triglycerides > 300 mg/dL; fasting total cholesterol > 350 mg/dL; UPE > 1 g/24 h; psychiatric disorders or any condition preventing full comprehension of the purposes and risks of the study; clinical evidence of any malignancy within 3 years before enrolment, except for adequately treated basal and squamous cell carcinomas of the skin; HIV-positive test Baseline characteristics • Number: intervention group 1 (19); intervention group 2 (18); control group (18)

RAPYD 2012 *(Continued)*

	• Mean age ± SD (years): intervention group 1 (43 ± 6); intervention group 2 (42 ± 11); control group (45 ± 7) • Sex (M/F): intervention group 1 (6/13); intervention group 2 (6/12); control group (9/9)

Interventions	Intervention group 1
	• Ramipril: 2.5 mg/d; increased by 1.25 mg/d every month to achieve BP < 120/80
	  ○ Rapamycin: 3 mg loading dose; maintenance dose of 1 mg/d to maintain blood levels 6 to 8 ng/mL
	Intervention group 2
	• Ramipril: 2.5 mg/d; increased by 1.25 mg/d every month to achieve BP < 120/80
	  ○ Rapamycin: no loading dose; maintenance dose of 1 mg/d to maintain blood levels 2 to 4 ng/mL
	Control group
	• Ramipril 2.5 mg/d; increased by 1.25 mg/d every month to achieve BP < 120/80
	Duration of intervention
	• 24 months

Outcomes	Reported outcomes • Cyst growth • Kidney function • MAP • Proteinuria • Safety
Notes	Additional information • Funding source: "The authors wish to acknowledge Wyeth and Pfizer, which supplied the study drug at free of cost."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by random number tables
Allocation concealment (selection bias)	Low risk	Block randomisation land adequately concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/55 (3.6%) patients analysed on ITT basis
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

RAPYD 2012 *(Continued)*

Other bias	Low risk	Medication supplied free of charge by Wyeth and Pfizer, no other involvement

RAPYD 2012 high

Study characteristics	
Methods	Study design • Parallel, open-label RCT • Duration of study: November 2007 to November 2008 • Follow-up: 24 months • ADPKD assessment: magnetic nuclear imaging • Country: Italy • Setting: multicentre (2 sites)
Participants	Study characteristics • Inclusion criteria: clinical, genetic and ultrasonographic diagnosis of type I ADPKD; 18 to 65 years; eGFR 40 to 80 mL/min/1.73 m^2 ○ Genetic details: All PKD1 • Exclusion criteria: evidence of active infection; evidence of infiltrate, cavitations or consolidation on chest X-ray; use of any investigational drug or treatment up to 4 weeks prior to the enrolment; known hypersensitivity to rapamycin and ramipril; screening/baseline total WCC < 3000/mm^3; platelet count < 100,000/mm^3; fasting triglycerides > 300 mg/dL; fasting total cholesterol > 350 mg/dL; UPE > 1 g/24 h; psychiatric disorders or any condition preventing full comprehension of the purposes and risks of the study; clinical evidence of any malignancy within 3 years before enrolment, except for adequately treated basal and squamous cell carcinomas of the skin; HIV-positive test Baseline characteristics (whole group; not reported for high BP subgroup) • Number: intervention group 1 (19); intervention group 2 (18); control group (18) • Mean age ± SD (years): intervention group 1 (43 ± 6); intervention group 2 (42 ± 11); control group (45 ± 7) • Sex (M/F): intervention group 1 (6/13); intervention group 2 (6/12); control group (9/9)

Interventions	Intervention group 1
	• Ramipril: 2.5 mg/d; increased by 1.25 mg/d every month to achieve BP < 120/80
	  ○ Rapamycin: 3 mg loading dose; maintenance dose of 1 mg/d to maintain blood levels 6 to 8 ng/mL
	Intervention group 2
	• Ramipril: 2.5 mg/d; increased by 1.25 mg/d every month to achieve BP < 120/80
	  ○ Rapamycin: no loading dose; maintenance dose of 1 mg/d to maintain blood levels 2 to 4 ng/mL
	Control group
	• Ramipril 2.5 mg/d; increased by 1.25 mg/d every month to achieve BP < 120/80
	Duration of intervention
	• 24 months

Outcomes	Reported outcomes • Cyst growth • Kidney function • MAP

RAPYD 2012 high *(Continued)*

- Proteinuria
- Safety

Notes	Additional information
	• Funding source: "The authors wish to acknowledge Wyeth and Pfizer, which supplied the study drug at free of cost."

RAPYD 2012 low

Study characteristics	
Methods	Study design • Parallel, open-label RCT • Duration of study: November 2007 to November 2008 • Follow-up: 24 months • ADPKD assessment: magnetic nuclear imaging • Country: Italy • Setting: multicentre (2 sites)
Participants	Study characteristics • Inclusion criteria: clinical, genetic and ultrasonographic diagnosis of type I ADPKD; 18 to 65 years; eGFR 40 to 80 mL/min/1.73 m^2 ◦ Genetic details: All PKD1 • Exclusion criteria: evidence of active infection; evidence of infiltrate, cavitations or consolidation on chest X-ray; use of any investigational drug or treatment up to 4 weeks prior to the enrolment; known hypersensitivity to rapamycin and ramipril; screening/baseline total WCC < 3000/mm^3; platelet count < 100,000/mm^3; fasting triglycerides > 300 mg/dL; fasting total cholesterol > 350 mg/dL; UPE > 1 g/24 h; psychiatric disorders or any condition preventing full comprehension of the purposes and risks of the study; clinical evidence of any malignancy within 3 years before enrolment, except for adequately treated basal and squamous cell carcinomas of the skin; HIV-positive test Baseline characteristics (whole group; not reported for low BP subgroup) • Number: intervention group 1 (19); intervention group 2 (18); control group (18) • Mean age ± SD (years): intervention group 1 (43 ± 6); intervention group 2 (42 ± 11); control group (45 ± 7) • Sex (M/F): intervention group 1 (6/13); intervention group 2 (6/12); control group (9/9)

Interventions	Intervention group 1
	• Ramipril: 2.5 mg/d; increased by 1.25 mg/d every month to achieve BP < 120/80
	  ◦ Rapamycin: 3 mg loading dose; maintenance dose of 1 mg/d to maintain blood levels 6 to 8 ng/mL
	Intervention group 2
	• Ramipril: 2.5 mg/d; increased by 1.25 mg/d every month to achieve BP < 120/80
	  ◦ Rapamycin: no loading dose; maintenance dose of 1 mg/d to maintain blood levels 2 to 4 ng/mL
	Control group
	• Ramipril 2.5 mg/d; increased by 1.25 mg/d every month to achieve BP < 120/80
	Duration of intervention
	• 24 months

RAPYD 2012 low *(Continued)*

Outcomes	Reported outcomes • Cyst growth • Kidney function • MAP • Proteinuria • Safety
Notes	Additional information • Funding source: "The authors wish to acknowledge Wyeth and Pfizer, which supplied the study drug at free of cost."

REPRISE 2017

Study characteristics	
Methods	Study design • Parallel, phase 3, placebo-controlled, double-blind RCT • Duration of study: May 2014 to March 2016 • Follow-up: 12 months treatment period, 3-week follow-up period • ADPKD assessment: modified Pei-Ravine criteria • Countries: 21 countries (North and South America, Europe, and Australia) • Setting: Multicentre (213 sites)
Participants	Study characteristics • Inclusion criteria: 18 to 55 years and eGFR of 25 to 65 mL/min/1.73 m^2 or 56 to 65 years and eGFR of 25 to 44 mL.min/1.73 m^2 (had to have historical evidence of a decline in the eGFR > 2.0 mL/min/1.73 m^2/year; tolvaptan naive; several cysts per kidney (3 if by sonography; 5 if by CT or MRI) • Exclusion criteria: women of childbearing potential who do not agree to practice 2 different methods of birth control or remain abstinent during the trial and for 30 days after the last dose of study medication; breastfeeding and/or who have a positive pregnancy test result prior to receiving study medication; need for chronic diuretic use; hepatic impairment or liver function abnormalities other than that expected for ADPKD with typical cystic liver disease during the pre-randomization period; advanced diabetes; evidence of additional significant kidney disease(s), renal cancer, single kidney, or recent (within last 6 months) renal surgery or AKI; contraindications to required trial assessments; in the opinion of the trial investigator or medical monitor, have a medical history or medical findings inconsistent with safety or compliance with trial assessments Baseline characteristics • Number (randomised/analysed): intervention group (683/668); control group (687/663) • Mean age ± SD (years): intervention group (47.3 ± 8.2); control group (47.2 ± 8.2) • Gender (M): intervention group (50.8%); control group (48.5%) • Mean eGFR ± SD (mL/min/1.73m^2): intervention group (40.7 ± 10.9); control group (41.4 ± 11.2) • Mean SBP/DBP ± SD (mm Hg): intervention group (129.3 ± 13.8/82.1 ± 9.6) control group (82.5 ± 9.7/41.4 ± 11.2) • Ethnicity (Caucasian/Asian/Black/other): intervention group: 626/22/25/10); control group (632/19/23/13) • Weight: intervention group (84.6 ± 19.9); control group (81.6 ± 19.3) • Mean BMI ± SD: intervention group (28.0 ± 5.8); control group (27.7 ± 5.6)
Interventions	Intervention group

REPRISE 2017 *(Continued)*

- Tolvaptan: daily split doses of tolvaptan were titrated to tolerance (30/15, 45/15, 60/30, or 90/30 mg)
- (Duration):

Control group

- Placebo: split dose

Duration of intervention

- Maintained for 12 months, after an 8-week pre-randomization period to screen out subjects unable to tolerate at least 60/30 mg for 3 weeks

Co-interventions

- Not reported

Outcomes

Reported outcomes

- Change in eGFR: with adjustment for the time each patient was in the trial and with interpolation to 1 year
- Slope of eGFR change
- Liver enzymes: > 3 times increase in ALT above ULN; >2 times increase total bilirubin level above ULN
- Hepatic adverse events leading to discontinuation of trial regimen
- Adverse events
- Serious adverse events
- Withdrawal due to adverse events

Notes

Additional information

- Protocol registration/published: yes
- Ethics: "Institutional review boards/independent Ethics Committees are required to approve the protocol and informed consent forms are completed in all participating centers according to regional requirements. The trial is conducted according to the International Conference of Harmonisation Good Clinical Practice Guidelines and all other applicable regulatory requirements and it adheres to the ethical principles that have their origin in the Declaration of Helsinki. Participant privacy is ensured by deidentifying all submitted data and by using a participant identification code. All patients have the right to withdraw from the study at any time during the trial. An independent data monitoring committee monitors study safety and efficacy."
- Declaration of interest/disclosures: "Disclosures V.E.T., O.D., A.B.C., R.T.G., R.D.P., J.O., and F.S.C. are members of the Steering committee of the TEMPO 3:4 and TEMPO 4:4 trials. V.E.T., O.D., A.B.C., R.T.G., and R.D.P. have received research funding from Otsuka Pharmaceutical Development and Commercialization, Inc. (Princeton, NJ, USA); A.B.C. has received consultancy fees from Otsuka Pharmaceutical Development and Commercialization, Inc. J.O., J.D.B., F.S.C., and O.S. are employees of Otsuka Pharmaceutical Development and Commercialization Inc."
- Funding declared: "Funded by Otsuka Pharmaceuticals Co., Ltd. Tokyo, Japan and Otsuka Pharmaceutical Development and Commercialization, Inc., Rockville, Maryland."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Low risk	Double-blind study

REPRISE 2017 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement. Registry information describes quadruple blinding but no mention of this in the primary study or protocol is provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	11% lost to follow-up, with most included in the ITT analysis
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported
Other bias	Low risk	No other obvious concerns

Ruggenenti 2005

Study characteristics	
Methods	Study design • Double-blind, cross-over RCT • Duration of study: not reported • Follow-up: 6 months • ADPKD assessment: clinical and echographic • Country: Italy • Setting: single centre
Participants	Study characteristics • Inclusion criteria: aged ≥ 18 years; SCr < 3.0 mg/dL, but > 1.2 mg/dL (males) or > 1.0 mg/dL (females) ○ Genetic details: PKD 1 and 2 • Exclusion criteria: patients with concomitant systemic, renal parenchymal or urinary tract disease; DM; overt proteinuria (UPE > 1 g/24 h); abnormal urinalysis suggestive of concomitant, clinically significant glomerular disease; urinary tract stones, infection or obstruction; biliary tract stones or obstruction; > 2 haemorrhagic or complicated cysts; cancer; major systemic diseases that could prevent completion of the planned follow-up or interfere with data collection or interpretation; psychiatric disorders Baseline characteristics • Number: 6 • Mean age (range): 44 years (35 to 58) • Sex (M/F): 9/3
Interventions	Intervention group • Long-acting octreotide: 40 mg IM every 28 days Control group • Placebo Duration of intervention • 6 months
Outcomes	Reported outcomes

Ruggenenti 2005 *(Continued)*

- Kidney and cyst volume
- Kidney function
- UAE
- BP

Notes	Additional information • Funding source: "Novartis Italia (Varese, Italy) freely supplied the study drug."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Blocks of four using a 1:1 allocation ratio
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors analysing liver and kidney volumes were blinded to treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All subjects completed the study
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Schaefer 2019

Study characteristics

Methods	Study design • Parallel, phase 3b, double-blind placebo-controlled RCT • Duration of study: 23 September 2016 to 17 November 2021 • Follow-up: 12 months with a 2-year open-label extension • ADPKD assessment: MRI • Country: Belgium • Setting: multicentre (5 sites)
Participants	Study characteristics • Inclusion criteria: 4 to 17 years; ADPKD defined by the presence of family history and/or genetic criteria AND who have at least 10 renal cysts, each of which measures at least 0.5 cm, confirmed upon MRI inspection; subjects under the age of 12 years must have at least 4 cysts that are at least 1 cm in size, confirmed by ultrasound; weight ≥ 20 kg; eGFR ≥ 60 mL/min/1.73 m^2 within 31 days prior to

Schaefer 2019 *(Continued)*

randomisation; independent in toileting; trial-specific written informed consent obtained from a parent/guardian and must provide age-appropriate informed assent at screening and must be able to understand that he or she can withdraw from the trial at any time; ability to swallow a tablet; ability to commit to remain fully abstinent or use two approved methods of birth control during the trial and for 30 days following the last dose of study drug for sexually active females of childbearing potential

- Exclusion criteria: breastfeeding and/or who have a positive pregnancy test result prior to receiving study drug; Liver function tests ≥ 1.5 times ULN; nocturnal enuresis; need for chronic diuretic use; advanced diabetes; evidence of additional significant kidney disease(s), renal cancer, single kidney, or recent (within last 6 months), renal surgery or AKI; known clinically significant allergic reactions to chemicals with structure similar to tolvaptan; disorders in thirst recognition or inability to access fluids; bladder dysfunction and/or difficulty voiding; critical electrolyte imbalances, as determined by the investigator; with or at risk of significant hypovolemia, as determined by investigator; history of substance abuse (within the last 6 months); 12 years of age and older having contraindications to, or interference with, MRI assessments; taking a vasopressin agonist; history of persistent noncompliance with antihypertensive or other important medical therapy; taking medications or having concomitant illnesses likely to confound endpoint assessments, including taking approved therapies for the purpose of affecting PKD cysts such as tolvaptan, vasopressin antagonists, anti-sense RNA therapies, rapamycin, sirolimus, everolimus, or somatostatin analogues; any medical condition that, in the opinion of the investigator, could interfere with evaluation of the trial objectives or safety of the subjects; deemed unsuitable for trial participation in the opinion of the investigator; received any investigational agent in a clinical trial within 30 days prior to screening; known lactose intolerance; had cyst reduction surgery within 6 weeks of the screening visit

Baseline characteristics

- Number: intervention group (48); control group (43)
- Mean age ± SD (years): intervention group (12.9 ± 3.2); control group (12.8 ± 2.8)
- Gender (M/F): intervention group (27/21); control group (20/23)
- Mean eGFR ± SD (mL/min/1.73 m^2): intervention group (93.9 ± 18.); control group (102.1 ± 15.4)
- Ethnicity (White/Asian/Black): intervention group (46/2/0); control group (42/0/1)

Interventions	Intervention group • Tolvaptan: 7.5, 15, and 30 mg IR tablets in split-dose regimens, with the first dose taken upon waking and the second taken 8 to 9 hours later. Starting doses are based on weight. After 1 week, subjects who tolerate their initial dose will up-titrate once Control group • Placebo: matching placebo as split-dose regimens, with the first dose taken upon waking and the second taken 8 to 9 hours later. Starting doses are based on weight. After 1 week, subjects who tolerate their initial dose will up-titrate once Duration of intervention • 12 months Co-interventions or additional treatments • Subjects are additionally encouraged to drink plain water per thirst throughout the day and one to two glasses of water before bedtime to help maintain a proper hydration status
Outcomes	Reported outcomes • Change in spot urine osmolality (pre-morning dose) after 1 week and 1 month of daily dosing • Change in specific gravity (pre-morning dose) after 1 week and 1 month of daily dosing • Per cent change in htTKV as measured by MRI • 24-hour fluid balance prior to week 1 • Change in eGFR at each clinic visit (week 1, month 1, month 6, and month 12)

Schaefer 2019 *(Continued)*

- Pharmacodynamic endpoints of urine volume (including 24-hour fluid volume), fluid intake and fluid balance, sodium, creatinine, and free water clearance during dense PKD sampling (after at least 1 month on study drug)
- Proportions of each Tanner stage by gender and age compared to normative populations at baseline, month 6, and month 12
- Description of changes from baseline percentiles for height and weight by gender and age at baseline, month 6, and month 12
- Safety variables (changes from baseline in creatinine, vital signs, laboratory values including liver function tests, rate of aquaretic adverse events) in placebo and tolvaptan
- Time to discontinuation due to any reasons
- Tolvaptan maximum (peak) plasma concentration, minimum plasma concentration, time to maximum peak concentration, and area under the concentration-time curve from time zero to 24 h following dense PK sampling
- PKD sampling for separate population analysis
- Tolvaptan metabolite concentrations from dense sampling
- Generic paediatric QoL assessments
- Daytime and nighttime void collection

Notes

Additional information

- Protocol registration/published: published as protocol
- Ethics: "The study was approved by the US Food and Drug Administration (IND 117464) and the Indiana University Institutional Review Board (1308084213)."
- Declaration of interest/disclosures: "FS has received fees for serving on Otsuka advisory boards. DM has received a research grant from Otsuka and serves on an Otsuka advisory board. FE has received fees as a member of the Otsuka safety committee for pediatric studies. RDG has nothing to disclose. DB has received consultation fees from Otsuka. MAC has served as a consultant to Otsuka. LS, AD, KS, and SES are employees of Otsuka."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed according to a computer-generated randomization schedule supplied by the sponsor to the treatment-blinded investigators and site staff" Comment: appropriate methods for sequence generation
Allocation concealment (selection bias)	Low risk	Quote: "The placebo was matched to the dosing of the intervention and Tolvaptan/placebo was administered with a recommended 240 mL of water within a 1-hour period. Participants were also encouraged to drink plain water per thirst throughout the day and one to two glasses of water before bedtime to help maintain proper hydration status." Comment: methods to adjust for increased thirst to prevent concealment of intervention to participants and study personnel
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The blind in phase A will be maintained in this dense PK subpopulation via an Interactive Response System" Comment: double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Subsequent measurement of kidney dimensions and evaluation of height-adjusted TKV will be performed at a central laboratory by individuals blinded to treatment assignment."

Schaefer 2019 *(Continued)*

		Comment: primary outcome assessors will be blinded to treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low lost to follow-up and intention to treat analysis undertaken
Selective reporting (reporting bias)	Low risk	No concerns identified
Other bias	Unclear risk	No other concerns identified

SIRENA 2010

Study characteristics	
Methods	Study design • Cross-over RCT • Duration of study: April 2007 to August 2009 • Follow-up: 6 months • ADPKD assessment: CT scan • Country: Italy • Setting: single centre
Participants	Study characteristics • Inclusion criteria: > 18 years; clinical and ultrasonographic diagnosis of ADPKD; eGFR > 40 mL/min/1.73 m^2 • Exclusion criteria: concomitant systemic renal parenchymal (proteinuria > 1 g/24 h); urinary tract disease; DM; cancer; psychiatric disorders Baseline characteristics • Number (randomised/analysed): 21/15 • Mean age (range): 39.1 years (28 to 46) • Sex (M/F): 12/3
Interventions	Intervention group • Sirolimus: starting dose 3 mg/d (drug levels to be maintained 5 to 10 ng/mL) Control group • Standard therapy Duration of intervention • 6 months
Outcomes	Reported outcomes • Kidney volume • Cyst volume • BP • mGFR • Albuminuria

SIRENA 2010 *(Continued)*

	• Proteinuria
Notes	Additional information • 6/21 patients withdrew (not included in study results) • Funding source: "Wyeth-Lederle S.p.A. (Aprilia, Latina, Italy) for freely supplying the study drug."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Kidneys were first manually outlined on all acquired digital images by a trained operator (AC), who was blind to the treatment phase"
Incomplete outcome data (attrition bias) All outcomes	High risk	6/21 patients withdrew. These patients were not included in final analyses
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Wyeth-Lederle S.p.A. supplied the study drug, role in the trial otherwise unclear

SIRENA 2 2016

Study characteristics

Methods	Study design • Parallel, open-label blinded endpoint RCT • Duration of study: September 2020 to March 2012 • Follow-up: planned follow-up was 3 years • ADPKD assessment: not reported • Country: Italy • Setting: single centre (Unit of Nephrology of the Azienda Ospedaliera Papa Giovanni XXII)
Participants	Study characteristics • Inclusion criteria: ≥ 18 years with ADPKD; eGFR 15 to 40 mL/min/1.73 m^2; proteinuria ≥ 0.5 g/24 h • Exclusion criteria: concomitant glomerular or urinary tract disease; diabetes; cancer; psychiatric disorders; any condition that might confound data interpretation or prevent full comprehension of the purposes and risks of the study; pregnant or breastfeeding women and women of childbearing potential without effective contraception

SIRENA 2 2016 *(Continued)*

	Baseline characteristics • Number: intervention group (21); control group (20) • Mean age ± SD (years): intervention group (49.0 ± 7.1); control group (47.6 ± 8.1) • Gender (M/F): intervention group (9/12); control group (8/12) • Median proteinuria, range (g/24 h): intervention group (0.25, 0.16 to 0.36); control group (0.24, 0.15 to 0.45) • Mean eGFR ± SD (mL/min/1.73 m^2): intervention group (26.8 ± 5.6); control group (30.8 ± 6.6) • Mean weight ± SD (kg): intervention group (73.5 ± 14.3); control group (73.8 ± 17.8)
Interventions	Intervention group • Sirolimus: started at 3 mg/d and subsequently titrated to target blood trough levels between 5 to 10 ng/mL Control group • Standard care: antihypertensive treatment Duration of intervention • The planned duration was 3 years
Outcomes	Reported outcome • eGFR (iohexol plasma clearance) at 1 year • Kidney failure • Adverse events • Withdrawal due to adverse events • Serious adverse events • Proteinuria • Albuminuria
Notes	Additional information • Study was terminated at 1 year • Protocol registration/published: Reported and online but not accessible • Ethics: " The study conformed to the principles of the Declaration of Helsinki and was approved by the local ethical committee." • Declaration of interest/disclosures: The authors declare no competing interests. • Funding declared: "TranCYST Marie Curie Initial Training Networks project within 7th European Community Framework programme EU-FP7/2007-2013 grant 317246 (TranCYST). Pfizer Italia (Latina, Italy) and formerly, Wyeth Lederle (Aprilia, Italy) freely supplied sirolimus but did not fund the study, and they were not involved in the planning and conducting of the study or the data analyses and reporting."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer–generated randomization list (1:1 ratio and four or eight random block size)
Allocation concealment (selection bias)	Low risk	Quote: "An independent investigator centrally randomized patients by telephone call." Comment: Appropriate methods

SIRENA 2 2016 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Patients and their physicians were aware of treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	80% of participants completed the study with similar dropout rates in both arms
Selective reporting (reporting bias)	Low risk	No concerns identified
Other bias	Low risk	The study was aborted, with the extension phase not undertaken

Soliman 2009

Study characteristics	
Methods	Study design • Parallel, single-blind RCT • Duration of study: not reported • Follow-up: 24 months • ADPKD assessment: magnetic nuclear imaging • Country: Egypt • Setting: single centre
Participants	Study characteristics • Inclusion criteria: 30 to 50 years; SCr < 2 mg/dL or GFR > 30 mL/min/1.73 m^2; UPE < 0.5 g/24 h; clinical and ultrasound diagnosis of ADPKD, documented kidney volume progression • Exclusion criteria: DM; clinically significant glomerular disease; urinary tract stones, infection, or obstruction; cancer; woman of childbearing potential who was planning to become pregnant, was pregnant and/or lactating, or unwilling to use an effective means of contraception; increased liver enzymes (twofold greater than normal values); fasting cholesterol > 220 mg/dL; hypertriglyceridaemia (> 150 mg/dL) not controlled by lipid lowering therapy; WCC < 3000/mm^3 or platelets < 100,000/mm^3; hepatitis B or C; HIV; past or present malignancy; mental illness that could interfere with the patient's ability to comply with the protocol; drug or alcohol abuse within 1 year of baseline; co-medication with strong inhibitor of CYP3A4 and or P-g P–like voriconazole, ketoconazole, diltiazem, verapamil, erythromycin; or co-medication with strong CYP3A4 and or P-g p inducer such as rifampicin, or known hypersensitivity to macrolides or to rapamycin Baseline characteristics • Number: intervention group (8); control group (8) • Mean age, range (years): intervention group (40, 32 to 50); control group (41, 30 to 49) • Sex (M/F): intervention group (7/1); control group (6/2)
Interventions	Intervention group • Sirolimus: 1 mg/d • Telmisartan: dosage not reported

Soliman 2009 *(Continued)*

	Control group • Telmisartan; dosage not reported Duration of intervention • 24 months
Outcomes	Reported outcomes • Kidney volume • Kidney function • Adverse events • BP
Notes	Additional information • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...observers were blinded to all clinical and radiologic data, as well as their first measurements and the results of the other observer"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

SUISSE ADPKD 2007

Study characteristics

Methods	Study design • Parallel, open-label RCT • Duration of study: March 2006 to March 2010 • Follow-up: 18 months • ADPKD assessment: magnetic nuclear imaging

SUISSE ADPKD 2007 *(Continued)*

- Country: Switzerland
- Setting: single centre

Participants	Study characteristics • Inclusion criteria: 18 to 40 years; eGFR > 70 mL/min • Exclusion criteria: increased liver enzymes (more than twice the upper reference limit); cholesterol > 309 mg/dL; triglycerides > 443 mg/dL; WCC < 3000/mm^3; platelet count < 100,000/mm^3; hepatitis B or C; HIV Baseline characteristics • Number: intervention group (50); control group (50) • Mean age ± SD (years): intervention group (31 ± 7); control group (32 ± 6) • Sex (M/F): intervention group (29/21); control group (32/18)
Interventions	Intervention group • Sirolimus: target dose 2 mg/d Control group • Standard therapy Duration of intervention • 18 months
Outcomes	Reported outcomes • Kidney volumes • Kidney function • Albuminuria • BP • Adverse events
Notes	Additional information • Funding source: "Supported by a grant from the Swiss National Science Foundation (310000-118166), by the Polycystic Kidney Foundation, by an unrestricted research grant from Wyeth (now Pfizer), and by the Binelli and Ehrsam Foundation. Wyeth Switzerland(now Pfizer) provided the sirolimus"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by biostatistics unit independent of study team
Allocation concealment (selection bias)	Low risk	Sealed sequentially numbered opaque envelopes were used
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Each observer was unaware of all clinical data and the findings of the other observer, and the measurements were performed in random order"

SUISSE ADPKD 2007 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	4/100 (4%) patients withdrew. These patients were analysed on an ITT basis
Selective reporting (reporting bias)	Low risk	All defined outcomes were reported
Other bias	Low risk	Quote: "Wyeth Switzerland (now Pfizer), provided the study drug and an unrestricted research grant. The company had no role in the design of the trial or in the collection, analysis, or interpretation of the data or the writing of the manuscript"

TAME-PKD 2018

Study characteristics

Methods

Study design

- Parallel, phase II, double-blind RCT
- Duration of study: 27 June 2016 to 7 December 2020
- Follow-up: 26 months
- ADPKD assessment: modified Pei-Ravine criteria
- Country: USA
- Setting: multicentre (2 sites)

Participants

Study characteristics

- Inclusion criteria: 18 to 60 years; ADPKD; eGFR of at least 50 mL/min/1.73 m^2
- Exclusion criteria: not on active military duty; not currently participating in another clinical trial; GFR < 50 mL/min/1.73 m^2; diabetes; systemic disease other than hypertension and PKD; solitary kidney; allergy or intolerance to metformin; pregnant or lactating or intending to become pregnant within the next 3 years; unstable or unclipped cerebral aneurysm; active coronary artery disease; MRI incompatible device/implant; severe claustrophobia; any solid organ transplant; vitamin B12 deficiency; taking medications that interact with metformin; takes or has taken (within 2 weeks) tolvaptan

Baseline characteristics

- Number: intervention group (49); control group (48)
- Mean age ± SD (years): intervention group (41.8 ± 10.4); control group (42.1 ± 10.1)
- Gender (M/F): intervention group (11/38); control group (16/32)
- Diagnosis of PKD (PKD 1/PKD 2/other/no mutation): intervention group 37/1/2/1/2); control group (28/10/4/4)
- Mayo Class (Class 2/1A/1B/1C/1D/1E): intervention group (2/9/13/14/6/4); control group (5/6/15/12/6/4)
- Hypertension: intervention group (12); control group (17)
- Diabetes: intervention group (1); control group (1)
- Mean SCr ± SD (mg/dL): intervention group (0.9 ± 0.2); control group (0.9 ± 0.2)
- Mean eGFR ± SD (mL/min/1.73 m^2): intervention group (86.1 ± 20.6); control group (85.9 ± 19)
- Mean htTKV ± SD (mL/min): intervention group (625.8 ± 386.5); control group (750.9 ± 547.8)
- Mean height-adjusted liver volume ± SD (mL/min): intervention group (1224 ± 490.7); control group (1019 ± 212.6)
- Mean time since diagnosis ± SD (years): intervention group (10.5 ± 6.4); control group)8.10 ± 6.3)

TAME-PKD 2018 *(Continued)*

- Means SBP/DBP ± SD (mm Hg): intervention group (122.2 ± 13.1/76.8 ± 8.9); control group (124.1 ± 13/74.6 ± 8.5)
- Mean weight ± SD (kg): intervention group (78.5 ± 16.9); control group (78.2 ± 17.4)
- Mean BMI ± SD: intervention group (27 ± 5.9); control group (26.6 ± 4.50

Interventions	Intervention group • Tolvaptan: target dose of 1000 mg twice/d; dosage was initiated at 500 mg/d and up-titrated at 2-week intervals depending on the eGFR, lactate levels, and tolerability. When eGFR was ≥ 30 mL/min/1.73 m^2 and ≤ 45 mL/min/1.73 m^2, maximum metformin/placebo dosage was 500 mg twice/d, and eGFR was monitored monthly. Study medication was discontinued if the eGFR was < 30 mL/min/1.73 m^2 but could be restarted if the eGFR improved to ≥ 30 mL/min/1.73 m^2 Control group • Placebo: matching dose Duration of intervention • 24 months

Outcomes	Reported outcomes
	• Medication tolerability
	  ◦ gastrointestinal symptom burden using the validated Gastrointestinal Symptoms Rating Scale (GSRS)
	  ◦ Response to the question "Can you tolerate this dose of the study drug for the rest of your life?"
	  ◦ Maximally tolerated dose at 24 months and safety
	• Safety: primary safety outcome was based on the proportion of participants experiencing at least 1 serious adverse event during 24 months of study follow-up
	• Adverse and serious adverse events, including prospectively defined and ascertained hypoglycaemia and lactic acidosis
	• Vitamin B12 levels monitored
	• ADPKD progression (height-adjusted TKV growth and eGFR decline)
	• Medication adherence
	• Patient-reported pain and health-related QoL
	• Kidney failure, death, hospitalisation
	• Progression of hepatic cystic disease (height-adjusted liver volume)
	• Health-related QoL

Notes	Additional information • Protocol registration/published: published • Ethics: "The study conformed to the principles of the Declaration of Helsinki. The institutional review board at each site approved the protocol, and written informed consent was obtained from all participants" • Declaration of interest/disclosures: "RDP has received research funding from Otsuka, Kadmon Corporation, Sanofi-Genzyme, and Reata and is a consultant to Palladiobio, Reata, Sanofi-Genzyme, Navitor, and Otsuka. TW has received research funding from Otsuka, Kadmon Corporation, Palladio Biosciences, Sanofi, and Reata. KRH has received research funding from Otsuka and Esperion Therapeutics. DCM has received research funding from Regulus and Dialysis Clinics, Inc. SLS has received research funding from Otsuka, Kadmon Corporation, Palladio Biosciences, Sanofi, and Reata. KTB is a consultant to Kadmon, Otsuka, and Sanofi. PCH reports research funding from Otsuka Pharmaceuticals, Navitor, and Acceleron; consulting for Otsuka Pharmaceuticals, Mitobridge, and Regulus; and is on the Advisory Board for Vertex Pharmaceuticals. All other authors declared no competing interests" • Funding declared: "Department of Defense contract W81XWH-15-1-0663, by the National Center for Advancing Translational Sciences, National Institutes of Health Award Numbers UL1TR002544 and 1UL1TR003098. This work also used resources developed by the Maryland Polycystic Kidney Disease

TAME-PKD 2018 *(Continued)*

Research and Translation Core Center P30 DK090868 and U54 DK126114. Mutation analysis by PCH was supported by the Mayo Translational PKD Center P30 DK090728 and NIH R01 DK058816."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was generated by the lead statistician at the data coordinating center, with participants assigned in a 1:1 ratio to receive metformin or matching placebo stratified by the clinical site." Comment: appropriate methods with no concerns
Allocation concealment (selection bias)	Low risk	Quote: "The schema was integrated into the web-based data management system to which the clinical sites and investigational pharmacies had secure access" Comment: appropriate methods
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar number of participants lost across groups and intention to treat analysis undertaken
Selective reporting (reporting bias)	Low risk	No obvious concerns with outcomes reported as indicated in the trial registration and protocol publication
Other bias	Unclear risk	No other concerns identified

Temmerman 2012

Study characteristics

Methods	Study design • Parallel RCT • Duration of study: not reported • Follow-up: 6 months • ADPKD assessment: CT scan • Country: Belgium, the Netherlands • Setting: multicentre (number of sites not reported)
Participants	Study characteristics • Inclusion criteria: not reported • Exclusion criteria: not reported Baseline characteristics

Temmerman 2012 *(Continued)*

- Number (ADPKD/total): 56/69
- Mean age ± SD (years): not reported
- Sex (M/F): not reported

Interventions	Intervention group • Lanreotide: 120 mg every 4 weeks Control group • Placebo Duration of intervention • 6 months
Outcomes	Reported outcomes • Kidney function
Notes	Additional information • Abstract-only publication • Separate data for ADPKD was not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

TEMPO 248 & 249 2005

Study characteristics

TEMPO 248 & 249 2005 *(Continued)*

Methods	Study design • Parallel phase IIB pilot RCT • Duration of study: not reported • Follow-up: 5 days • ADPKD assessment: unclear • Country: USA • Setting: multicentre (number of sites not reported)
Participants	Study characteristics • Inclusion criteria: not reported • Exclusion criteria: not reported Baseline characteristics • Number: intervention group (8); control group (3) • Mean age ± SD (years): not reported • Sex (M/F): not reported
Interventions	Intervention group • Tolvaptan: increasing single doses (15, 30, 60 and 120 mg/d) Control group • Placebo Duration of intervention • 5 days
Outcomes	Reported outcomes • AVP • Urinary volume and osmolality • Urinary Aquaporin-2 levels • Sodium and electrolyte levels
Notes	Additional information • Abstract-only publications

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement

TEMPO 248 & 249 2005 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Sponsored by Otsuka pharmaceutical

TEMPO 250 2011

Study characteristics	
Methods	Study design • Parallel RCT • Duration of study: not reported • Follow-up: 36 months • ADPKD assessment: Ravine criteria; magnetic nuclear imaging • Country: USA • Setting: multicentre (number of sites not reported)
Participants	Study characteristics • Inclusion criteria: > 18 years; ADPKD; prior participation in a phase 1 tolvaptan ADPKD trial; willingness to adhere to contraceptive precautions • Exclusion criteria: inability to comply with study procedures; eGFR < 30 mL/min/1.73 m^2; anticipation of KRT within 1 year; active treatment that would affect endpoint measures (e.g. diuretics) Baseline characteristics • Number: intervention group 1 (22); intervention group 2 (24) • Mean age ± SD (years): not reported • Sex (M/F): not reported
Interventions	Intervention group 1 • Tolvaptan: 45/15 mg split dose/d Intervention group 2 • Tolvaptan: 60/30 mg split dose/d Duration of intervention • 16 months

Outcomes	Reported outcomes
	• Long-term safety and tolerability of tolvaptan
	• Pilot efficacy data
	  ○ Urine osmolality
	  ○ Kidney volumes

TEMPO 250 2011 *(Continued)*

- Kidney function
- BP

Notes	Additional information • Funding source: "supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)." "The TEMPO4 2 trial was funded by Otsuka Pharmaceutical Development& Commercialization, Inc; the 002 trial was funded by Otsuka Pharmaceutical, Ltd"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Sponsored by Otsuka pharmaceutical

TEMPO 3:4 2011

Study characteristics

Methods	Study design • Parallel, double-blind RCT • Duration of study: January 2007 to January 2009 • Follow-up: 36 months • ADPKD assessment: magnetic nuclear imaging • Country: international (countries not reported) • Setting: multicentre (129 sites)
Participants	Study characteristics • Inclusion criteria: ADPKD; 18 to 50 years; total kidney volume ≥ 750 mL (magnetic nuclear imaging); eGFR ≥ 60 mL/min • Exclusion criteria: patients with safety risk, medical conditions likely to require an extended interruption or discontinuation or history of substance abuse or non-adherence; contraindications to or in-

TEMPO 3:4 2011 *(Continued)*

	terference with magnetic nuclear imaging assessments; using medications or having concomitant illnesses likely to confound endpoint assessments; using other experimental (i.e. non marketed) therapies or approved therapies for the purpose of affecting ADPKD cysts; history of using tolvaptan Baseline characteristics • Number: intervention group (961); control group (484) • Mean age ± SD (years): intervention group (39 ± 7); control group (39 ± 7) • Sex (M/F): intervention group (495/466); control group (251/233)
Interventions	Intervention group • Tolvaptan: 60 to 120 mg/d Control group • Placebo Duration of intervention • 36 months
Outcomes	Reported outcomes • Kidney volume • Kidney function • Kidney pain • BP
Notes	Additional information • Funding source: "Supported by Otsuka Pharmaceuticals and Otsuka Pharmaceutical Development and Commercialization."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Low risk	Allocation was performed in a 2:1 ratio to receive tolvaptan or placebo, and with stratification
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded radiologists used proprietary software to measure the volume of both kidneys.
Incomplete outcome data (attrition bias) All outcomes	High risk	Data analysed on ITT basis. 221/961 (22.9%) and 67/483 (13.8%) patients, in the intervention and control group respectively, discontinued the study
Selective reporting (reporting bias)	Low risk	All selected outcomes were reported

TEMPO 3:4 2011 *(Continued)*

Other bias	High risk	Supported by Otsuka Pharmaceuticals and Otsuka Pharmaceutical Development and Commercialization. The sponsor collected and analysed the data

Tesar 2017

Study characteristics

Methods	Study design • Parallel, phase 2, multicentre, double-blind placebo-controlled RCT • Duration of study: October 2010 to June 2011 • Follow-up: 50 months • ADPKD assessment: Ravine criteria • Country: 17 countries • Setting: multicentre (47 sites)
Participants	Study characteristics • Inclusion criteria: 18 to 50 years; ADPKD; eGFR > 60 mL/min/1.73 m^2 • Exclusion criteria: biopsy-proven kidney disease other than ADPKD; severe acute or chronic medical condition (e.g., liver impairment) Baseline characteristics • Number: intervention group 1 (58); intervention group 2 (31); intervention group 3 (24); control group (56) • Mean age, range (years): intervention group 1 (37.9, 21 to 50); intervention group 2 (41.3, 31 to 50); intervention group 3 (36.4, 18 to 47); control group (38.5, 20 to 50) • Gender (M/F): intervention group 1 (30/28); intervention group 2 (17/14); intervention group 3 (9/15); control group (21/35) • Median eGFR, range (mL/min/1.73 m^2): intervention group 1 (85.86, 64.63 to 128.02); intervention group 2 (83.32, 57.46 to 113.54); intervention group 3 (94.01, 56.87 to 129.11); control group (86.94, 43.19 to 120.50) • Median time since diagnosis, range (years): intervention group 1 (10.2, 0 to 28.2); intervention group 2 (12.2, 0.3 to 37.3); intervention group 3 (6.2, 0 to 31.7); control group (10.2, 0.3 to 29.9) • Ethnicity (white/Black/Asian/other): intervention group 1 (53/1/3/1); intervention group 2 (30/0/1/0); intervention group 3 (21/0/3/0); control group (53/0/3/0)
Interventions	Intervention group 1 • Bosutinib: 200 mg/d Intervention group 2 • Bosutinib: 400 mg/d Intervention group 3 • Bosutinib: 400/200 mg/d Control group • Placebo Duration of intervention • 24 months

Tesar 2017 *(Continued)*

Outcomes	Reported outcome • Annualized rate of kidney enlargement versus placebo • eGFR decline rate versus placebo • Time to first occurrence (or worsening) of clinical measures of disease progression (back and/or flank pain, hypertension, haematuria, proteinuria, or ESKD requiring dialysis for ≥ 56 days) • Four-component composite disease progression endpoint was also assessed, including onset/worsening of hypertension, renal pain, proteinuria, and kidney function (defined as a 25% change from baseline in reciprocal SCr levels) • Treatment-emergent adverse events • Liver function testing (including total protein, albumin, total bilirubin, direct bilirubin, lactate dehydrogenase, alkaline phosphatase, AST, ALT) • Physical examinations and vital signs, 12-lead electrocardiograms, ECG, and multigated acquisition scan • Pharmacokinetics were also assessed from blood samples collected predose (0 hours) and postdose on days 1 (1, 3, 5, and 24 hours) and 15 (1–4, 6, 8, and 24 hours)
Notes	Additional information • Protocol registration/published: not reported • Ethics: "The protocol was approved by each site's ethics committee; informed consent was obtained in compliance with the Declaration of Helsinki." • Declaration of interest/disclosures: "V.T. was a paid consultant of Pfizer Inc at the time of this study; K.C., Y.P., I.B., and A.S. report no disclosures; M.S., R.L., J.H.W., and S.A. are employees of Pfizer Inc. M.L. was an employee of Pfizer Inc at the time of this study" • Funding declared: "This study was sponsored by Pfizer Inc. Editorial support for this manuscript was provided by Simon J. Slater, PhD, of Complete Healthcare Communications, LLC, and was funded by Pfizer Inc."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were stratified at randomization by baseline TKV 750–1500ml versus >=1500 ml (central imaging reader) and were concurrently randomized (1:1:1) to bosutinib 200, 400 mg/d, or placebo" Comment: insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Independent data board involved in monitoring the trial but no information on their assessment
Incomplete outcome data (attrition bias) All outcomes	High risk	44% did not complete the intital treatment period. Similar number across groups
Selective reporting (reporting bias)	High risk	Quote: "The external data monitoring committee recommended a protocol amendment (October 7, 2013) to reduce bosutinib dose from 400 to 200 mg/d. Patients were then divided between the original bosutinib 400-, 200-mg/d, and

Tesar 2017 *(Continued)*

		placebo groups and an additional mixed 400/200-mg/d group consisting of all patients originally randomized to 400 mg/d but reducing to 200 mg/d" Comment: concerns about changing of endpoints and the influence on results findings
Other bias	Unclear risk	Sponsored by Pfizer Inc. not obvious how funder may have influenced trial endpoint switching

Uchiyama 2021

Study characteristics	
Methods	Study design • Open-label cross-over RCT • Duration of study: July 2019 to September 2020 • Follow-up: 28 weeks • ADPKD assessment: Japan-specific diagnostic criteria • Country: Japan • Setting: single centre (Nephrology Department of the Japanese Red Cross Medical Center in Tokyo)
Participants	Study characteristics • Inclusion criteria: stable patients > 20 years; ADPKD; receiving high-dose tolvaptan (> 60 mg/d) whose disease was complicated with hypertension (home BP > 135/85 mm Hg, office BP > 140/90 mm Hg) or those currently using antihypertensive drugs, considering that trichlormethiazide is primarily used to treat hypertension • Exclusion criteria: uncontrolled BP (> 180/110 mm Hg or < 100/60 mm Hg); apparent electrolyte disturbance that may worsen by trichlormethiazide use (serum sodium < 135 mEq/L or serum potassium < 3.5 mEq/L); symptomatic coronary artery disease or cerebrovascular disease within 3 months before recruitment; current uncontrolled heart failure (NYHA classes III and IV); symptomatic and fatal arrhythmia; and significant valvular heart disease; allergic to any of the thiazide drugs Baseline characteristics • Number: 10 • Median age (range): 49 years (44 to 71) • Gender (M/F): 4/6 • Smoking: 0 • Median tolvaptan dose (range): 120 mg (90 to 120) • Mean SBP/DBP ± SD (years): 129.8 ± 11.7/81.2 ± 12.4 • Median BMI (range): 24.1 (22.6 to 27.5) • Mean eGFR ± SD: 39.3 ± 20.7 mL/min/1.73 m^2 • Median UPCR (range): 0.15 g/g (0.10 to 0.30)
Interventions	Intervention group • Trichlormethiazide: 2 or 4 mg when the patient's GFR was ≥ 30 or < 30 mL/min/1.73 m^2, respectively, with a target BP of 110/70 to 130/80 Control group • Standard care Duration of treatment; washout period

Uchiyama 2021 *(Continued)*

- 12 weeks; 4 weeks

Co-interventions

- Antihypertensive: generally, a RAS inhibitor and/or a CCB was used as the antihypertensive drug

Outcomes	Reported outcome • Osmolality of 24-h urine • Health-related QoL • Rate of decline in kidney function • Serum/urinary electrolytes • Serum/urinary biomarkers associated with CKD • ADPKD progression • Office BP • Pharmacokinetics were also assessed from blood samples collected predose (0 hours) and postdose on days 1 (1, 3, 5, and 24 hours) and 15 (1–4, 6, 8, and 24 hours)
Notes	Additional information • Protocol registration/published: not reported • Ethics: "The study protocol was reviewed and approved by the ethics committee of the Japanese Red Cross Medical Center (approval number: 979) and adhered to the principles of the Declaration of Helsinki. Written informed consent was obtained from all participant" • Declaration of interest/disclosures: "The authors declare no competing interests." • Funding declared: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "block randomization with a block size of two using computer-generated random numbers" Comment: appropriate methods with no concerns
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "participants and CKD doctors were not blinded to group assignment considering that control of BP during the study period was extremely important, i.e., without knowing the allocation, a transient decrease or increase in BP was inevitable during 4 weeks before the first follow-up of each trial when transitioning between the trial phases of treatment with and without trichlormethiazide. In our short-term pilot study, we observed that variations in BP during the short period of 4 weeks might affect patient outcomes, including urinary volume, Uosm, and ADPKD-associated parameters. Therefore, a blinded study design was not approved by the ethics committee in the present study" Comment: open-label but justification provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Independent data board involved in monitoring the trial but no information on their assessment
Incomplete outcome data (attrition bias)	Low risk	All participants completed the trial

Uchiyama 2021 *(Continued)*

All outcomes

Selective reporting (reporting bias)	Low risk	No obvious concerns with outcomes reported as indicated in the trial registration and protocol publication
Other bias	Low risk	No other concerns identified

Ulusoy 2010

Study characteristics

Methods	Study design • Parallel RCT • Duration of study: not reported • Follow-up: 12 months • ADPKD assessment: Echo • Country: Turkey • Setting: single centre
Participants	Study characteristics • Inclusion criteria: stage 1-2 hypertensive ADPKD patients (according to the JNC VII classification); eGFR > 30 mL/min/1.73 m^2; 18 to 70 years • Exclusion criteria: other kidney illness or comorbidity, including DM; CHF; liver function failure; pregnancy, lactation; using anti-arrhythmic; oral contraceptive use; immunosuppressive and steroid use; psychiatric disorders Baseline characteristics • Number: intervention group (19); control group (13) • Mean age ± SD (years): intervention group (51 ± 10); control group (48 ± 13) • Sex (M/F): intervention group (6/13); control group (7/6)
Interventions	Intervention group • Losartan: 50 to 100 mg/d Control group • Ramipril: 2.5 to 10 mg/d Duration of intervention • 12 months
Outcomes	Reported outcomes • BP • LVMI • Kidney function
Notes	Additional information • Funding source: not reported

Risk of bias

Ulusoy 2010 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

van Dijk 2001

Study characteristics	
Methods	Study design • Double-blind, cross-over RCT • Duration of study: not reported • Follow-up: 4 weeks • ADPKD assessment: Echo • Country: the Netherlands • Setting: single centre
Participants	Study characteristics • Inclusion criteria: GFR > 50 mL/min; no medications; normal sodium diet • Exclusion criteria: not reported Baseline characteristics • Number: 10 • Mean age ± SD: 35 ± 13 years • Sex (M/F): 6/4
Interventions	Intervention group • Simvastatin: 40 mg/d Control group

van Dijk 2001 *(Continued)*

	• Placebo Duration of intervention • 4 weeks
Outcomes	Reported outcomes • Kidney blood flow • Vascular reactivity • Kidney function • Cholesterol
Notes	Additional information • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

van Dijk 2003

Study characteristics

Methods	Study design • Parallel, partly double-blind/ partly open-label RCT • Duration of study: January 1994 to September 1996 • Follow-up: 36 months • ADPKD assessment: Echo • Country: the Netherlands

van Dijk 2003 *(Continued)*

- Setting: multicentre (number of sites not reported)

Participants	Study characteristics • Inclusion criteria: ADPKD patients aged 18 to 70 years; SCr < 225 mmol/L • Exclusion criteria: presence of other kidney disease (excluding nephrolithiasis); DM; CHF, MI, CVA in the past 6 months; PVD; pregnancy; significant hepatic dysfunction; chronic (> 3 months) use of immunosuppressants, NSAIDs, uricosurics and levodopa; previous adverse reactions to ACEi Baseline characteristics • Number: intervention group (45); control group (44) • Mean age ± SD (years): normotensive intervention group (36 ± 2); normotensive control group (37 ± 2); hypertensive intervention group (40 ± 3); hypertensive control group (33 ± 3) • Sex (M/F): intervention group (16/29); control group (19/25)
Interventions	Intervention group • Enalapril: 5 to 10 mg/d in normotensive patients, up to 20 mg/d in hypertensive patients Control group • Normotensive patients: placebo • Hypertensive patients: up to 100 mg/d atenolol Duration of intervention • 36 months
Outcomes	Reported outcomes • BP • Measured kidney function (by inulin clearance)
Notes	Additional information • 61 normotensive and 28 hypertensive ADPKD patients were included. The normotensive group participated in a randomised double-blind placebo-controlled study, using enalapril. The hypertensive group was randomised for open-label treatment with enalapril or the beta blocker atenolol • Funding source: "Enalapril and placebo were provided by Merck, Sharp and Dohme"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization was performed for each patient in the pharmacy of our hospital"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The normotensive group (72) participated in a randomised double-blind placebo-controlled study while the hypertensive group (35) was randomised for open-label
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement

van Dijk 2003 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	10/72 normotensive and 7/35 hypertensive patients did not complete the 36 months follow-up and were not included in the final analysis. Complete data were available in 89/106 (83.9%) patients
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Quote: "Enalapril and placebo were provided by Merck, Sharp and Dohme" Otherwise unclear on sponsors and their role

Vendramini 2021

Study characteristics	
Methods	Study design • Parallel, placebo-controlled RCT • Study dates: not reported • Follow-up: 3 months • ADPKD assessment: Pei criteria • Country: Brazil • Setting: single centre (outpatient Polycystic Kidney Disease Unit of the Universidade Federal de Sao Paulo)
Participants	Study characteristics • Inclusion criteria: ADPKD • Exclusion criteria: age < 18 years; serum calcium >10.5 md/dL; current/past use of calcium or vitamin D Baseline characteristics • Number: intervention group (21); control group (21) • Mean age ± SD (years): intervention group (38.3 ± 12.3); control group (44.9 ± 10.5) • Gender (M/F): intervention group (10/11); control group (6/15) • Hypertension: intervention group (12); control group (17) • Diabetes: intervention group (1); control group (1) • Mean eGFR ± SD (mL/min/1.73 m^2): intervention group (79.3 ± 38.2); control group (71.3 ± 30.8) • Median htTKV, IQR (mL/min): intervention group (817, 331 to 1206); control group (718, 317 to 1094) • Mean time since diagnosis ± SD (years): intervention group (10.5 ± 6.4); control group (8.10 ± 6.3) • Ethnicity (Afro-Brazilians/Caucasians): intervention group (5/16); control group (1/20)
Interventions	Intervention group • Cholecalciferol (Vitamin D supplementation): single oral monthly dose (200,000 IU in the 1st and 2nd months and 50,000 UI in the 3rd month) • Duration: 3 months Control group • Placebo • Duration: 12 months Co-interventions or additional treatments • All patients were instructed to use sunscreen (SPF 30) during the study period

Vendramini 2021 *(Continued)*

Outcomes	Reported outcomes • SBP and DBP • Inflammatory markers (IL-6, IL-10, TNG, FNK-B) • Vitamin D (25(OH)D) • Vitamin D regulatory enzymes (CYP27B1, CYP24A1)
Notes	Additional information • Ethics: "The study was reviewed and approved by the Ethics Advisory Committee of the Universidade Federal de Sao Paulo, and each patient signed the informed consent form." • Declaration of interest/disclosures: Not reported • Funding declared: "Fundaçao de Amparo a Pesquisa do Estado de Sao Paulo (FAPESP 2012/09219–2), Conselho Nacional de Desenvolvimento Científico e Tecnologico (CNPq), Grant 309045/2018–5 (I.P.H.), Coordenaçao de Aperfeiçoamento Pessoal de Nível Superior (CAPES) and Fundaçao Oswaldo Ramos - Hospital do Rim (HRIM)"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 patients lost to follow-up from both arms - unlikely to cause concern
Selective reporting (reporting bias)	Low risk	No obvious concerns with outcomes reported as indicated in the trial registration
Other bias	Low risk	No other concerns identified

Walz 2010

Study characteristics

Methods	Study design • Parallel, double-blind RCT • Duration of study: December 2006 to September 2007 • Follow-up: 24 months • ADPKD assessment: magnetic nuclear imaging

Walz 2010 *(Continued)*

- Country: Germany
- Setting: multicentre (24 sites)

Participants	Study characteristics • Inclusion criteria: clinical diagnosis of both ADPKD and CKD stage 2 or 3 or CKD stage 1; estimated single kidney volume > 1000 mL • Exclusion criteria: subarachnoid bleeding; severe infection; life-threatening urinary tract or cyst infection; severe liver disease, cancer, hypercholesterolaemia, hypertriglyceridaemia, thrombocytopenia; medical condition necessitating long-term anticoagulation therapy Baseline characteristics • Number: intervention group (213); control group (216) • Mean age ± SD (years): intervention group (44 ± 10); control group (44 ± 10) • Sex (M/F): intervention group (109/104); control group (100/116)
Interventions	Intervention group • Everolimus: 2.5 mg twice/d Control group • Placebo Duration of intervention • 24 months
Outcomes	Reported outcomes • Kidney volume • Cyst volume • Parenchymal volume • Kidney function • Urinary protein excretion • BP • Safety • Death
Notes	Additional information • Funding source: "Supported by Novartis"; "an academic executive committee in collaboration with the medical and statistical staff of Novartis (the sponsor) designed the study. Data collection and management were the responsibility of the sponsor"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Low risk	1:1 ratio
Blinding of participants and personnel (performance bias)	Low risk	Double-blind study

Walz 2010 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	5/213 and 6/216 patients in the intervention and control groups respectively withdrew
Selective reporting (reporting bias)	Low risk	All defined outcomes were reported
Other bias	Unclear risk	Sponsor: Novartis Quote: "Data collection and management were the responsibility of the sponsor"

Watson 1999

Study characteristics	
Methods	Study design • Parallel RCT • Duration of study: not reported • Follow-up: 36 months • ADPKD assessment: Echo • Country: UK • Setting: not reported
Participants	Study characteristics • Inclusion criteria: not reported • Exclusion criteria: not reported Baseline characteristics • Number (overall): 54 • Mean age ± SD (years): not reported • Sex (M/F): not reported
Interventions	Intervention group • Atenolol: dosage not reported Control group • Enalapril: dosage not reported Duration of intervention • 36 months
Outcomes	Reported outcomes • BP

Watson 1999 *(Continued)*

	• Kidney function
Notes	Additional information • Abstract-only publication; numbers of patients in both groups not provided • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Zeltner 2008

Study characteristics

Methods	Study design • Parallel, double-blind RCT • Duration of study: 1998 to 2000 • Follow-up: 36 months • ADPKD assessment: Echo • Country: Germany • Setting: single centre
Participants	Study characteristics • Inclusion criteria: confirmed diagnosis of ADPKD; aged 18 to 65 years; hypertension (casual BP ≥ 140/90 mm Hg and/or presence of antihypertensive medication); SCr ≤ 4.0 mg/dL • Exclusion criteria: SCr > 4.0 mg/dL; MI or CVA in the past 12 months; known intolerance to study medication; pregnancy or females without contraception; severe hepatic disease; immunosuppressant or NSAID use; CHF; alcohol abuse or consumption of narcotics; malignant disease; noncompliance

Zeltner 2008 *(Continued)*

	Baseline characteristics • Number: intervention group (17); control group (20) • Mean age ± SD (years): intervention group (41 ± 22); control group (41 ± 19) • Sex (M/F): intervention group (10/7); control group (7/13)
Interventions	Intervention group • Ramipril: 2.5 to 5 mg/d Control group • Metoprolol: 50 to 100 mg/d Duration of intervention • 36 months
Outcomes	Reported outcomes • Combined endpoint of doubling SCr, 50% reduction in GFR, or the need for KRT • SCr • UPE • LVMI
Notes	Additional information • Funding source: "This research was supported by Astra-Zeneca who provided the study medication"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors (echo-data) were blinded to patients
Incomplete outcome data (attrition bias) All outcomes	High risk	7/23 (30.4%) and 2/23 (8.6%) of patients in the intervention and control group respectively withdrew
Selective reporting (reporting bias)	Low risk	All defined outcomes were reported
Other bias	Unclear risk	Quote: "This research was supported by Astra-Zeneca who provided the study medication"

ACEi: angiotensin-converting enzyme inhibitor; ADPKD: autosomal dominant polycystic kidney disease; AKI: acute kidney injury; ARB: angiotensin receptor blockers; AST: aminotransferase; AVP: arginine vasopressin; BMI: body mass index; BP: blood pressure; CHF: congestive heart failure; CrCl: creatinine clearance; CVA: cerebrovascular accident; CVD: cardiovascular disease; DBP: diastolic BP; DM: diabetes mellitus; ECG: echocardiography; ESKD: end-stage kidney disease; eGFR: estimated GFR; GFR: glomerular filtration rate; htTKV: height-adjusted TKV; HbA1c: glycated haemoglobin; HD: haemodialysis; IHD: ischaemic heart disease; IM: intramuscular; IQR: interquartile range; IR: immediate release; ITT: intention-to-treat; LDL: low-density lipoprotein; LVMI: KRT: kidney replacement therapy; left ventricular mass index; M/F: male/female; MAP: mean arterial pressure; MDRD: Modification of Diet in Renal Disease; mGFR: measured GFR; MI: myocardial infarction; MR: modified release; MRI: magnetic resonance imaging; mTOR: mammalian target of rapamycin; NMR: nuclear magnetic resonance; NSAID: nonsteroidal anti-inflammatory drug; NYHA: New York Heart Association; PLD: polycystic liver disease; PP: per protocol; PVD: peripheral vascular disease; QoL: quality of life; RAS: renin-angiotensin system; RCT: randomised control trial; SBP: systolic BP; SC: subcutaneous; SCr: serum creatinine; SD: standard deviation; TKV: total kidney volume; UACR: urinary albumin-creatinine ratio; UAE: urinary albumin excretion; ULN: upper limit of normal; UPE: urinary protein excretion; UTI: urinary tract infection; WCC: white cell count

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Davis 2018	Wrong population: transplant recipients
Dinh 2023	Wrong population: healthy volunteers
Doulton 2006	Outcomes of interest not reported
Elue 2018	Wrong intervention: smart bottle adherence
FALCON 2021	Study terminated due to discontinuation of all bardoxolone CKD programs
Hogan 2016	Wrong population: not all ADPKD
ISRCTN57653760	Study terminated: halted in 2008 due to lack of funding; no results published
MANGROVE 2022	Study terminated April 2023
Nakamura 2005a	Outcomes of interest not reported
Naver 2023	Wrong study design: before and after water intake
NCT05281328	Wrong population: PLD with or without ADPKD

ADPKD: autosomal dominant polycystic kidney disease; CKD: chronic kidney disease; PLD: polycystic liver disease; RCT: randomised controlled trial

Characteristics of studies awaiting classification *[ordered by study ID]*

BEET-PKD 2022

Methods	Study design • Parallel, double-blind, placebo-controlled RCT • Duration of study: May 2022 to March 2023 • Follow-up: 4 weeks • ADPKD assessment: not reported • Country: Australia • Setting: single centre
Participants	Study characteristics

BEET-PKD 2022 *(Continued)*

	• Inclusion criteria: ADPKD; > 18 years; eGFR > 30 mL/min/1.73 m^2; treatment with at least one anti-hypertensive • Exclusion criteria: inability to provide informed consent; labile, unstable, uncontrolled hypertension and/or changes in BP treatment 28 days prior to the screening visit; non-compliance with study procedures and/or daily BP measurements during the screening period; medical conditions or treatments that might interfere with the generation of NO metabolites or the primary endpoint (e.g. nitrate drugs; cigarette smoking; unwilling to stop using antiseptic mouthwash; severe, uncontrolled hypercholesterolaemia; pregnancy or post-partum and lactating); any serious or other medical conditions that might interfere with follow-up or stability of blood pressure (e.g. current active malignancies; uncontrolled DM with elevated HbA1c > 10%); dislike of taste of beetroot juice; allergy to beetroot; enrolled in other clinical trials • Planned enrolment: 60
Interventions	Intervention group • Beetroot juice: 70 mL/day (400 mg nitrate) Control group • Nitrated-deplete beetroot juice: 700 mL/day Duration of intervention • 4 weeks
Outcomes	Planned outcomes • BP • UACR • Serum nitrate/nitrite • Asymmetric dimethylarginine
Notes	Additional information • Current status: complete; protocol data only available • Funding: "This study was funded by a grant from PKD Australia to GR. PS was supported by an ICPMR Jerry Koutts Scholarship. The funding bodies have no role in the study design, execution, analyses, interpretation of the data, or decision to submit results"

IMPROVE-PKD 2023

Methods	Study design • Parallel RCT • Duration of study: not reported • Follow-up: not reported • ADPKD assessment: not reported • Country: France • Setting: not reported
Participants	Study characteristics • Inclusion criteria: ADPKD • Exclusion criteria: not reported Baseline characteristics • Number: intervention group (9); control group (10)

IMPROVE-PKD 2023 *(Continued)*

	• Mean age ± SD (years): not reported • Gender (M/F): not reported
Interventions	Intervention group • Rotigotine: 2 mg/day Control group • Standard care Duration of treatment • 2 months
Outcomes	Planned/reported outcomes • Radial artery endothelium-dependent flow-mediated dilatation • SCr • Copeptin
Notes	Abstract-only publications; no data available

KETO-ADPKD 2023

Methods	Study design • Parallel RCT • Duration of study: 10 January 2021 to 12 August 2022 • Follow-up: 3 months • ADPKD assessment: genetics and imaging • Country: Germany • Setting: single centre
Participants	Study design • Inclusion criteria: ADPKD patients ≥ 18 and ≤ 60 years; indicators of rapid progression (Mayo class 1C-E, truncating PKD1 mutation, onset of arterial hypertension/urological symptoms < 35 years; first- or second-degree family members reaching ESKD at < 60 years, eGFR loss > 2.5 mL/min/y, PROPKD score > 6); CKD-stages G1-3 as determined by eGFR; written informed consent • Exclusion criteria: BMI ≤ 18.5 kg/m^2 or ≥ 35 kg/m^2; exposure to a ketogenic diet (classical ketogenic diet or modified Atkins)for more than 2 weeks within the last 6 months; participation in a weight-loss program within the last 6 months based on patient history; vegetarian or vegan lifestyle; current treatment (or within the last 6 months) with tolvaptan or a somatostatin analogue; inability to give informed consent; conditions prohibiting the use of a ketogenic diet (liver damage, pancreatic failure, pyruvate-carboxylase deficiency, defects in fatty acid oxidation/gluconeogenesis/ketolysis/-neogenesis, hyperinsulinism); diagnosis with any disorder of fatty acid metabolism; eating disorder based on patient history; alcohol abuse; type 1 DM; insulin-dependent type 2 DM; contraindication regarding the MRI exam; may be at risk from the blood loss due to scheduled blood draws at the discretion of the physician; pregnancy or breastfeeding; absence of safe contraceptive measures or non-occurrence of menopause (in women); participation in other interventional trials; in a dependency/employment relationship with the investigators; accommodation in an institution by judicial or administrative order • Actual enrolment: 63
Interventions	Intervention group 1 • Classical ketogenic diet for 3 months

KETO-ADPKD 2023 *(Continued)*

	Intervention group 2 • Water fasting on 3 consecutive days within the first 14 days of each of the 3 months • On all other days of the intervention period they are allowed to eat ad libitum Control group • Allowed to eat ad libitum, but will be advised that low salt intake (< 5 to 7 g/day) and sufficient fluid intake (> 3 L/day)
Outcomes	Planned outcomes • Adherence • Patient-reported feasibility • TKV • BMI • Insulin sensitivity • CRP • QoL • Diet-related emergent adverse events
Notes	Current status: completed, no published results

Nowak 2021

Methods	Study design • Parallel, open-label RCT • Duration of study: June 2018 to October 2020 • Follow-up: 1 year • ADPKD assessment: Pei-Ravine criteria • Country: USA • Setting: single centre
Participants	Study characteristics • Inclusion criteria: 18 to 65 years; ADPKD; BMI 25 to 45 kg/m^2; normal to mildly declined kidney function with an eGFR ≥ 30 mL/min/1.73 m^2; access to the internet with video chat capabilities; no plans for extended travel (> 2 weeks) during the 3-month intensive period; not currently participating in another interventional study or weight loss program; ability to provide informed consent • Exclusion criteria: DM; current nicotine use or history of use in the past 12 months; alcohol or substance abuse (self-report or undergoing treatment); history of hospitalisation or major surgery within the last 3 months; untreated dyslipidaemia; uncontrolled hypertension (BP > 160/90 mm Hg); pregnancy, lactation, or unwillingness to use adequate birth control; cardiovascular disease, peripheral vascular disease, cerebrovascular disease, significant pulmonary or gastrointestinal disease, cancer (within the last 5 years, except skin cancer or other cancers considered cured with excellent prognosis); abnormal resting electrocardiogram (ECG); regular use of prescription or over-the-counter medications that may affect weight, appetite, food intake, or energy metabolism; regular use of obesity pharmacotherapeutic agents within the last 6 months; history of clinically diagnosed eating disorder including anorexia nervosa, bulimia, binge-eating disorder; weight loss > 5% in past 3 months for any reason except post-partum weight loss; weight gain > 5% in past 3 months requires assessment by PI to determine reason for weight gain and if it is appropriate for the subject to participate in the study; untreated hyper- or hyperthyroidism; current severe depression or history of severe depression within the previous year; history of other significant psychiatric illness which in the opinion of the Study MD would interfere with ability to adhere to dietary interventions; inability to cooperate with/clinical contraindication for MRI

Nowak 2021 *(Continued)*

	• Enrolment: 29
Interventions	Intervention group 1 • Caloric restriction Intervention group 2 • Intermittent fasting
Outcomes	Planned outcomes • Feasibility of retaining participants • Percent change from baseline body weight (Weight Loss) • Safety and tolerability, measured as adverse events • QoL: 12 weeks and 1 year • TKV
Notes	Additional information • Study completed October 2020; abstract-only publication available

Rastogi 2023

Methods	Study design • Parallel, phase 2 RCT • Duration of study: not reported • Follow-up: 24 months (planned) • ADPKD assessment: Ravine criteria • Country: USA • Setting: multicentre (number of sites not reported)
Participants	Study characteristics • Inclusion criteria: ADPKD; 16 to 60 years; eGFR 25 to 90 mL/min/1.73 m2; TKV: 18 to 35 years ≥ 500 mL, 36 to 49 years ≥ 700 mL, 50 to 60 years ≥ 900 mL; • Exclusion criteria: not reported Baseline characteristics • Number: 78 • Median age: 46 years • Gender (M/F): 36/42
Interventions	Intervention group • KD019: 50 mg/day Control group • Placebo
Outcomes	Planned/reported outcomes • htTKV • TEAEs • Death

Rastogi 2023 *(Continued)*

	• eGFR
Notes	Additional information • Abstract-only publication; data cannot be meta-analysed • Funding: not reported

Staged-PKD 2020

Methods	Study design • Parallel; double-blind, placebo-controlled RCT • Duration of study: 4 October 2018 to 3 August 2021 • Follow-up: 24 months • ADPKD assessment: Pie criteria • Countries: international • Setting: multicentre (95 sites)
Participants	Study characteristics • Inclusion criteria: ADPKD; 18 to 50 years; eGFR between 45 and 89.9 mL/min/1.73 m^2; able to read, comprehend, and respond to the study questionnaires; voluntary written informed consent before performance of any study-related procedures not part of standard medical care; no access to tolvaptan at the time of study start or tolvaptan was not indicated for treatment of participant according to treating physician; not pregnant; female participants of childbearing potential and male participants must have had agreed to practice true abstinence in line with their preferred and usual lifestyle or to use double-contraceptive methods for the entire duration of the study and for at least 6 weeks for females and 90 days for males following their last dose of study drug • Exclusion criteria: SBP > 160 mm Hg; administration within 3 months prior to the screening visit of tolvaptan or other PKD-modifying agents (somatostatin analogues); participation in another investigational interventional study or use of IMP within 3 months or 5 half-lives; positive result for hepatitis B surface antigen, anti-hepatitis C virus antibodies, anti HIV1 and anti-HIV2 Ab; history of drug and/or alcohol abuse within the past year prior to the screening visit; history of alcohol dependence within the 5 years prior to the screening visit; scheduled for in-patient hospitalisation including elective surgery, during the study; clinically significant, uncontrolled medical condition that, in the opinion of the investigator, would put the safety of the participant at risk through participation, effect the efficacy or safety analysis if the condition exacerbated during the study, or that might significantly interfere with study compliance; in the opinion of the investigator, was unable to adhere to the requirements of the study or unable to undergo study assessments; any country-related specific regulation that would prevent the participant from entering the study; did not adhere to treatment < 70% compliance rate in the run-in; according to World Health Organization (WHO) Grading, a cortical cataract ≥ one-quarter of the lens circumference or a posterior subcapsular cataract ≥ 2 mm or nuclear cataracts; receiving potentially cataractogenic medications, including a chronic regimen (more frequently than every 2 weeks) of any route of corticosteroids or any medication that might cause cataract; had received strong or moderate inducers or inhibitors of CYP3A4 within 14 days or 5 half-lives, whichever was longer, prior to randomisation including the consumption of grapefruit, grapefruit juice, or grapefruit containing products within 72 hours of starting venglustat administration; pregnant or lactating; Liver enzymes or total bilirubin > 2 times the ULN unless the participant had the diagnosis of Gilbert syndrome severe depression and/or a history of a major affective disorder within 1 year of the screening visit; known hypersensitivity to venglustat or any component of the excipients • Enrolment: 478
Interventions	Intervention group • Venglustat: 8 mg/d

Staged-PKD 2020 *(Continued)*

	Control group • Placebo Duration of intervention • 24 months
Outcomes	Planned outcomes • Annualized slope of change in TKV to 18 months • Annualized slope of change in eGFR to 24 months • Pain • Fatigue • Pharmacokinetics of venglustat • Treatment-emergent adverse events • Haematological abnormalities • Clinical chemistry abnormalities • Urinalysis
Notes	Additional information • Study completed 3 October 2021; abstract-only results available

Trillini 2023

Methods	Study design • Pilot, placebo-controlled, cross-over RCT • Duration of study: December 2018 to December 2023 • Follow-up: 4 weeks • ADPKD assessment: ultrasound • Country: Italy • Setting: single centre
Participants	Study characteristics • Inclusion criteria: >18 years; clinical and ultrasonographic diagnosis of ADPKD; SCr < 1.0 mg/dL (for men) and < 1.2 mg/dL (for women) and changes in serum creatinine (and creatinine clearance when available) < 30% over the last six months; CrCl > 80 mL/min/1.73m^2 measured one to two weeks apart during the pre-screening period; • GFR ≥ 80 mL/min/1.73 m^2 at screening and baseline evaluations; TKV ranging between 1000 and 2000 mL at screening (by ultrasound imaging) and at baseline (by MRI) evaluations; female participants must be of non-childbearing potential or must agree to abstinence or use a highly effective form of contraception; written informed consent • Exclusion criteria: concomitant systemic, renal parenchymal or urinary tract disease; diabetes; overt proteinuria; abnormal urinalysis suggestive of concomitant, clinically significant glomerular disease, urinary tract lithiasis, infection or obstruction, biliary tract lithiasis or obstruction; haemorrhagic or complicated cysts which might acutely affect kidney function and volumes; QT-related ECG abnormalities; cancer and major systemic diseases that could prevent completion of the planned follow-up or interfere with data collection or interpretation; hypersensitivity to the IMP active substance or to any of the excipients or to benzazepine or benzazepine derivatives; concomitant treatment with drugs that may affect glomerular haemodynamics during the three months before the beginning of the study; elevated liver enzymes and/or signs or symptoms of liver injury prior to initiation of treatment that meet the requirements for permanent discontinuation of tolvaptan; anuria, volume depletion and hypernatraemia; cannot perceive or respond to

Trillini 2023 *(Continued)*

	thirst; ferro-magnetic prosthesis, aneurysm clips, severe claustrophobia or any other contraindication to MRI evaluation; psychiatric disorders and any condition that could prevent full comprehension of the purposes and risks of the study; pregnant or lactating; participation in another interventional clinical trial within the 4 weeks prior to screening Baseline characteristics • Number: intervention group (9); control group (10) • Mean age ± SD (years): intervention group (44 ± 12); control group (38 ± 12) • Gender (M/F): intervention group (4/5); control group (6/4)
Interventions	Pre-intervention run-in period • All patients received 4 weeks of tolvaptan. The dose started at 45/15 mg (morning/afternoon). Dose up-titrated every 2 days to 60/30 mg, then 90/30 mg according to tolerability Intervention group • Tolvaptan: maintenance dose achieved at the end of titration period for 4 weeks • Octreotide (long-acting release): 2 x 20 mg IM injections at the start of the treatment period Control group • Tolvaptan: maintenance dose achieved at the end of titration period for 4 weeks • Placebo: 2 x 20 mg IM injections at the start of the treatment period Washout period • 2 weeks
Outcomes	Planned/reported outcomes • GFR • TKV • Blood pressure • QoL • Biochemistry
Notes	Additional information • Funding: "Otsuka Pharmaceutical Italy SRL funded the study but was not involved in study conduction and data analyses and interpretation."

WATER 2024

Methods	Study design • Cross-over RCT • Duration of study: 2020 to 2022 • Follow-up: 8 weeks • ADPKD assessment: Ravine criteria • Country: the Netherlands • Setting: single centre
Participants	Study characteristics • Inclusion criteria: ≥ 18 years; diagnosis of ADPKD; on a stable, highest tolerable dose of tolvaptan; eGFR > 30 mL/min/1.73 m^2; were able to comply with the recommended diet

WATER 2024 *(Continued)*

	• Exclusion criteria: conditions that, in the opinion of the investigator, may present a safety risk, patients unlikely to comply with the trial procedures; pregnant or breastfeeding; BP > 160/100 mm Hg; chronic use of systemic corticosteroids, diuretics, mineralocorticoid receptor antagonists, sodium-glucose cotransporter 2 inhibitors or non-steroidal anti-inflammatory drugs; DM and diabetes insipidus; other medication or diseases likely to confound endpoint assessments Baseline characteristics • Number: 12 • Mean age ± SD: 49 ± 8 years • Gender (M/F): 3/9
Interventions	Intervention group 1 • Low salt/low protein Intervention group 2 • Low salt/regular protein Intervention group 3 • Regular salt/low protein Intervention group 4 • Regular salt/regular protein Duration of treatment • 2 weeks • Washout period: not reported
Outcomes	Planned/reported outcomes • 24-hour urine volume • Copeptin • GFR • MAP
Notes	Additional information • Funding: "This study was sponsored by Dutch Kidney Foundation grant 18OKG04. The sponsor had no role in the design, analysis or writing of this study."

ADPKD: autosomal dominant polycystic kidney disease; BMI: body mass index; BP: blood pressure; CrCl: creatinine clearance; DM: diabetes mellitus; GFR: glomerular filtration rate; htTKV: height-adjusted TKV; RCT: randomised controlled trial; SCr: serum creatinine; TEAE: treatment-emergent adverse events; TKV: total kidney volume; UPE: urinary protein excretion

Characteristics of ongoing studies *[ordered by study ID]*

CTRI/2022/05/042904

Study name	A clinical trial to study effect of a drug metformin in slowing progression of autosomal dominant polycystic kidney disease
Methods	Study design • Parallel RCT • Duration of study: from June 2022 • Follow-up: 6 months

CTRI/2022/05/042904 *(Continued)*

- ADPKD assessment: updated Ravine criteria
- Country: India
- Setting: not reported

Participants	Study characteristics • ADPKD; eGFR ≥ 45 mL/min/1.73 m^2; controlled BP < 130/80 on a stable regimen of antihypertensive drugs • Exclusion criteria: ADPKD patients likely rapid disease progression at baseline; DM; intolerance to metformin; uncontrolled hypertension; pregnancy / lactation; systemic diseases which contribute to kidney disease other than hypertension; acute or chronic disease causing tissue hypoxia; systemic infection; essential drugs with drug interactions with metformin including nifedipine and furosemide • Planned enrolment: 40
Interventions	Intervention group • Metformin: maximum dose 2 g/day Control group • Standard of care: fluid intake >3 L/d; BP control Duration of treatment • 6 months
Outcomes	Planned outcomes • Change to height-adjusted TKV • Adherence • Association of baseline copeptin levels with disease progression • BP • UPE • Annualised slope of eGFR
Starting date	Planned first enrolment: 1 June 2022
Contact information	Jasmine Sethi Email: jasmine227021@gmail.com
Notes	Current status: not yet recruiting

CTRI/2022/09/045945

Study name	Tolvaptan versus water therapy in autosomal dominant polycystic kidney disease
Methods	Study design • Pilot, parallel RCT • Duration of study: from October 2022 • Follow-up: 1 year • ADPKD assessment: Mayo class 1C, 1D, 1E • Country: India • Setting: not reported

CTRI/2022/09/045945 *(Continued)*

Participants	Study design • Inclusion criteria: eGFR 60 to 70 mL/min/1.73 m^2; patients with estimated GFR of 25 to 60 ml/min/1.73 m^2); ADPKD Mayo class 1C, 1D, 1E (as per study definitions given below) with eGFR of > 25 mL/min/1.73 m^2 • Exclusion criteria: imaging suggestive of atypical ADPKD; liver disease other than presence of cystic liver disease consistent with ADPKD; elevation of liver enzymes in the pre-randomisation period with serum transaminases 3 times ULN, elevations in the total bilirubin 2 times ULN; requiring diuretic therapy; severe cardiopulmonary disease preventing high water intake; DM • Planned enrolment: 64
Interventions	Intervention group • High water therapy: water intake to achieve target serum osmolality Control Intervention • Tolvaptan: 30 mg and 15 mg in the morning and evening, respectively. Doses will be increased weekly by 15 mg in the morning and evening to a maximum of 90 mg and 30 mg, according to patient-reported tolerability and achievement of target serum osmolality
Outcomes	Planned outcomes • Change in TKV at 1 year • Genetic analysis of patients • Change in eGFR • Average urine osmolality, copeptin levels • Adverse effects
Starting date	Planned start date: 1 October 2022
Contact information	DR SMITA DIVYAVEER Email: divyaveer.ss@gmail.com
Notes	Current status: not yet recruiting

Gan 2019

Study name	*Yinang* formulation versus placebo granules as a treatment for chronic kidney disease stages III–IV in patients with autosomal dominant polycystic kidney disease: study protocol for a double-blind placebo-controlled randomized clinical trial
Methods	Study design • Parallel, double-blind RCT • Duration of study: 24 weeks • Follow-up: 48 weeks • ADPKD assessment: family history, imaging features or genetic testing • Country: China • Setting: multicentre (3 sites)
Participants	Study characteristics • Inclusion criteria: 18 to 75 years; ADPKD; CKD stages 3-4 with the spleen, kidney deficiency, and blood stasis syndrome; eGFR 15 to 60 mL/min/1.73 m^2

Gan 2019 *(Continued)*

	• Exclusion criteria: KRT; chronic hepatitis, hepatic dysfunction, cardiovascular diseases, or any other life-threatening conditions; allergy to ingredients in test drug; contraindications to MRI; taking medications likely to affect ADPKD outcomes; recent participation in another clinical trial • Planned enrolment: 72
Interventions	Intervention group • Yinang formulation • Conventional therapy Control group • Placebo • Conventional therapy Duration of intervention • 24 weeks
Outcomes	Planned outcomes • eGFR • TKV • SCr • BUN • TCM symptoms • Pain • Composite: incidence rates of safety events
Starting date	Protocol published 2019
Contact information	Shengqiang Yu: Department of Nephrology, Shanghai Changzheng Hospital Affiliated to Second Military Medical University, 415 Fengyang Road, Shanghai, 200433, China
Notes	Analysis was planned for completion December 2020

Gitomer 2024

Study name	Statin therapy in patients with early stage ADPKD
Methods	Study design • Parallel, double-blind, placebo-controlled RCT • Duration of study: from August 2017 • Follow-up: 2 years • ADPKD assessment: not reported • Country: USA • Setting: single centre
Participants	Study characteristics • Inclusion criteria: ADPKD; TKV > 500 mL; eGFR ≥ 60 mL/min/1.73 m^2; controlled BP < 140/80 mm Hg • Exclusion criteria: uncontrolled hypertension; DM; kidney disease, renal cancer, single kidney, recent renal surgery, or AKI; unstable angina; coronary artery disease; prior ischaemic stroke; other clinical indication for a statin; history of hospitalisations within the last 3 months; hepatic impairment or liver function abnormalities; secondary hypercholesterolaemia or hypercholestero-

Gitomer 2024 *(Continued)*

	laemia; use of tolvaptan, gemfibrozil, other fibrates, niacin, clarithromycin, or cyclosporine; hypersensitivity to statins; immunosuppressive therapy within the last year; clinical contraindication for an MRI; hypersensitivity to iodine; pregnant or breastfeeding; current tobacco use; alcohol abuse or dependence • Actual enrolment: 150
Interventions	Intervention group • Pravastatin: 40 mg/d Control group • Placebo Duration of intervention • 6 weeks if well tolerated will continue to take for 2 years
Outcomes	Planned outcomes • TKV • Renal blood flow • Kidney function • Circulating inflammatory markers • Circulating markers of oxidative stress
Starting date	31 August 2017
Contact information	Michel Chonchol, MD University of Colorado, Denver
Notes	Additional information • Current status: active; not recruiting • Funding: "The study is supported by the Department of Defense Award # W81XWH-17-1-0382 and by the Zell Family Foundation."

GREASE II 2020

Study name	GREASE II. A phase II randomized, 12-month, parallel-group, superiority study to evaluate the efficacy of a modified Atkins Diet in autosomal dominant polycystic kidney disease patients
Methods	Study design • Parallel, phase II RCT • Duration of study: not reported • Follow-up: 12 months • ADPKD assessment: Pei criteria • Country: Italy • Setting: single centre
Participants	Study characteristics • Inclusion criteria: ADPKD; 18 to 60 years.eGFR > 24 mL/min/1.73 m^2; Mayo score 1C-1D-1E (TKV calculated by MRI)

GREASE II 2020 *(Continued)*

	• Exclusion criteria: types I and II Diabetes; BMI < 20 Kg/m^2; gastrointestinal malabsorption problems; eating behaviour disorders (anorexia, bulimia); personal history of renal stones; dyslipidaemia; familial hypercholesterolaemia • Planned enrolment: 90
Interventions	Intervention group • Modified Atkins diet Control group • Balanced normal calorie diet
Outcomes	Planned outcomes • TKV • Safety and tolerability • Slow down the kidney function decline
Starting date	Not reported
Contact information	Riccardo Magistroni: Riccardo.magistroni@unimore.it
Notes	Additional information • Clinical trials number not reported

HYDRO-PROTECT 2024

Study name	HYDROchlorothiazide to PROTECT polycystic kidney disease patients and improve their quality of life (HYDRO-PROTECT)
Methods	Study design • Parallel, placebo-controlled RCT • Study duration: from 2024 to 2029 • Follow-up: • ADPKD assessment: modified Ravine criteria • Countries: Belgium, France, Germany, the Netherlands, Spain, UK • Setting: multicentre (13 sites)
Participants	Study characteristics • Inclusion criteria: ADPKD; ≥18 years; eGFR > 25 mL/min/1.73 m^2; on stable treatment with the highest tolerated dose of V2RA for a minimum of 3 months • Exclusion criteria: known intolerance to hydrochlorothiazide; use of any diuretic; orthostatic hypotension complaints or blood pressure < 105/65 mm Hg during screening visit; uncontrolled hypertension (blood pressure > 160/100 mm Hg); hypokalemia (< 3.5 mmol/L); history of active gout on maintenance preventive treatment for gout (allopurinol, desuric and/or colchicine), defined as ≥ 2 episodes during the last year; history of skin cancer (basal cell, squamous cell and melanoma) • Planned enrolment: 300
Interventions	Intervention group • Oral hydrochlorothiazide: 25 mg once/day Control group

HYDRO-PROTECT 2024 *(Continued)*

	• Matching placebo Duration of intervention • 156 weeks
Outcomes	Planned outcomes • Kidney function (eGFR) • Changes in kidney function • > 30% decrease in eGFR • QoL • Change in V2R antagonist dose • Biochemistry: serum sodium, potassium, calcium, phosphate • Serious adverse events
Starting date	Planned: March 2024
Contact information	**Name:** Dr. E Meijer **Email:** esther.meijer@umcg.nl
Notes	Current status: not yet recruiting

IMPEDE-PKD 2021

Study name	Implementation of metformin theraPy to Ease DEcline of kidney function in PKD (IMPEDE-PKD)
Methods	Study design • Parallel, phase III quadruple blind RCT • Duration of study: up to 104 weeks • Follow-up: 24 months • ADPKD assessment: radiological ± genetic criteria • Country: Australia • Setting: multicentre (13 sites)
Participants	Study characteristics • Inclusion criteria: willing to participate and provide informed consent; 18 to 70 years; ADPKD; eGFR 38 to 90 mL/min/1.73 m^2 • Exclusion criteria: DM; BP > 160/80 mm Hg; clinically significant heart failure; non-polycystic liver disease; contraindication to metformin; currently taking metformin; pregnancy or breastfeeding; comorbidities with potential to contaminate trial outcomes; history of dialysis • Planned enrolment: 1174
Interventions	Intervention group • Metformin XR: up to 2000 mg Control group • Placebo Duration of intervention • 2 years

IMPEDE-PKD 2021 *(Continued)*

Outcomes	Planned outcomes • eGFR • Kidney failure • Death • QoL • Safety events
Starting date	December 2022
Contact information	Misa Matsuyama, PhD: +61 437 759 894 Laura Robison, B.Sci (Hons): +61 427 911 414 impedepkd@uq.edu.au
Notes	Additional information • Estimated completion: May 2027 • Currently recruiting (August 2024)

jRCT2011230055

Study name	Phase IIa clinical trial of tamibarotene in patients with autosomal dominant polycystic kidney disease
Methods	Study design • Parallel, phase II, placebo-controlled, single blind RCT • Duration of study: not reported • Follow-up: 52 weeks • ADPKD assessment: Pei-Ravine criteria • Country: Japan • Setting: not reported
Participants	Study characteristics • Inclusion criteria: 26 to 55 years; ADPKD eGFR ≥ 60 mL/min/1.73 m^2; judged to be hard to treat with tolvaptan or who do not wish to be treated with tolvaptan at the time of obtaining consent; BP < 140/90 mm Hg; for patients receiving ACEi or ARB, the dose must be constant for at least 6 weeks before obtaining informed consent • Exclusion criteria: pregnant or may be pregnant; breastfeeding; females with childbearing potential or male subjects with a fertile partner who is unable to use contraception for the following periods: females from informed consent to 2 years after the last administration of the study drug, males from informed consent to 6 months after the last administration of the study drug; within 12 weeks from the last dose of a drug that affects renal cysts, such as tolvaptan, to the first dose of the study drug; complications of intracranial aneurysm, malignant tumour, uncontrolled diabetes, osteoporosis, uncontrolled dyslipidaemia, or abnormal liver function • Planned enrolment: 70
Interventions	Intervention group • Tamibarotene Control group

jRCT2011230055 *(Continued)*

	• Placebo Duration of treatment • 52 weeks
Outcomes	Planned outcomes • Efficacy
Starting date	Planned first enrolment: 12 December 2023
Contact information	Ayuto Hayashi Email: info@regenephro.co.jp
Notes	Current recruitment status: pending

NCT00345137

Study name	Effects of systemic NO-inhibition on renal hemodynamics in patients with polycystic kidney disease and chronic glomerulonephritis
Methods	Study design • Single-blinded, cross-over, phase 1 RCT • Duration of study: not reported • Follow-up: not reported • ADPKD assessment: not reported • Country: Denmark
Participants	Study characteristics • Inclusion criteria: adult polycystic kidney disease (APKD): diagnosis of APKD by family history and kidney ultrasound or kidney angiography; SCr < 250 µmol/L; weight < 100 kg; age 20 to 60 years • Exclusion criteria: history of diseases of the heart and blood vessels, liver and pancreas, endocrine organs, lungs, myocardial infarction, cerebrovascular insult or neoplastic disease; current medication other than antihypertensive therapy; drugs or alcohol abuse; pregnancy; previously within one year received more than 0.2 m SV radioactive treatment or diagnostic substances • Planned enrolment: 75 (24 June 2006)
Interventions	Intervention group • Ng-monomethyl-L-arginine Control group • Placebo
Outcomes	Planned outcomes • Kidney haemodynamics • Kidney sodium excretion and lithium clearance • BP and heart rate • plasma levels of vasoactive hormones
Starting date	2006

NCT00345137 *(Continued)*

Contact information	Prof Erling B Pedersen, Dept. of Medicine, Holstebro Hospital, 7500 Holstebro, Denmark
Notes	Additional information • This study is completed, but no results have been posted (August 2024)

NCT01932450

Study name	Radiofrequency ablation for ADPKD blood pressure and disease progression control (RAFALE)
Methods	Study design • Open-label RCT • Duration of study: not reported • Follow-up: 12 months • ADPKD assessment: not reported • Country: China • Setting: single centre
Participants	Study characteristics • Inclusion criteria: ADPKD; hypertension (BP ≥140/90 mm Hg, and using 2 antihypertensive drugs and receiving a stable antihypertensive treatment regimen without change in dose or medication in the previous 30 days; 20 years to 60 years; eGFR ≥ 30 mL/min/1.73 m^2; followed-up kidney and cyst volume at least 6 months in Shanghai Changzheng Hospital; signed Informed Consent after being informed • Exclusion criteria: documented renal vascular disease; congenital absence of a kidney; systemic illness with renal involvement; Spot UACR > 0.5 g/g and/or findings suggestive of kidney disease other than ADPKD; exclusions specific to MRI acquisition and measurement; contraindications to the catheter-based renal denervation procedure by RFA; contraindications on ethical grounds; pregnant or breastfeeding or intention to become pregnant during the course of the study; lack of safe contraception; other clinically significant concomitant disease states (hepatic dysfunction, cardiovascular disease, metastatic cancer); known or suspected non-compliance, drug or alcohol abuse; inability to follow the procedures of the study, e.g. due to language problems, psychological disorders, dementia or confusional state of the subject; participation in another study with investigational drug within the 30 days preceding and during the present study; previous enrolment into the current study.; enrolment of the investigator, his/her family members, employees and other dependent persons • Planned enrolment: 100
Interventions	Intervention group 1 • Renal sympathetic denervation Intervention group 2 • Antihypertensive drugs
Outcomes	Planned outcomes • BP • 24 h ambulatory SBP • Number and does for BP tablets • eGFR • Albuminuria • TKV

NCT01932450 *(Continued)*

- Procedure-related complications
- Renal artery lesion
- Embolic events
- Hypotension
- Hypertension
- AKI
- Total cyst volume

Starting date	August 2013
Contact information	Name: Changlin Mei, MD Email: chlmei1954@126.com
Notes	Current status: unknown

NCT02127437

Study name	Lanreotide In Polycystic Kidney Disease Study (LIPS)
Methods	Study design • Parallel, double-blind placebo-controlled RCT • Duration of study: September 2014 to July 2019 • Follow-up: not reported • ADPKD assessment: clinical, familial, imaging • Country: France • Setting: single centre
Participants	Study characteristics • Inclusion criteria: ADPKD; measured GFR 30 to 89 mL/min/1.73 m^2; > 18 years; affiliated with health insurance; written informed consent • Exclusion criteria: iohexol /iodine allergy; DM; other associated nephropathy suspected; evolutive or recent malignant disease (in the previous 5 years); cholelithiasis; uncontrolled hypertension (BP > 160/100 mm Hg); cardiac failure of grade III or IV according to the NYHA classification; liver failure; psychiatric illness; pregnancy, lactation, lack of contraception; use of somatostatin analogues during the last 6 months • Actual enrolment: 159
Interventions	Intervention group • Lanreotide (SC): 120 mg once every 4 weeks Control group • Saline (SC): once every 4 weeks
Outcomes	Planned outcomes • GFR • Safety, tolerance • Onset or worsening of hypertension • QoL

NCT02127437 *(Continued)*

Starting date	19 September 2014
Contact information	Principal Investigator: Dominique JOLY
Notes	Additional information • Completed: 31 July 2019; no results posted

NCT05228574

Study name	Treatment of vascular stiffness in patients with autosomal dominant polycystic kidney disease
Methods	Study design • Parallel, double-blinded, placebo-controlled RCT • Duration of study: • Follow-up: 6 weeks • ADPKD assessment: Ravine criteria • Country: the Netherlands • Setting: single centre
Participants	Study characteristics • Inclusion criteria: adults with typical ADPKD; eGFR ≥ 60 mL/min/1.73 m^2; ability to provide informed consent • Exclusion criteria: uncontrolled hypertension, BP ≥ 160/90 mm Hg with or without antihypertensive treatment; concomitant use of ≥ 3 antihypertensive medications; when antihypertensive treatment is prescribed for any other treatment indication than hypertension (e.g. cardia arrhythmia); serum potassium levels > 5.5 mmol/L; history of liver disease (excluding liver cysts due to ADPKD); history of heart failure (cardiac ejection fraction < 35%) or cardiac arrhythmia; history of DM; active infection or antibiotic therapy; immunosuppressive therapy within the last year; concomitant use of drugs that could influence BP and/or disease progression, excluding < 3 antihypertensive drugs; actual pregnancy or unwillingness to adhere to reproductive precautions during the duration of the study • Planned enrolment: 54
Interventions	Intervention group • NaCl: 6 g/d Control group • Placebo Duration of treatment • 4 weeks
Outcomes	Planned/reported outcomes • Arterial stiffness • BP • Salt tasting threshold • Skin sodium accumulation • Markers of (vascular) inflammation and endothelial dysfunction

NCT05228574 *(Continued)*

Starting date	Actual: 11 March 2022
Contact information	L. Xue, MSc Email: l.xue@erasmusmc.nl
Notes	Current status: recruiting

NCT05460169

Study name	Effect of renal denervation in hypertensive patients with autosomal dominant polycystic kidney disease
Methods	Study design • Parallel, open-label RCT • Duration of study: start date June 2022 • Follow-up: 36 months • ADPKD assessment: not reported • Country: Germany • Setting: single centre
Participants	Study characteristics • Inclusion criteria: ADPKD; ≥ 18 years; BP ≥ 130/80 mm Hg; adhering to a stable drug regimen without changes for a minimum of 4 weeks • Exclusion criteria: eGFR < 40 mL/min/1.73m^2; anatomically significant renal artery abnormality in either renal artery which in the eyes of the interventionalist would interfere with safe catheter placement; prior renal denervation procedure; BP ≥/110180 mm Hg; 24-hour ambulatory SBP ≥160 mm Hg; other cause of hypertension that can be treated by intervention/surgery; type 1 DM; UPCR >3g/g; contraindication to MRI; has experienced a MI, unstable angina pectoris, or a cerebrovascular accident within 3 months of the screening visit; pregnant, nursing, or intends to become pregnant; enrolment in another interventional research protocol; any condition that, at the discretion of the investigator, would preclude participation in the study • Planned enrolment: 44
Interventions	Intervention group • Immediate renal denervation Control group • Delayed renal denervation: 3 months after randomisation
Outcomes	Planned/reported outcomes • SBP • DBP • SCr • eGFR • CrCl • Proteinuria • Albuminuria • Pain • QoL

NCT05460169 *(Continued)*

	• Copeptin
Starting date	Actual date: 14 June 2022
Contact information	Roland E. Schmieder, MD Email: roland.schmieder@uk-erlangen.de
Notes	Current status: recruiting

NCT05510115

Study name	Feasibility of study of empagliflozin in patients with autosomal dominant polycystic kidney disease
Methods	Study design • Parallel, phase 2 RCT • Duration of study: started 18 November 2022 • Follow-up: 12 months • ADPKD assessment: modified Pei-Ravine criteria • Country: USA • Setting: single centre
Participants	Study characteristics • Inclusion criteria: ADPKD; 18 to 55 years; 30 to 90 mL/min/1.73 m^2; Mayo imaging-based risk classification 1C, 1D, or 1E; stable kidney function over prior 3 months • Exclusion criteria: known DM; fasting glucose > 120 mg/dL; HbA1C ≥ 6.5%; seated SBP <100 or > 160 mm Hg; known heart failure with reduced ejection fraction; current use of loop diuretic; current use of tolvaptan or other V2 receptor antagonist; current urinary tract or urogenital infection; pregnant or lactating; vascular claudication, lower extremity skin infection or ulcers; contraindication to magnetic resonance imaging • Planned enrolment: 50
Interventions	Intervention group • Empagliflozin: 10 to 25 mg Control group • Placebo
Outcomes	Planned/reported outcomes • Adverse events • Drop out rate • Returned number of tablets • htTKV • Aortic pulse wave velocity • Mechanistic biomarkers • QoL
Starting date	Actual date: 18 November 2022
Contact information	Michel B Chonchol, MD

NCT05510115 *(Continued)*

	University of Colorado, Denver
Notes	Current status: recruiting

NCT05521191

Study name	A phase 1b, double-blind, placebo-controlled, multiple ascending dose and an open-label fixed-dose study in patients with autosomal dominant polycystic kidney disease to evaluate the safety, tolerability, pharmacodynamics, and pharmacokinetics of RGLS8429
Methods	Study design • Parallel, phase 1 RCT • Duration of study: started 6 October 2022 • Follow-up: 7 weeks • ADPKD assessment: MRI • Country: USA • Setting: multicentre (28 sites)
Participants	Study characteristics • Inclusion criteria: male or female ADPKD patients; 18 to 70 years; Class 1C, 1D, or 1E Mayo Imaging Classification of ADPKD eGFR 30 to 90 mL/min/1.73 m^2; BMI 18 to 35 kg/m^2; must understand and consent to the study procedures • Exclusion criteria: administration of tolvaptan in the 28 days before randomisation; mentally incapacitated or has significant emotional problems; any medical condition or social circumstance that, in the opinion of the Investigator, may make the subject unlikely to complete the study or comply with study procedures and requirements; or may pose a risk to the subject's safety; history or presence of alcoholism or drug abuse within the past 2 years prior to screening; only one kidney or kidney transplant recipient; participation in another clinical trial and/or exposure to any investigational drug or approved therapy for investigational use within 28 days or 5 half-lives of the investigational drug's dosing, whichever is longer, prior to dosing • Planned enrolment: 70
Interventions	Intervention group • RGLS8429: SC injection/week Control group • Placebo: SC injection/week Duration of treatment • 7 doses
Outcomes	Planned/reported outcomes • Adverse events • htTKV • Pharmacokinetic properties
Starting date	Actual date: 6 October 2024
Contact information	Name: Kristen Gillotti Email: kgillotti@regulusrx.com

NCT05521191 *(Continued)*

Notes	Current status: recruiting

NCT05870007

Study name	Atorvastatin and alkali therapy in patients with autosomal dominant polycystic kidney disease, a pilot trial for safety and feasibility
Methods	Study design • Parallel, open-label RCT • Duration of study: not reported • Follow-up: 12 months • ADPKD assessment: scan • Country: Taiwan • Setting: multicentre (3 sites)
Participants	Study characteristics • Inclusion criteria: ADPKD; voluntarily gives informed consent to participate in the study; ≥ 18 years; eGFR ≥ 30 mL/min; plasma bicarbonate ≤ 25 mMol/L; metabolic acidosis • Exclusion criteria: known allergy or sensitive to atorvastatin or $NaHCO_3$; acute coronary disease, liver disease, muscle disease, or a history of pulmonary oedema; creatine phosphokinase > 2 ULN (2.5 ULN in African Americans); systemic disease that impacts kidney per Investigator's decision; known unstable cerebral aneurysm per Investigator's decision; pregnancy or lactation, or patients who refuse to use recommended contraception methods; proteinuria > 1000 mg/day; history of non-compliance of medication per Investigator's decision; uncontrolled hypertension, oedema, or development of severe MA as per Investigator's decision; history of cancer; history of liver disease: hepatic failure/shock, cirrhosis; current or planned use of any of prohibited concomitant medication; history of nephrolithiasis • Planned enrolment: 30
Interventions	Intervention group 1 • Atorvastatin: 20 mg/day Intervention group 2 • Atorvastatin: 20 mg/day • Sodium bicarbonate: 600 to 1800 mg/day Control group • Standard treatment
Outcomes	Planned/reported outcomes • eGFR • BUN, serum sodium, serum potassium • Liver function • Creatine phosphokinase • Muscle tenderness • BP
Starting date	Estimated start date: May 2023

NCT05870007 *(Continued)*

Contact information	Not reported
Notes	Current status: enrolling by invitation

NCT06289998

Study name	Phase IIa clinical trial of tamibarotene in patients with autosomal dominant polycystic kidney disease
Methods	Study design • Parallel RCT • Duration of study: started 22 December 2023 • Follow-up: 52 weeks • ADPKD assessment: Pei-Ravine • Country: Japan • Setting: multicentre (8 sites)
Participants	Study characteristics • Inclusion criteria: 26 to 55 years; eGFR ≥ 60 mL/min/1.73 m^2; judged to be hard to treat with tolvaptan or who do not wish to be treated with tolvaptan, at the time of obtaining consent: BP < 140/90 mm Hg; for patients receiving ACEi or ARB, the dose must be constant for at least 6 weeks before obtaining informed consent • Exclusion criteria: pregnant or may be pregnant or nursing mother; within 12 weeks from the last dose of a drug that affects renal cysts, such as tolvaptan, to the first dose of the study drug; complications of intracranial aneurysm, malignant tumour, uncontrolled diabetes, osteoporosis, uncontrolled dyslipidaemia, or abnormal liver function • Planned enrolment: 70
Interventions	Intervention group • Tamibarotene: 4 mg/d Control group • Placebo Duration of treatment • 52 weeks
Outcomes	Planned/reported outcomes • TKV • eGFR • Safety
Starting date	Actual date: 22 December 2023
Contact information	Ayuto Hayashi Email: info@regenephro.co.jp
Notes	Current status: recruiting

NCT06291116

Study name	Safety of rotigotine in patients with autosomal dominant polycystic kidney disease (ETERNAL-PKD)
Methods	Study design • Parallel, phase 2 RCT • Duration of study: not started • Follow-up: 24 months • ADPKD assessment: not reported • Country: not reported • Setting: not reported
Participants	Study characteristics • Inclusion criteria: ADPKD; aged 18 to 60 years; normotensive or hypertensive patients treated controlled (BP < 135/85 mm Hg less than 3 months old); read and understood the information letter and signed the consent form; effective contraception in women of childbearing age; benefiting from a social protection scheme • Exclusion criteria: stage 4 or 5 renal insufficiency (GFR CKD-EPI < 30 mL/min); kidney transplant patients; dialysis patients; history of MI or stroke less than 6 months old; severe hepatic insufficiency (Child-Pugh class C); currently being treated or treated in the 6 months preceding the trial with a dopamine agonist or antagonist; systolic heart failure requiring hospitalisation in the 6 months preceding inclusion or known heart failure with an LVEF < 30%; orthostatic hypotension (decrease > 20 mm Hg); pregnant, breastfeeding woman, or proven absence of contraception; excessive alcohol consumption (> 20 g/day); history of addictive behaviour; drug addiction or suspected illicit drug use; taking other sedative medications or other central nervous system depressants; hypersensitivity to the active ingredient, rotigotine, or to one of its excipients • Known allergy to sulphites; deprived of liberty by an administrative or judicial decision or person placed under judicial protection, or guardianship or curatorship • Planned enrolment: 120
Interventions	Intervention group • Rotigotine: 4 mg/d • Standard care Control group • Standard care Duration of treatment • 24 months
Outcomes	Planned/reported outcomes • Adverse events
Starting date	Planned start date: 1 January 2025
Contact information	Not reported
Notes	Current status: not yet recruiting

NCT06391450

Study name	Study of empagliflozin in patients with autosomal dominant polycystic kidney disease (EMPA-PKD)
Methods	Study design • Parallel RCT • Duration of study: started 15 June 2024 • Follow-up: 18 months • ADPKD assessment: scan • Country: Germany • Setting: single centre
Participants	Study characteristics • Inclusion criteria: male and female patients ≥ 18 years; eGFR ≥ 25 and ≤ 90 mL/min/1.73 m^2 if ≥ 18 and ≤ 50 years or eGFR ≥ 25 and ≤ 65 mL/min/1.73 m^2 > if 50 years; ADPKD; Mayo Class I C, D, E; with and without tolvaptan; patients with tolvaptan use will be included if tolvaptan has been taken for ≥ 3 months at study entry; willing and able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures; evidence of signed written informed consent • Exclusion criteria: kidney or any other solid organ transplant recipient; currently receiving SGLT2-inhibitor; concomitant treatment with steroids or any other immunosuppressive agent; hypersensitivity to empagliflozin or any of the excipients (e.g. lactose); ketoacidosis in the past 5 years; type 1 DM; ongoing urinary tract or genital infections; inability to fully understand the possible risks and benefits related to study participation; inability to undergo MRI exam; women who are pregnant or breastfeeding; unwilling to practice acceptable methods of birth control during study participation; participation in another clinical trial at the time of enrolment or within 30 days prior to enrolment • Planned enrolment: 44
Interventions	Intervention group • Empagliflozin: 10 mg Control group • Placebo Duration of treatment • 18 months
Outcomes	Planned/reported outcomes • TKV • eGFR
Starting date	Actual start date: 15 June 2024
Contact information	Name: Elisabeth Bahlmann-Kroll Email: studienzentrum@mh-hannover.de
Notes	Current status: recruiting

NCT06435858

Study name	Short-term effects of an SGLT2 inhibitor on divalent ions in autosomal dominant polycystic kidney disease (SIDIA)
Methods	Study design • Cross-over, phase 4 RCT • Duration of study: not reported • Follow-up: 2 weeks • ADPKD assessment: not reported • Country: Switzerland • Setting: single centre
Participants	Study characteristics • Inclusion criteria: 18 to 75 years; ADPKD, defined according to international diagnostic and classification criteria; treated at Cantonal Hospital Graubünden (KSGR) and the University Hospital Zürich (USZ) independent of baseline treatment with the vasopressin receptor antagonist tolvaptan; informed consent as documented by signature • Exclusion criteria: KRT or kidney allograft recipient; CDK KDIGO Stage G4 (eGFR < 30 mL/min/1.73 m^2); type 1 DM; recurrent UTI; uncontrolled hypertension (ambulatory SBP > 180 mm Hg); liver cirrhosis (Child Pugh B and C); not able or not willing to stop medications during the study period of participation in the trial (thiazide diuretics, carbonic anhydrase inhibitors, sodium bicarbonate, 1, 25 (OH) vitamin D (calcitriol), bisphosphonate, denosumab, teriparatide); pregnant or lactating women; known allergy to study drug; inability to understand and follow the protocol • Planned enrolment: 40
Interventions	Intervention group • Empagliflozin: 10 mg Control group • Placebo Duration of treatment • 2 weeks Washout period • 2 weeks
Outcomes	Planned/reported outcomes • Calcium, phosphate, magnesium • Diuresis • Kidney function • BP • Adverse events • Safety
Starting date	Planned start date: 1 September 2024
Contact information	Name: Patrick Hofmann, MD Email: hofmannpatrick@bluewin.ch
Notes	Current status: not yet recruiting

NCT06496542

Study name	Renal oxygen consumption, insulin sensitivity, and daily caloric restriction in ADPKD (EXPLORE)
Methods	Study design • Parallel RCT • Duration of study: started 13 January 2023 • Follow-up: 2 years • ADPKD assessment: Pei-Ravine criteria • Country: USA • Setting: single centre
Participants	Study characteristics • Inclusion criteria: 18 to 65 years; ADPKD; BMI 25 to 45 kg/m^2; eGFR ≥ 30 mL/min/1.73 m^2; htTKV > 600 mL; access to the internet with video chat capabilities; no plans for extended travel (> 2 weeks) without internet access during the 12-month intensive period; not currently participating in or planning to participate in any formal weight loss or physical activity program, or another interventional study; ability to provide informed consent • Exclusion criteria: DM; current smokers or history of smoking in the past 12 months; alcohol dependence or abuse; hospitalisation or major surgery within the last 3 months; untreated dyslipidaemia; uncontrolled hypertension; pregnancy, lactation, or unwillingness to use adequate birth control; cardiovascular disease, peripheral vascular disease, or symptoms suggestive of cardiovascular disease: chest pain, shortness of breath at rest or with mild exertion, syncope; abnormal resting ECG; significant pulmonary disease; regular use of prescription or over-the-counter medications that may affect weight, appetite, food intake, or energy metabolism; clinically diagnosed eating disorder; weight loss of > 5% in the past 3 months for any reason except post-partum weight loss; weight gain > 5% requires assessment by PI; major psychiatric disorder; inability to cooperate with or clinical contraindication for magnetic resonance imaging; previous obesity treatment with surgery or weight loss device • Planned enrolment: 20
Interventions	Intervention group • Daily caloric restriction and increased physical activity Control group • Standard advice Duration of treatment • 2 years
Outcomes	Planned/reported outcomes • Renal oxygen consumption • Insulin sensitivity
Starting date	Actual start date: 13 January 2023
Contact information	Name: Cortney Steele, PhD Email: cortney.steele@cuanschutz.edu
Notes	Current status: recruiting

Steele 2023

Study name	Time restricted feeding in autosomal dominant polycystic kidney disease
Methods	Study design • Parallel, double-blind RCT • Duration of study: 9 February 2021 to 31 March 2023 • Follow-up: 12 months • ADPKD assessment: Peei-Ravine criteria • Country: USA • Setting: single centre
Participants	Study characteristics • Inclusion criteria: 18 to 65 years; ADPKD; BMI 25 to 45 kg/m^2; eGFR ≥ 30mL/min/1.73 m2; access to internet for video chat; typical eating duration > 12 h/d; provide informed consent • Exclusion criteria: DM; current nicotine use or history of use in the past 12 months; alcohol or substance abuse (self-report or undergoing treatment); history of hospitalisation or major surgery within the last 3 months; untreated dyslipidaemia; uncontrolled hypertension (BP > 160/90 mm Hg); pregnancy, lactation, or unwillingness to use adequate birth control; cardiovascular disease, peripheral vascular disease, cerebrovascular disease, significant pulmonary or gastrointestinal disease, cancer (within the last 5 years, except skin cancer or other cancers considered cured with excellent prognosis); abnormal resting electrocardiogram (ECG); regular use of prescription or over-the-counter medications that may affect weight, appetite, food intake, or energy metabolism; regular use of obesity pharmacotherapeutic agents within the last 6 months; history of clinically diagnosed eating disorder including anorexia nervosa, bulimia, binge eating disorder; weight loss > 5% in past 3 months for any reason except post-partum weight loss; weight gain > 5% in past 3 months requires assessment by PI to determine reason for weight gain and if it is appropriate for the subject to participate in the study; untreated hyper- or hyperthyroidism; current severe depression or history of severe depression within the previous year; history of other significant psychiatric illness which in the opinion of the Study MD would interfere with ability to adhere to dietary interventions; inability to cooperate with/clinical contraindication for MRI • Enrolment: 29
Interventions	Intervention group • Time-restricted feeding (8-hour window) Control group • Healthy eating without time-restricted feeding
Outcomes	Planned outcomes • Adherence (1 year) • Feasibility to enrol and retain • Safety and tolerability • Change in body weight • QoL • Change in kidney volume • Pain
Starting date	September 2020
Contact information	Principal Investigator: Kristen Nowak, University of Colorado, Denver
Notes	Completed: 31 March 2023; no published results

Vienna RAP 2015

Study name	Pulsed oral sirolimus in autosomal dominant polycystic kidney disease (RAP)
Methods	Study design • Parallel, placebo-controlled, double-blind RCT • Duration of study: not reported • Follow-up: 24 months • ADPKD assessment: imaging • Country: Austria • Setting: single centre
Participants	Study characteristics • Inclusion criteria: ADPKD; ≥ 18 years; eGFR < 60 mL/min/1.73 m^2; negative serum pregnancy test prior to administration of sirolimus and agreement to use contraception throughout the study and three months after; written informed consent • Exclusion criteria: need for KRT; pregnancy/lactation or plans to become pregnant in the near future; refusal to use sufficient contraception; UPCR >1000 or 1 g/d; history of life-threatening complications of ADPKD; Evidence of active systemic- or localized major infection; evidence of infiltrate or consolidation on chest X-ray; use of any investigational drug or -treatment up to 4 weeks prior to enrolment and during the study; known allergy/hypersensitivity to sirolimus and its derivatives; medication that will interfere with the cytochrome P450 (CYP3A4/CYP3A5) system; Total WWC ≤ 3000/mm^3; platelet count ≤ 100,000/mm^3; fasting triglycerides ≥ 400 mg/dL; fasting total cholesterol ≥ 300 mg/dL; concomitant glomerular diseases; psychiatric disorders and any condition that might prevent full comprehension of the purposes and risks of the study; history of malignancy, with the exception of adequately treated basal cell- and squamous cell carcinoma of the skin; HIV positivity • Planned enrolment: 68
Interventions	Intervention group • Sirolimus: 3 mg once/week Control group • Placebo Duration of intervention • 24 months
Outcomes	Planned outcomes • Kidney function: 50% reduction in doubling of SCr • Safety • Proteinuria • UACR, UPCR
Starting date	April 2014
Contact information	Markus Riegersperger, MD
Notes	Current status unknown (August 2024)

ACEi: angiotensin-converting-enzyme inhibitors; ADPKD: autosomal dominant polycystic kidney disease; AKI: acute kidney injury; ARB: angiotensin receptor blocker; BMI: body mass index; BNP: b-type natriuretic peptide; BP: blood pressure; BUN: blood urea nitrogen;

CKD: chronic kidney disease; DM: diabetes mellitus; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; Hb: haemoglobin; HbA1c: glycolated Hb; HIV: human immunodeficiency virus; KRT: kidney replacement therapy; LVEF: left ventricular ejection fraction; LVMI: left ventricular mass index; MI: myocardial infarction; MRI: magnetic resonance imaging; NO: nitric oxide; NSAID: nonsteroidal anti-inflammatory drug; NYHA: New York Heart Association; QoL: quality of life; RCT: randomised controlled trial; SC: subcutaneous; SCr: serum creatinine; TCM: Traditional Chinese Medicine; TKV: total kidney volume; UACR: urinary albumin-creatinine ratio; UAE: urinary albumin excretion; ULN: upper limit of normal; UACR: urinary albumin-creatinine ratio; UPCR: urinary protein-creatinine ratio; UTI: urinary tract infection; WCC: white cell count; XR: extended release

DATA AND ANALYSES

Comparison 1. Vasopressin type 2 receptor (V2R) antagonists versus control (placebo or standard therapy)

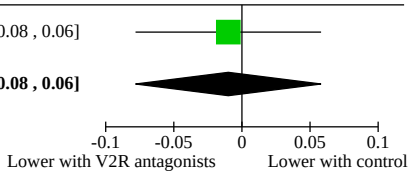
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Serum creatinine [mg/dL]	1	1154	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.08, 0.06]
1.2 Doubling of serum creatinine	1	1444	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.73, 1.25]
1.3 Mean change in eGFR [mL/min/1.73 m^2]	3	2758	Mean Difference (IV, Random, 95% CI)	1.26 [0.73, 1.78]
1.3.1 Studies ≤ 1 year	2	1452	Mean Difference (IV, Random, 95% CI)	1.59 [-0.10, 3.28]
1.3.2 Studies > 1 year	1	1306	Mean Difference (IV, Random, 95% CI)	1.13 [0.25, 2.01]
1.4 GFR: descriptive data	0		Other data	No numeric data
1.5 Death	1	1370	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.01, 8.22]
1.6 Pain	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.6.1 Kidney pain	4	3076	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.28, 1.00]
1.6.2 Back pain	2	1457	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.35, 0.90]
1.6.3 Pain in extremity	1	91	Risk Ratio (M-H, Random, 95% CI)	0.07 [0.00, 1.19]
1.7 Systolic blood pressure [mm Hg]	1	1422	Mean Difference (IV, Random, 95% CI)	-3.00 [-4.50, -1.50]
1.8 Diastolic blood pressure [mm Hg]	1	1422	Mean Difference (IV, Random, 95% CI)	-1.40 [-2.48, -0.32]
1.9 Total kidney volume [mL/cm]	1	1307	Mean Difference (IV, Random, 95% CI)	-2.70 [-3.24, -2.16]
1.10 Height-adjusted total kidney volume [mL/cm]	1	113	Mean Difference (IV, Random, 95% CI)	0.09 [-0.40, 0.59]
1.10.1 12-17 year olds	1	57	Mean Difference (IV, Random, 95% CI)	0.70 [-0.66, 2.06]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.10.2 4-11 year olds	1	56	Mean Difference (IV, Random, 95% CI)	0.00 [-0.53, 0.53]
1.11 Total kidney volume: descriptive data	0		Other data	No numeric data
1.12 Albuminuria [mg/mmol]	1	1157	Mean Difference (IV, Random, 95% CI)	-1.60 [-3.95, 0.75]
1.13 Spot urine osmolality [mOsm/kg]	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.13.1 One week	1	91	Mean Difference (IV, Random, 95% CI)	-303.00 [-383.66, -222.34]
1.13.2 One month	1	91	Mean Difference (IV, Random, 95% CI)	-323.00 [-426.47, -219.53]
1.14 Urine specific gravity [mOsm/kg]	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.14.1 One week	1	91	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.01, -0.00]
1.14.2 One month	1	91	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.01, -0.01]
1.15 Serious adverse events	4	3076	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.68, 1.66]
1.16 Adverse events	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.16.1 Headache	4	2996	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.89, 1.24]
1.16.2 Diarrhoea	4	3076	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.66, 1.55]
1.16.3 Dizziness	3	1710	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.90, 1.72]
1.16.4 Dry mouth	4	2996	Risk Ratio (M-H, Random, 95% CI)	5.13 [0.63, 41.71]
1.16.5 Nausea	3	1710	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.40, 1.16]
1.16.6 Polyuria	2	1457	Risk Ratio (M-H, Random, 95% CI)	17.63 [2.41, 128.96]
1.16.7 Nocturia	2	1457	Risk Ratio (M-H, Random, 95% CI)	7.81 [0.64, 95.51]
1.16.8 Thirst	4	3076	Risk Ratio (M-H, Random, 95% CI)	5.30 [1.05, 26.70]
1.16.9 Liver enzyme elevation	3	2901	Risk Ratio (M-H, Random, 95% CI)	2.08 [1.43, 3.02]
1.16.10 Hypertension	2	1541	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.21, 1.17]
1.16.11 Upper respiratory tract infection	2	1457	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.15, 2.99]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.16.12 Urinary tract infection	1	1366	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.07, 0.30]
1.16.13 Pollakiuria	1	91	Risk Ratio (M-H, Random, 95% CI)	17.06 [1.02, 284.67]
1.16.14 Increased creatinine	1	91	Risk Ratio (M-H, Random, 95% CI)	2.69 [0.78, 9.29]
1.16.15 Fatigue	3	1632	Risk Ratio (M-H, Random, 95% CI)	2.53 [1.65, 3.87]
1.17 Withdrawal due to adverse events	3	1632	Risk Ratio (M-H, Random, 95% CI)	3.94 [2.34, 6.65]

Analysis 1.1. Comparison 1: Vasopressin type 2 receptor (V2R) antagonists versus control (placebo or standard therapy), Outcome 1: Serum creatinine [mg/dL]

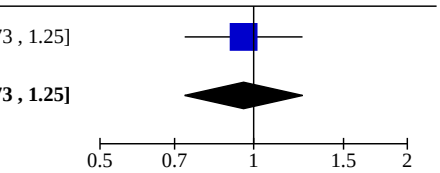
	V2R antagonists			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
TEMPO 3:4 2011	1.25	0.5	740	1.26	0.6	414	100.0%	-0.01 [-0.08 , 0.06]	
Total			**740**			**414**	**100.0%**	**-0.01 [-0.08 , 0.06]**	



Test for overall effect: Z = 0.29 (P = 0.77)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable

Analysis 1.2. Comparison 1: Vasopressin type 2 receptor (V2R) antagonists versus control (placebo or standard therapy), Outcome 2: Doubling of serum creatinine

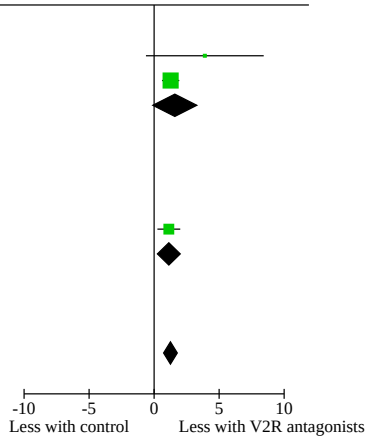
	V2R antagonists		Control			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
TEMPO 3:4 2011	135	961	71	483	100.0%	0.96 [0.73 , 1.25]	
Total		**961**		**483**	**100.0%**	**0.96 [0.73 , 1.25]**	
Total events:	135		71				



Test for overall effect: Z = 0.33 (P = 0.74)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable

Analysis 1.3. Comparison 1: Vasopressin type 2 receptor (V2R) antagonists versus control (placebo or standard therapy), Outcome 3: Mean change in eGFR [mL/min/1.73 m^2]

Study or Subgroup	V2R antagonists Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.3.1 Studies ≤ 1 year								
Schaefer 2019	0.4	10.3	48	-3.5	10.9	38	1.4%	3.90 [-0.63 , 8.43]
REPRISE 2017	-2.34	6.263	681	-3.61	6.2814	685	62.7%	1.27 [0.60 , 1.94]
Subtotal (Wald{fn})			**729**			**723**	**64.0%**	**1.59 [-0.10 , 3.28]**
Test for overall effect: Z = 1.85 (P = 0.06)								
Heterogeneity: Tau² = 0.73; Chi² = 1.27, df = 1 (P = 0.26); I² = 21%								
1.3.2 Studies > 1 year								
TEMPO 3:4 2011	-2.55	9.767	842	-3.682	6.361	464	36.0%	1.13 [0.25 , 2.01]
Subtotal			**842**			**464**	**36.0%**	**1.13 [0.25 , 2.01]**
Test for overall effect: Z = 2.53 (P = 0.01)								
Heterogeneity: Not applicable								
Total (Wald{fn})			**1571**			**1187**	**100.0%**	**1.26 [0.73 , 1.78]**
Test for overall effect: Z = 4.67 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.22, df = 1 (P = 0.64), I² = 0%								
Heterogeneity: Tau² = 0.00; Chi² = 1.39, df = 2 (P = 0.50); I² = 0%								



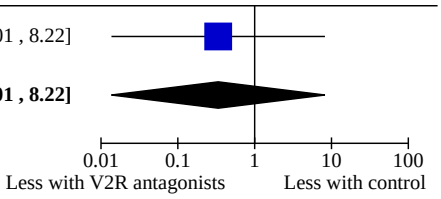
Analysis 1.4. Comparison 1: Vasopressin type 2 receptor (V2R) antagonists versus control (placebo or standard therapy), Outcome 4: GFR: descriptive data

GFR: descriptive data

Study	Description of outcome
TEMPO 3:4 2011	The slope of kidney function (as assessed by means of the reciprocal of the SCr level) from the end of dose escalation to month 36, favoured V2R antagonists, with a slope of −2.61 (mg/mL/year, as compared with −3.81 (mg/mL/year with placebo; the treatment effect was an increase of 1.20 (mg/mL/year (95% CI 0.62 to 1.78; P < 0.001)

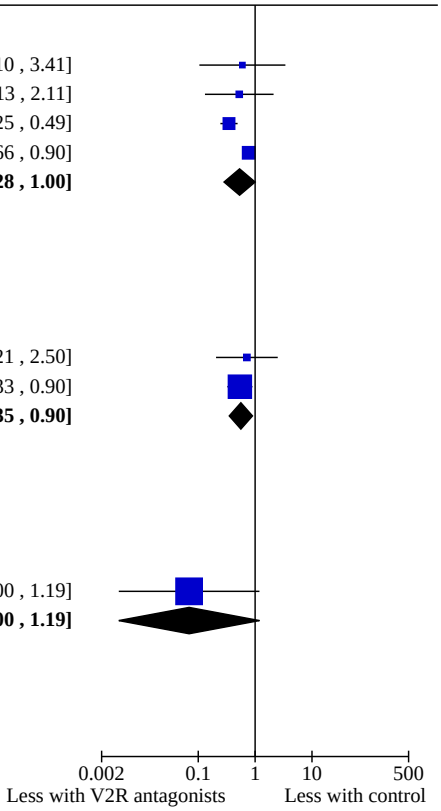
Analysis 1.5. Comparison 1: Vasopressin type 2 receptor (V2R) antagonists versus control (placebo or standard therapy), Outcome 5: Death

Study or Subgroup	V2R antagonists Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
REPRISE 2017	0	683	1	687	100.0%	0.34 [0.01 , 8.22]
Total		**683**		**687**	**100.0%**	**0.34 [0.01 , 8.22]**
Total events:	0		1			
Test for overall effect: Z = 0.67 (P = 0.50)						
Test for subgroup differences: Not applicable						
Heterogeneity: Not applicable						



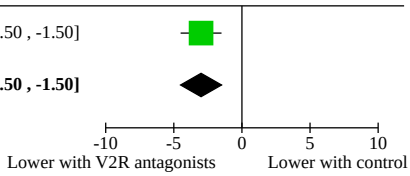
Analysis 1.6. Comparison 1: Vasopressin type 2 receptor (V2R) antagonists versus control (placebo or standard therapy), Outcome 6: Pain

Study or Subgroup	V2R antagonists Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 Kidney pain						
Schaefer 2019	2	48	3	43	9.9%	0.60 [0.10 , 3.41]
NOCTURNE 2020	5	133	3	42	13.7%	0.53 [0.13 , 2.11]
REPRISE 2017	39	681	113	685	36.5%	0.35 [0.25 , 0.49]
TEMPO 3:4 2011	259	961	169	483	40.0%	0.77 [0.66 , 0.90]
Subtotal (Wald{fn})		**1823**		**1253**	**100.0%**	**0.53 [0.28 , 1.00]**
Total events:	305		288			
Test for overall effect: Z = 1.96 (P = 0.05)						
Heterogeneity: Tau² = 0.25; Chi² = 17.47, df = 3 (P = 0.0006); I² = 83%						
1.6.2 Back pain						
Schaefer 2019	4	48	5	43	14.2%	0.72 [0.21 , 2.50]
REPRISE 2017	22	681	41	685	85.8%	0.54 [0.33 , 0.90]
Subtotal (Wald{fn})		**729**		**728**	**100.0%**	**0.56 [0.35 , 0.90]**
Total events:	26		46			
Test for overall effect: Z = 2.41 (P = 0.02)						
Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 1 (P = 0.68); I² = 0%						
1.6.3 Pain in extremity						
Schaefer 2019	0	48	6	43	100.0%	0.07 [0.00 , 1.19]
Subtotal		**48**		**43**	**100.0%**	**0.07 [0.00 , 1.19]**
Total events:	0		6			
Test for overall effect: Z = 1.84 (P = 0.07)						
Heterogeneity: Not applicable						
Test for subgroup differences: Chi² = 2.03, df = 2 (P = 0.36), I² = 1.3%						



Analysis 1.7. Comparison 1: Vasopressin type 2 receptor (V2R) antagonists versus control (placebo or standard therapy), Outcome 7: Systolic blood pressure [mm Hg]

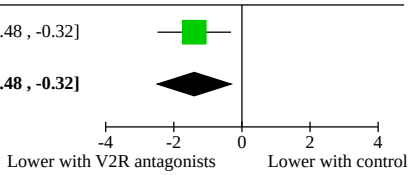
Study or Subgroup	V2R antagonists Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
TEMPO 3:4 2011	126	13	940	129	14	482	100.0%	-3.00 [-4.50 , -1.50]
Total			**940**			**482**	**100.0%**	**-3.00 [-4.50 , -1.50]**
Test for overall effect: Z = 3.92 (P < 0.0001)								
Test for subgroup differences: Not applicable								
Heterogeneity: Not applicable								



Analysis 1.8. Comparison 1: Vasopressin type 2 receptor (V2R) antagonists versus control (placebo or standard therapy), Outcome 8: Diastolic blood pressure [mm Hg]

Study or Subgroup	V2R antagonists Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
TEMPO 3:4 2011	81.2	9.5	940	82.6	10	482	100.0%	-1.40 [-2.48 , -0.32]
Total			**940**			**482**	**100.0%**	**-1.40 [-2.48 , -0.32]**

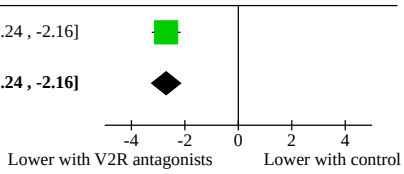
Test for overall effect: Z = 2.54 (P = 0.01)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 1.9. Comparison 1: Vasopressin type 2 receptor (V2R) antagonists versus control (placebo or standard therapy), Outcome 9: Total kidney volume [mL/cm]

Study or Subgroup	V2R antagonists Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
TEMPO 3:4 2011	2.8	4.435103	842	5.5	4.938063	465	100.0%	-2.70 [-3.24 , -2.16]
Total			**842**			**465**	**100.0%**	**-2.70 [-3.24 , -2.16]**

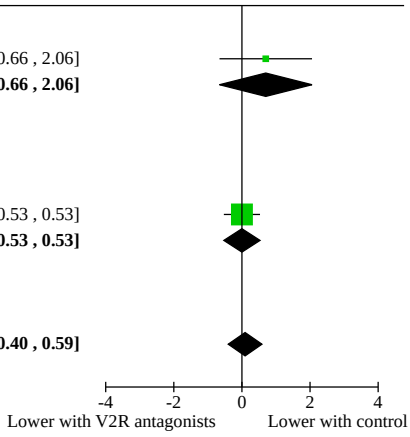
Test for overall effect: Z = 9.81 (P < 0.00001)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 1.10. Comparison 1: Vasopressin type 2 receptor (V2R) antagonists versus control (placebo or standard therapy), Outcome 10: Height-adjusted total kidney volume [mL/cm]

Study or Subgroup	V2R antagonists Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.10.1 12-17 year olds								
Schaefer 2019	3.5	3.7	30	2.8	0.8	27	13.3%	0.70 [-0.66 , 2.06]
Subtotal			**30**			**27**	**13.3%**	**0.70 [-0.66 , 2.06]**
Test for overall effect: Z = 1.01 (P = 0.31)								
Heterogeneity: Not applicable								
1.10.2 4-11 year olds								
Schaefer 2019	2.8	1.2	29	2.8	0.8	27	86.7%	0.00 [-0.53 , 0.53]
Subtotal			**29**			**27**	**86.7%**	**0.00 [-0.53 , 0.53]**
Test for overall effect: Z = 0.00 (P = 1.00)								
Heterogeneity: Not applicable								
Total (Wald{fn})			**59**			**54**	**100.0%**	**0.09 [-0.40 , 0.59]**

Test for overall effect: Z = 0.37 (P = 0.71)
Test for subgroup differences: Chi² = 0.89, df = 1 (P = 0.35), I² = 0%
Heterogeneity: Tau² = 0.00; Chi² = 0.89, df = 1 (P = 0.35); I² = 0%



Analysis 1.11. Comparison 1: Vasopressin type 2 receptor (V2R) antagonists versus control (placebo or standard therapy), Outcome 11: Total kidney volume: descriptive data

Total kidney volume: descriptive data

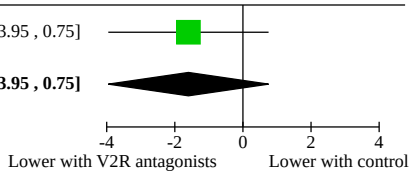
Study	Description of outcome
NOCTURNE 2020	Quote: "The pooled tolvaptan treatment groups (MR+IR) (–2.07%, P = 0.0127), the tolvaptan MR 80 mg group (–2.55%, P = 0.0108), and the tolvaptan MR 50 mg group

	(–2.46%, P = 0.0155) each exhibited a significantly greater mean percent decrease in TKV from baseline to week 3 versus the placebo group (0.09%)"
TEMPO 3:4 2011	TEMPO 3-4 Quote: "Over the 3-year period, total kidney volume increased by 2.8% per year (95% confidence interval [CI], 2.5 to 3.1) with V2R-antagonists versus 5.5% per year (95% CI, 5.1 to 6.0) with placebo" TEMPO 4-4 Early treated subjects were those who received tolvaptan therapy during TEMPO3:4, and delayed treated subjects took placebo during TEMPO3:4. TKV was measured from baseline of TEMPO3:4 until month 24 of TEMPO4:4, this time frame includes 36 months in TEMPO3:4, 13-829 days off treatment and 24 months in TEMPO4:4. Quote: "TKV increased by 29.9% in early-versus 31.6% in delayed-treated subjects (P = 0.38)"... "TKV slopes in TEMPO 4:4 were higher in early- compared with delayed-treated subjects (6.16 versus 4.96% per year; treatment difference 1.011, 95% CI, 1.00, 1.02, P = 0.05").
TEMPO 3:4 2011	

Analysis 1.12. Comparison 1: Vasopressin type 2 receptor (V2R) antagonists versus control (placebo or standard therapy), Outcome 12: Albuminuria [mg/mmol]

Study or Subgroup	V2R antagonists Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
TEMPO 3:4 2011	7.5	18.7	740	9.1	20.1	417	100.0%	-1.60 [-3.95 , 0.75]
Total			**740**			**417**	**100.0%**	**-1.60 [-3.95 , 0.75]**

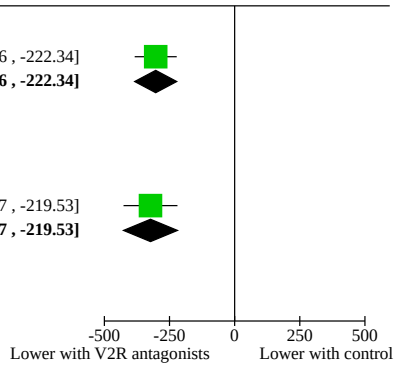
Test for overall effect: Z = 1.33 (P = 0.18)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 1.13. Comparison 1: Vasopressin type 2 receptor (V2R) antagonists versus control (placebo or standard therapy), Outcome 13: Spot urine osmolality [mOsm/kg]

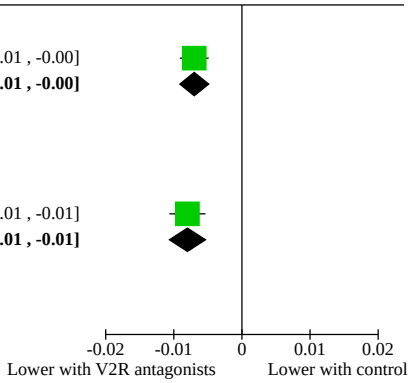
Study or Subgroup	V2R antagonists Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.13.1 One week								
Schaefer 2019	250	142	48	553	234	43	100.0%	-303.00 [-383.66 , -222.34]
Subtotal			**48**			**43**	**100.0%**	**-303.00 [-383.66 , -222.34]**
Test for overall effect: Z = 7.36 (P < 0.00001)								
Heterogeneity: Not applicable								
1.13.2 One month								
Schaefer 2019	275	169	48	598	307	43	100.0%	-323.00 [-426.47 , -219.53]
Subtotal			**48**			**43**	**100.0%**	**-323.00 [-426.47 , -219.53]**
Test for overall effect: Z = 6.12 (P < 0.00001)								
Heterogeneity: Not applicable								

Test for subgroup differences: Chi² = 0.09, df = 1 (P = 0.77), I² = 0%



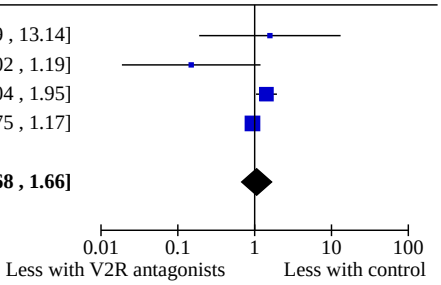
Analysis 1.14. Comparison 1: Vasopressin type 2 receptor (V2R) antagonists versus control (placebo or standard therapy), Outcome 14: Urine specific gravity [mOsm/kg]

Study or Subgroup	V2R antagonists Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.14.1 One week								
Schaefer 2019	1.008	0.004	48	1.015	0.006	43	100.0%	-0.01 [-0.01 , -0.00]
Subtotal			**48**			**43**	**100.0%**	**-0.01 [-0.01 , -0.00]**
Test for overall effect: Z = 6.47 (P < 0.00001)								
Heterogeneity: Not applicable								
1.14.2 One month								
Schaefer 2019	1.009	0.004	48	1.017	0.008	43	100.0%	-0.01 [-0.01 , -0.01]
Subtotal			**48**			**43**	**100.0%**	**-0.01 [-0.01 , -0.01]**
Test for overall effect: Z = 5.93 (P < 0.00001)								
Heterogeneity: Not applicable								
Test for subgroup differences: Chi² = 0.33, df = 1 (P = 0.56), I² = 0%								



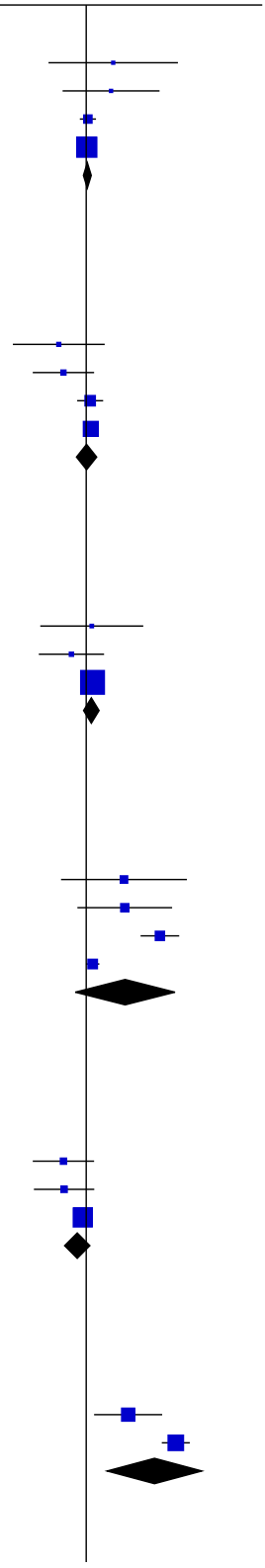
Analysis 1.15. Comparison 1: Vasopressin type 2 receptor (V2R) antagonists versus control (placebo or standard therapy), Outcome 15: Serious adverse events

Study or Subgroup	V2R antagonists Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
NOCTURNE 2020	5	133	1	42	4.1%	1.58 [0.19 , 13.14]
Schaefer 2019	1	48	6	43	4.3%	0.15 [0.02 , 1.19]
REPRISE 2017	85	681	60	685	43.3%	1.42 [1.04 , 1.95]
TEMPO 3:4 2011	177	961	95	483	48.3%	0.94 [0.75 , 1.17]
Total (Wald{fn})		**1823**		**1253**	**100.0%**	**1.06 [0.68 , 1.66]**
Total events:	268		162			
Test for overall effect: Z = 0.26 (P = 0.80)						
Test for subgroup differences: Not applicable						
Heterogeneity: Tau² = 0.09; Chi² = 8.16, df = 3 (P = 0.04); I² = 63%						



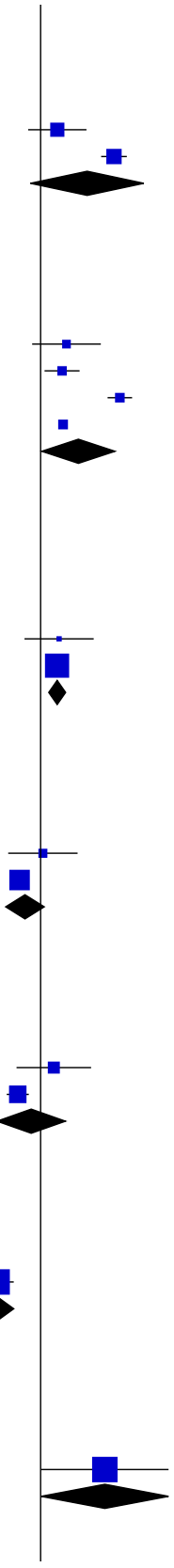
Analysis 1.16. Comparison 1: Vasopressin type 2 receptor (V2R) antagonists versus control (placebo or standard therapy), Outcome 16: Adverse events

Study or Subgroup	V2R antagonists Events	V2R antagonists Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.16.1 Headache						
TEMPO 248 & 249 2005	3	8	0	3	0.4%	3.11 [0.21 , 47.18]
NOCTURNE 2020	9	133	1	42	0.7%	2.84 [0.37 , 21.78]
REPRISE 2017	63	681	59	685	23.5%	1.07 [0.77 , 1.51]
TEMPO 3:4 2011	245	961	120	483	75.5%	1.03 [0.85 , 1.24]
Subtotal (Wald{fn})		**1783**		**1213**	**100.0%**	**1.05 [0.89 , 1.24]**
Total events:	320		180			
Test for overall effect: Z = 0.56 (P = 0.57)						
Heterogeneity: Tau² = 0.00; Chi² = 1.62, df = 3 (P = 0.66); I² = 0%						
1.16.2 Diarrhoea						
NOCTURNE 2020	2	133	2	42	4.5%	0.32 [0.05 , 2.17]
Schaefer 2019	3	48	7	43	9.4%	0.38 [0.11 , 1.39]
REPRISE 2017	27	681	23	685	32.9%	1.18 [0.68 , 2.04]
TEMPO 3:4 2011	128	961	53	483	53.1%	1.21 [0.90 , 1.64]
Subtotal (Wald{fn})		**1823**		**1253**	**100.0%**	**1.02 [0.66 , 1.55]**
Total events:	160		85			
Test for overall effect: Z = 0.07 (P = 0.94)						
Heterogeneity: Tau² = 0.06; Chi² = 4.62, df = 3 (P = 0.20); I² = 35%						
1.16.3 Dizziness						
NOCTURNE 2020	4	133	1	42	2.3%	1.26 [0.15 , 10.99]
Schaefer 2019	3	48	5	43	5.6%	0.54 [0.14 , 2.12]
TEMPO 3:4 2011	109	961	42	483	92.1%	1.30 [0.93 , 1.83]
Subtotal (Wald{fn})		**1142**		**568**	**100.0%**	**1.24 [0.90 , 1.72]**
Total events:	116		48			
Test for overall effect: Z = 1.30 (P = 0.19)						
Heterogeneity: Tau² = 0.00; Chi² = 1.51, df = 2 (P = 0.47); I² = 0%						
1.16.4 Dry mouth						
TEMPO 248 & 249 2005	5	8	0	3	19.9%	4.89 [0.35 , 68.83]
NOCTURNE 2020	16	133	1	42	23.1%	5.05 [0.69 , 36.97]
REPRISE 2017	132	681	6	685	28.0%	22.13 [9.83 , 49.81]
TEMPO 3:4 2011	154	961	59	483	29.0%	1.31 [0.99 , 1.73]
Subtotal (Wald{fn})		**1783**		**1213**	**100.0%**	**5.13 [0.63 , 41.71]**
Total events:	307		66			
Test for overall effect: Z = 1.53 (P = 0.13)						
Heterogeneity: Tau² = 3.92; Chi² = 54.46, df = 3 (P < 0.00001); I² = 94%						
1.16.5 Nausea						
Schaefer 2019	3	48	7	43	14.3%	0.38 [0.11 , 1.39]
NOCTURNE 2020	5	133	4	42	14.7%	0.39 [0.11 , 1.40]
TEMPO 3:4 2011	98	961	57	483	71.0%	0.86 [0.64 , 1.18]
Subtotal (Wald{fn})		**1142**		**568**	**100.0%**	**0.69 [0.40 , 1.16]**
Total events:	106		68			
Test for overall effect: Z = 1.40 (P = 0.16)						
Heterogeneity: Tau² = 0.08; Chi² = 2.68, df = 2 (P = 0.26); I² = 25%						
1.16.6 Polyuria						
Schaefer 2019	13	48	2	43	44.7%	5.82 [1.39 , 24.35]
REPRISE 2017	472	681	11	685	55.3%	43.16 [23.97 , 77.73]
Subtotal (Wald{fn})		**729**		**728**	**100.0%**	**17.63 [2.41 , 128.96]**
Total events:	485		13			
Test for overall effect: Z = 2.83 (P = 0.005)						
Heterogeneity: Tau² = 1.77; Chi² = 6.69, df = 1 (P = 0.010); I² = 85%						



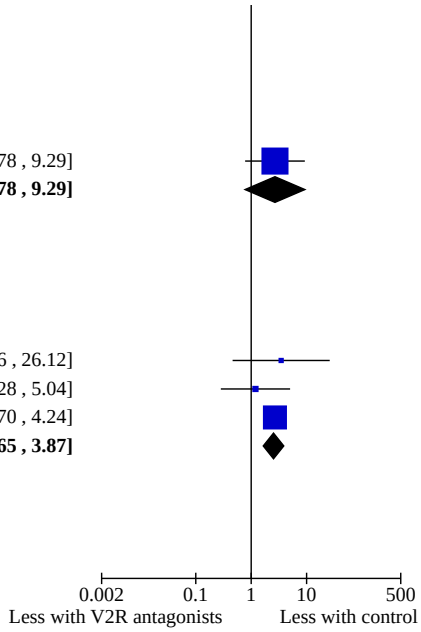
Analysis 1.16. (Continued)

Test for overall effect: Z = 2.83 (P = 0.005)						
Heterogeneity: Tau² = 1.77; Chi² = 6.69, df = 1 (P = 0.010); I² = 85%						
1.16.7 Nocturia						
Schaefer 2019	7	48	3	43	47.3%	2.09 [0.58 , 7.58]
REPRISE 2017	305	681	12	685	52.7%	25.57 [14.50 , 45.07]
Subtotal (Wald{fn})		**729**		**728**	**100.0%**	**7.81 [0.64 , 95.51]**
Total events:	312		15			
Test for overall effect: Z = 1.61 (P = 0.11)						
Heterogeneity: Tau² = 3.01; Chi² = 12.69, df = 1 (P = 0.0004); I² = 92%						
1.16.8 Thirst						
Schaefer 2019	7	48	2	43	21.7%	3.14 [0.69 , 14.29]
NOCTURNE 2020	49	133	6	42	25.3%	2.58 [1.19 , 5.59]
REPRISE 2017	428	681	13	685	26.1%	33.12 [19.27 , 56.91]
TEMPO 3:4 2011	531	961	99	483	26.8%	2.70 [2.24 , 3.24]
Subtotal (Wald{fn})		**1823**		**1253**	**100.0%**	**5.30 [1.05 , 26.70]**
Total events:	1015		120			
Test for overall effect: Z = 2.02 (P = 0.04)						
Heterogeneity: Tau² = 2.53; Chi² = 97.62, df = 3 (P < 0.00001); I² = 97%						
1.16.9 Liver enzyme elevation						
Schaefer 2019	0	48	0	43		Not estimable
TEMPO 3:4 2011	9	961	2	483	5.9%	2.26 [0.49 , 10.43]
REPRISE 2017	74	681	36	685	94.1%	2.07 [1.41 , 3.04]
Subtotal (Wald{fn})		**1690**		**1211**	**100.0%**	**2.08 [1.43 , 3.02]**
Total events:	83		38			
Test for overall effect: Z = 3.85 (P = 0.0001)						
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%						
1.16.10 Hypertension						
NOCTURNE 2020	7	133	2	42	23.1%	1.11 [0.24 , 5.12]
REPRISE 2017	31	681	79	685	76.9%	0.39 [0.26 , 0.59]
Subtotal (Wald{fn})		**814**		**727**	**100.0%**	**0.50 [0.21 , 1.17]**
Total events:	38		81			
Test for overall effect: Z = 1.59 (P = 0.11)						
Heterogeneity: Tau² = 0.20; Chi² = 1.62, df = 1 (P = 0.20); I² = 38%						
1.16.11 Upper respiratory tract infection						
Schaefer 2019	4	48	2	43	37.3%	1.79 [0.35 , 9.30]
REPRISE 2017	21	681	58	685	62.7%	0.36 [0.22 , 0.59]
Subtotal (Wald{fn})		**729**		**728**	**100.0%**	**0.66 [0.15 , 2.99]**
Total events:	25		60			
Test for overall effect: Z = 0.54 (P = 0.59)						
Heterogeneity: Tau² = 0.89; Chi² = 3.31, df = 1 (P = 0.07); I² = 70%						
1.16.12 Urinary tract infection						
REPRISE 2017	8	681	55	685	100.0%	0.15 [0.07 , 0.30]
Subtotal		**681**		**685**	**100.0%**	**0.15 [0.07 , 0.30]**
Total events:	8		55			
Test for overall effect: Z = 5.13 (P < 0.00001)						
Heterogeneity: Not applicable						
1.16.13 Pollakiuria						
Schaefer 2019	9	48	0	43	100.0%	17.06 [1.02 , 284.67]
Subtotal		**48**		**43**	**100.0%**	**17.06 [1.02 , 284.67]**
Total events:	9		0			
Test for overall effect: Z = 1.98 (P = 0.05)						



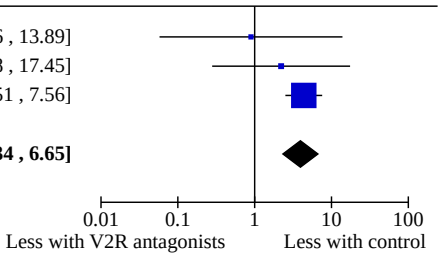
Analysis 1.16. (Continued)

Total events:	9		0			
Test for overall effect: Z = 1.98 (P = 0.05)						
Heterogeneity: Not applicable						
1.16.14 Increased creatinine						
Schaefer 2019	9	48	3	43	100.0%	2.69 [0.78 , 9.29]
Subtotal		**48**		**43**	**100.0%**	**2.69 [0.78 , 9.29]**
Total events:	9		3			
Test for overall effect: Z = 1.56 (P = 0.12)						
Heterogeneity: Not applicable						
1.16.15 Fatigue						
NOCTURNE 2020	11	133	1	42	4.5%	3.47 [0.46 , 26.12]
Schaefer 2019	4	48	3	43	8.8%	1.19 [0.28 , 5.04]
REPRISE 2017	64	681	24	685	86.8%	2.68 [1.70 , 4.24]
Subtotal (Wald{fn})		**862**		**770**	**100.0%**	**2.53 [1.65 , 3.87]**
Total events:	79		28			
Test for overall effect: Z = 4.27 (P < 0.0001)						
Heterogeneity: Tau² = 0.00; Chi² = 1.21, df = 2 (P = 0.55); I² = 0%						
Test for subgroup differences: Chi² = 82.92, df = 14 (P < 0.00001), I² = 83.1%						



Analysis 1.17. Comparison 1: Vasopressin type 2 receptor (V2R) antagonists versus control (placebo or standard therapy), Outcome 17: Withdrawal due to adverse events

	V2R antagonists		Control			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
Schaefer 2019	1	48	1	43	3.6%	0.90 [0.06 , 13.89]	
NOCTURNE 2020	7	133	1	42	6.4%	2.21 [0.28 , 17.45]	
REPRISE 2017	65	681	15	685	90.0%	4.36 [2.51 , 7.56]	
Total (Wald{fn})		**862**		**770**	**100.0%**	**3.94 [2.34 , 6.65]**	
Total events:	73		17				
Test for overall effect: Z = 5.14 (P < 0.00001)							
Test for subgroup differences: Not applicable							
Heterogeneity: Tau² = 0.00; Chi² = 1.55, df = 2 (P = 0.46); I² = 0%							

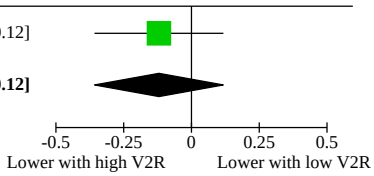


Comparison 2. High versus low dose vasopressin type 2 receptor (V2R) antagonists

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Serum creatinine [mg/dL]	1	46	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.36, 0.12]
2.2 Systolic blood pressure [mm Hg]	1	46	Mean Difference (IV, Random, 95% CI)	-9.00 [-16.98, -1.02]
2.3 Diastolic blood pressure [mm Hg]	1	46	Mean Difference (IV, Random, 95% CI)	-6.00 [-11.21, -0.79]

Analysis 2.1. Comparison 2: High versus low dose vasopressin type 2 receptor (V2R) antagonists, Outcome 1: Serum creatinine [mg/dL]

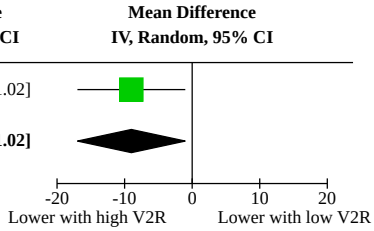
Study or Subgroup	High V2R Mean	SD	Total	Low V2R Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
TEMPO 250 2011	1.27	0.36	22	1.39	0.46	24	100.0%	-0.12 [-0.36 , 0.12]
Total			**22**			**24**	**100.0%**	**-0.12 [-0.36 , 0.12]**



Test for overall effect: Z = 0.99 (P = 0.32)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable

Analysis 2.2. Comparison 2: High versus low dose vasopressin type 2 receptor (V2R) antagonists, Outcome 2: Systolic blood pressure [mm Hg]

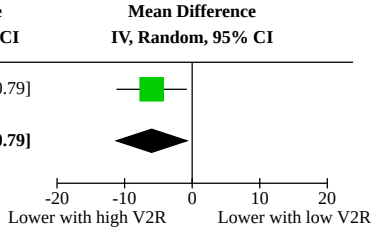
Study or Subgroup	High V2R Mean	SD	Total	Low V2R Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
TEMPO 250 2011	117	10	22	126	17	24	100.0%	-9.00 [-16.98 , -1.02]
Total			**22**			**24**	**100.0%**	**-9.00 [-16.98 , -1.02]**



Test for overall effect: Z = 2.21 (P = 0.03)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable

Analysis 2.3. Comparison 2: High versus low dose vasopressin type 2 receptor (V2R) antagonists, Outcome 3: Diastolic blood pressure [mm Hg]

Study or Subgroup	High dose Mean	SD	Total	Low dose Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
TEMPO 250 2011	74	9	22	80	9	24	100.0%	-6.00 [-11.21 , -0.79]
Total			**22**			**24**	**100.0%**	**-6.00 [-11.21 , -0.79]**



Test for overall effect: Z = 2.26 (P = 0.02)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable

Comparison 3. Immediate release (IR) versus modified release (MR) tolvaptan

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Nocturia QoL Questionnaire	0		Other data	No numeric data
3.2 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.2.1 Any adverse event	1	74	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.72, 2.16]
3.2.2 Polyuria	1	74	Risk Ratio (M-H, Random, 95% CI)	2.15 [0.93, 4.99]

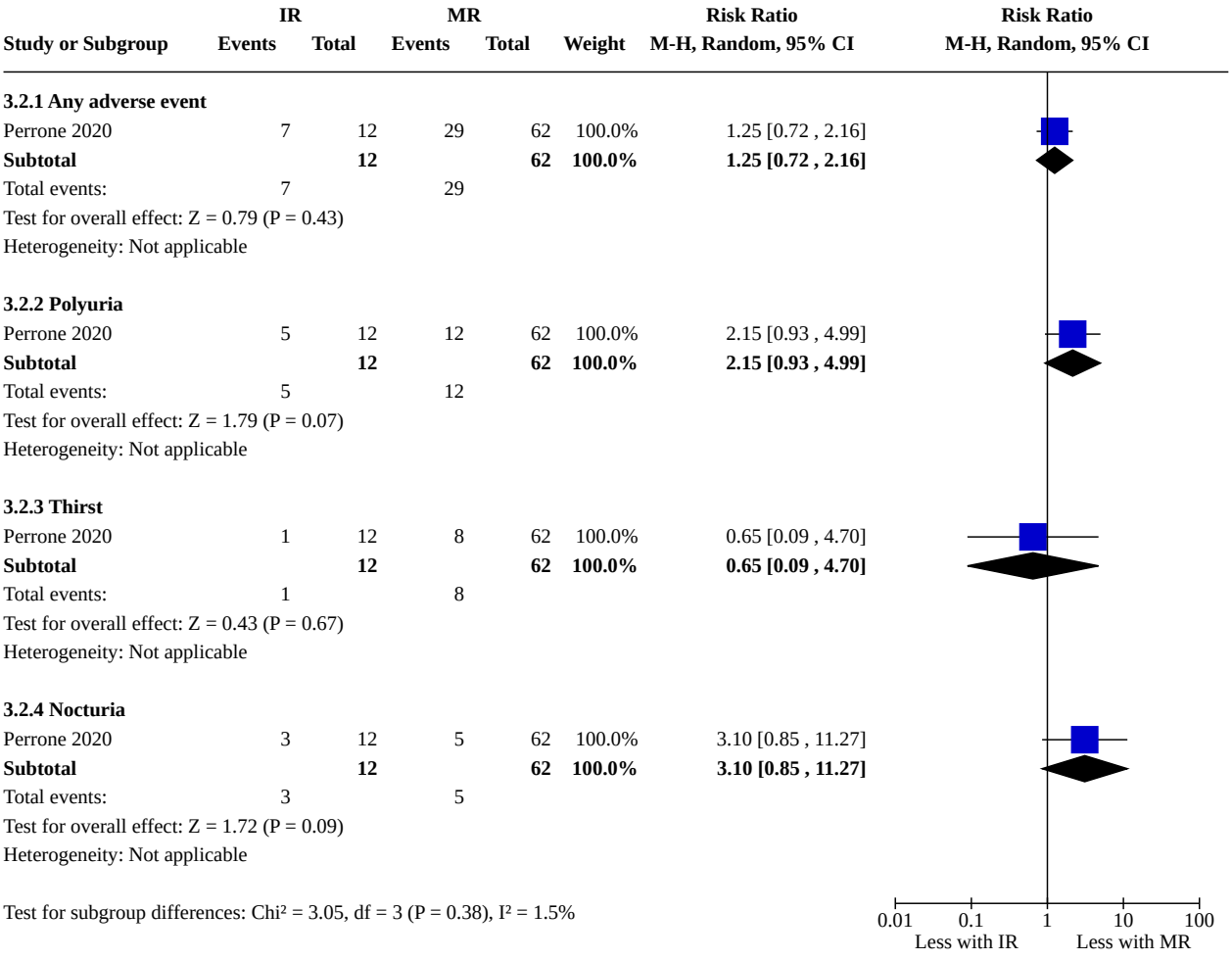
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2.3 Thirst	1	74	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.09, 4.70]
3.2.4 Nocturia	1	74	Risk Ratio (M-H, Random, 95% CI)	3.10 [0.85, 11.27]

Analysis 3.1. Comparison 3: Immediate release (IR) versus modified release (MR) tolvaptan, Outcome 1: Nocturia QoL Questionnaire

Nocturia QoL Questionnaire

Study	Narrative Results
Perrone 2020	During treatment, reported patient burden due to nocturia increased as mean scores decreased, by 1.5 points for MR 20 mg, 6.9 points for MR 20.20 mg, 5.1 points for MR 60 mg, 15.0 points for MR 120 mg, and 13.1 points for IR 90.30 mg.

Analysis 3.2. Comparison 3: Immediate release (IR) versus modified release (MR) tolvaptan, Outcome 2: Adverse events

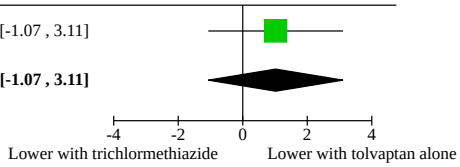


Comparison 4. Trichlormethiazide plus tolvaptan versus tolvaptan alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 eGFR change [mL/min/1.73 m^2/month]	1	10	Mean Difference (IV, Random, 95% CI)	1.02 [-1.07, 3.11]
4.2 Systolic blood pressure [mm Hg]	1	10	Mean Difference (IV, Random, 95% CI)	-4.10 [-15.26, 7.06]
4.3 Diastolic blood pressure [mm Hg]	1	10	Mean Difference (IV, Random, 95% CI)	-1.00 [-8.93, 6.93]
4.4 Quality of life scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.4.1 KDQOL overall health rating	1	10	Mean Difference (IV, Random, 95% CI)	3.70 [-10.46, 17.86]
4.4.2 SF-36 physical component summary	1	10	Mean Difference (IV, Random, 95% CI)	0.50 [-11.84, 12.84]
4.4.3 SF-36 mental component summary	1	10	Mean Difference (IV, Random, 95% CI)	2.40 [-7.12, 11.92]
4.5 Urinary albumin-creatinine ratio [mg/g]	1	10	Mean Difference (IV, Random, 95% CI)	-4.60 [-110.95, 101.75]

Analysis 4.1. Comparison 4: Trichlormethiazide plus tolvaptan versus tolvaptan alone, Outcome 1: eGFR change [mL/min/1.73 m^2/month]

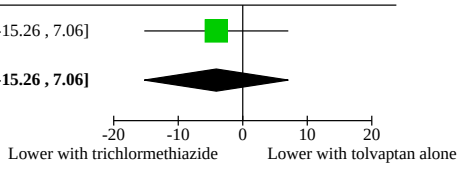
Study or Subgroup	Trichlormethiazide+ Mean	SD	Total	Tolvaptan alone Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Uchiyama 2021	0.73	1.49	5	-0.29	1.86	5	100.0%	1.02 [-1.07 , 3.11]
Total			**5**			**5**	**100.0%**	**1.02 [-1.07 , 3.11]**



Test for overall effect: Z = 0.96 (P = 0.34)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable

Analysis 4.2. Comparison 4: Trichlormethiazide plus tolvaptan versus tolvaptan alone, Outcome 2: Systolic blood pressure [mm Hg]

Study or Subgroup	Trichlormethiazide+ Mean	SD	Total	Tolvaptan alone Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Uchiyama 2021	124.9	9.2	5	129	8.8	5	100.0%	-4.10 [-15.26 , 7.06]
Total			**5**			**5**	**100.0%**	**-4.10 [-15.26 , 7.06]**

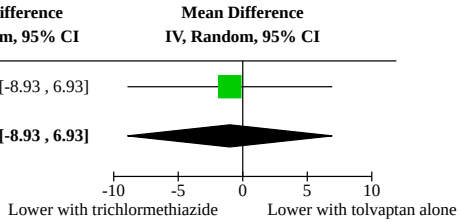


Test for overall effect: Z = 0.72 (P = 0.47)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable

Analysis 4.3. Comparison 4: Trichlormethiazide plus tolvaptan versus tolvaptan alone, Outcome 3: Diastolic blood pressure [mm Hg]

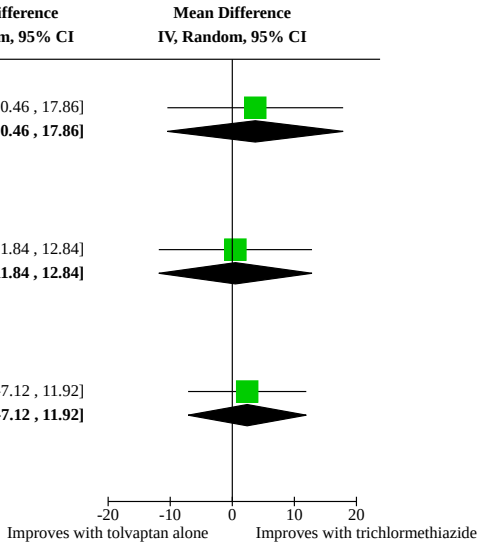
Study or Subgroup	Trichlormethiazide+ Mean	SD	Total	Tolvaptan alone Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Uchiyama 2021	80.9	6.3	5	81.9	6.5	5	100.0%	-1.00 [-8.93 , 6.93]
Total			**5**			**5**	**100.0%**	**-1.00 [-8.93 , 6.93]**

Test for overall effect: Z = 0.25 (P = 0.80)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 4.4. Comparison 4: Trichlormethiazide plus tolvaptan versus tolvaptan alone, Outcome 4: Quality of life scores

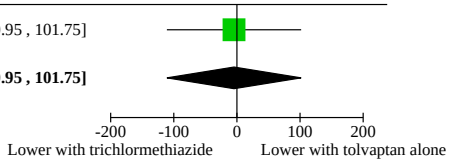
Study or Subgroup	Trichlormethiazide+ Mean	SD	Total	Tolvaptan alone Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
4.4.1 KDQOL overall health rating								
Uchiyama 2021	83.6	10.7	5	79.9	12.1	5	100.0%	3.70 [-10.46 , 17.86]
Subtotal			**5**			**5**	**100.0%**	**3.70 [-10.46 , 17.86]**
Test for overall effect: Z = 0.51 (P = 0.61)								
Heterogeneity: Not applicable								
4.4.2 SF-36 physical component summary								
Uchiyama 2021	44.7	8.4	5	44.2	11.3	5	100.0%	0.50 [-11.84 , 12.84]
Subtotal			**5**			**5**	**100.0%**	**0.50 [-11.84 , 12.84]**
Test for overall effect: Z = 0.08 (P = 0.94)								
Heterogeneity: Not applicable								
4.4.3 SF-36 mental component summary								
Uchiyama 2021	51.7	8.7	5	49.3	6.5	5	100.0%	2.40 [-7.12 , 11.92]
Subtotal			**5**			**5**	**100.0%**	**2.40 [-7.12 , 11.92]**
Test for overall effect: Z = 0.49 (P = 0.62)								
Heterogeneity: Not applicable								



Analysis 4.5. Comparison 4: Trichlormethiazide plus tolvaptan versus tolvaptan alone, Outcome 5: Urinary albumin-creatinine ratio [mg/g]

Study or Subgroup	Trichlormethiazide+ Mean	SD	Total	Tolvaptan alone Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Uchiyama 2021	68	94.5	5	72.6	76.1	5	100.0%	-4.60 [-110.95 , 101.75]
Total			**5**			**5**	**100.0%**	**-4.60 [-110.95 , 101.75]**

Test for overall effect: Z = 0.08 (P = 0.93)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



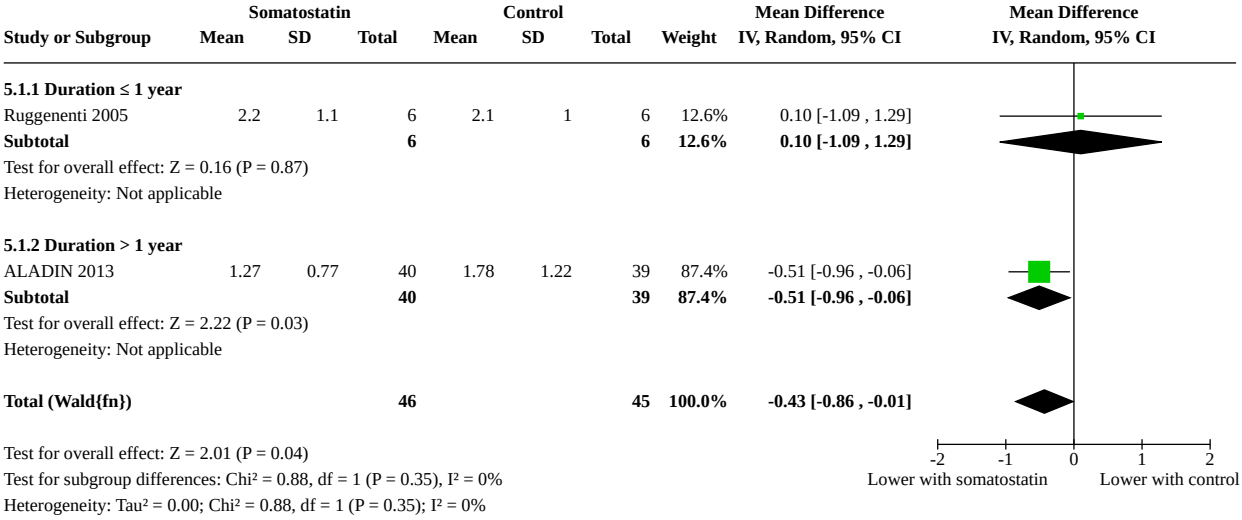
Comparison 5. Somatostatin analogues versus control (placebo or standard therapy)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Serum creatinine [mg/dL]	2	91	Mean Difference (IV, Random, 95% CI)	-0.43 [-0.86, -0.01]
5.1.1 Duration ≤ 1 year	1	12	Mean Difference (IV, Random, 95% CI)	0.10 [-1.09, 1.29]
5.1.2 Duration > 1 year	1	79	Mean Difference (IV, Random, 95% CI)	-0.51 [-0.96, -0.06]
5.2 GFR [mL/min/1.73 m^2]	4	180	Mean Difference (IV, Random, 95% CI)	4.11 [-3.19, 11.41]
5.2.1 Duration ≤ 1 year	2	41	Mean Difference (IV, Random, 95% CI)	-0.39 [-17.74, 16.95]
5.2.2 Duration > 1 year	2	139	Mean Difference (IV, Random, 95% CI)	5.07 [-2.97, 13.12]
5.3 Change in GFR [mL/min/1.73 m^2]	3	404	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.70, 0.50]
5.3.1 Duration ≤ 1 year	1	29	Mean Difference (IV, Random, 95% CI)	2.10 [-10.01, 14.21]
5.3.2 Duration > 1 year	2	375	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.71, 0.50]
5.4 eGFR: descriptive data	0		Other data	No numeric data
5.5 Kidney failure	2	405	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.16, 2.49]
5.6 Kidney failure or doubling of serum creatinine	1	100	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.21, 0.81]
5.7 30% or more decrease in GFR or kidney failure	1	305	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.43, 1.20]
5.8 Acute kidney injury	1	100	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.22, 2.70]
5.9 Death	1	309	Risk Ratio (M-H, Random, 95% CI)	3.02 [0.12, 73.55]
5.10 Back or flank pain	1	100	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.33, 1.79]
5.11 Health-related quality of life	1	305	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.12, 0.08]
5.12 Depression and anxiety	1	100	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.01, 3.91]
5.13 Systolic blood pressure [mm Hg]	2	91	Mean Difference (IV, Random, 95% CI)	0.79 [-3.54, 5.13]
5.14 Diastolic blood pressure [mm Hg]	2	91	Mean Difference (IV, Random, 95% CI)	-0.38 [-3.68, 2.92]

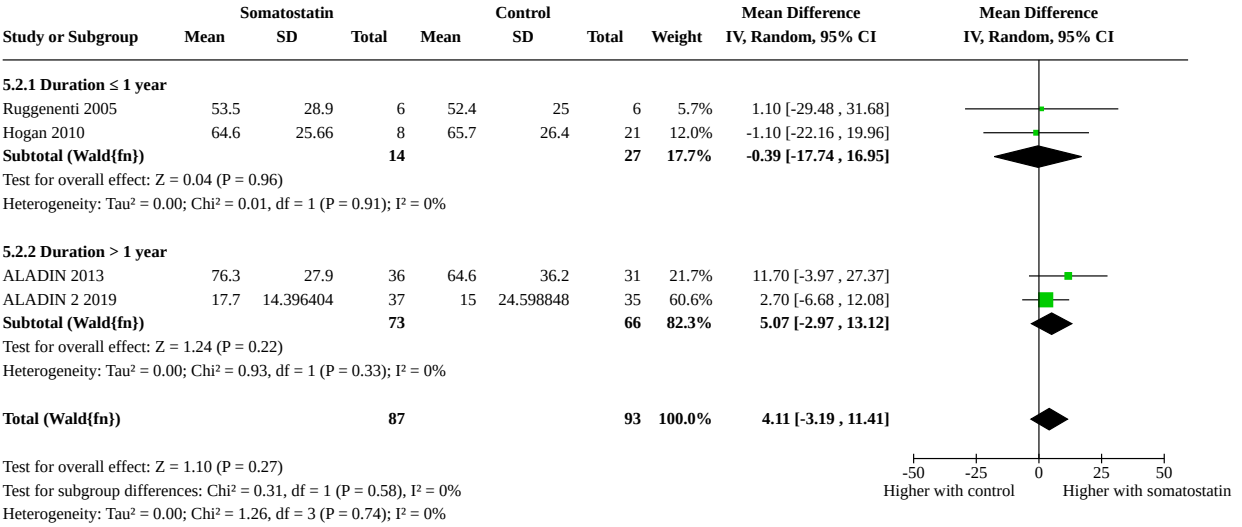
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.15 Mean arterial pressure [mm Hg]	1	79	Mean Difference (IV, Random, 95% CI)	-0.10 [-3.66, 3.46]
5.16 Total kidney volume [L]	3	114	Mean Difference (IV, Random, 95% CI)	-0.62 [-1.22, -0.01]
5.17 Total kidney volume (TKV), height-adjusted TKV and absolute change (pooled)	6	500	Std. Mean Difference (IV, Random, 95% CI)	-0.33 [-0.51, -0.16]
5.18 Cyst volume [L]	2	82	Mean Difference (IV, Random, 95% CI)	-0.50 [-1.18, 0.18]
5.19 Parenchymal volume [mL]	2	82	Mean Difference (IV, Random, 95% CI)	-67.67 [-249.45, 114.12]
5.20 Proteinuria [g/24 hours]	1	79	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.17, 0.07]
5.21 Albuminuria [g/24 hours]	2	91	Mean Difference (IV, Random, 95% CI)	-17.71 [-86.96, 51.55]
5.22 Serious adverse events	2	405	Risk Ratio (M-H, Random, 95% CI)	1.81 [1.01, 3.25]
5.23 Adverse events	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.23.1 Alopecia	3	484	Risk Ratio (M-H, Random, 95% CI)	8.58 [1.53, 48.03]
5.23.2 Anaemia	3	484	Risk Ratio (M-H, Random, 95% CI)	1.65 [0.28, 9.72]
5.23.3 Chest pain	1	305	Risk Ratio (M-H, Random, 95% CI)	5.96 [1.36, 26.19]
5.23.4 Diarrhoea or abnormal faeces	4	496	Risk Ratio (M-H, Random, 95% CI)	5.59 [2.05, 15.23]
5.23.5 Dizziness	3	484	Risk Ratio (M-H, Random, 95% CI)	2.24 [1.25, 4.02]
5.23.6 Epigastric pain	1	305	Risk Ratio (M-H, Random, 95% CI)	4.97 [0.24, 102.62]
5.23.7 Gastrointestinal symptoms	1	100	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.14, 1.30]
5.23.8 Fever	1	305	Risk Ratio (M-H, Random, 95% CI)	4.97 [0.24, 102.62]
5.23.9 Headache	1	100	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.03, 2.07]
5.23.10 Infection	3	484	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.59, 1.24]
5.23.11 Renal cyst infection	1	305	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.20, 4.84]
5.23.12 Urinary tract infection	1	305	Risk Ratio (M-H, Random, 95% CI)	2.98 [0.12, 72.59]
5.23.13 Fatigue	2	405	Risk Ratio (M-H, Random, 95% CI)	1.79 [1.21, 2.67]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.24 Withdrawal due to adverse events	1	305	Risk Ratio (M-H, Random, 95% CI)	32.79 [1.98, 541.63]

Analysis 5.1. Comparison 5: Somatostatin analogues versus control (placebo or standard therapy), Outcome 1: Serum creatinine [mg/dL]

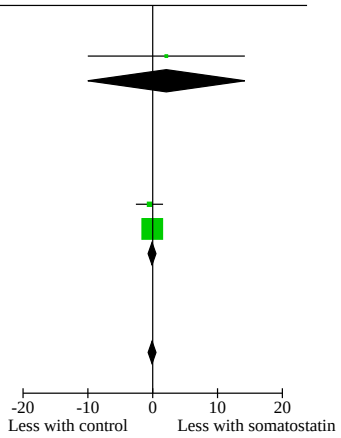


Analysis 5.2. Comparison 5: Somatostatin analogues versus control (placebo or standard therapy), Outcome 2: GFR [mL/min/1.73 m2]



Analysis 5.3. Comparison 5: Somatostatin analogues versus control (placebo or standard therapy), Outcome 3: Change in GFR [mL/min/1.73 m²]

Study or Subgroup	Somatostatin Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
5.3.1 Duration ≤ 1 year								
Hogan 2010	-5.1	15.46	8	-7.2	13.21	21	0.2%	2.10 [-10.01 , 14.21]
Subtotal			**8**			**21**	**0.2%**	**2.10 [-10.01 , 14.21]**
Test for overall effect: Z = 0.34 (P = 0.73)								
Heterogeneity: Not applicable								
5.3.2 Duration > 1 year								
ALADIN 2 2019	-5.2	3.929993	35	-4.7	4.948881	35	8.3%	-0.50 [-2.59 , 1.59]
DIPAK 1 2014	-3.53	2.901563	152	-3.46	2.723424	153	91.4%	-0.07 [-0.70 , 0.56]
Subtotal (Wald{fn})			**187**			**188**	**99.8%**	**-0.11 [-0.71 , 0.50]**
Test for overall effect: Z = 0.34 (P = 0.73)								
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.70); I² = 0%								
Total (Wald{fn})			**195**			**209**	**100.0%**	**-0.10 [-0.70 , 0.50]**
Test for overall effect: Z = 0.33 (P = 0.74)								
Test for subgroup differences: Chi² = 0.13, df = 1 (P = 0.72), I² = 0%								
Heterogeneity: Tau² = 0.00; Chi² = 0.28, df = 2 (P = 0.87); I² = 0%								



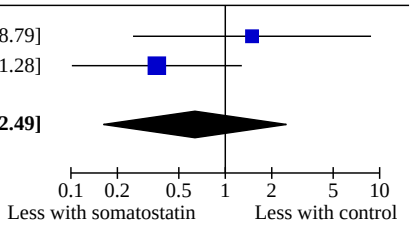
Analysis 5.4. Comparison 5: Somatostatin analogues versus control (placebo or standard therapy), Outcome 4: eGFR: descriptive data

eGFR: descriptive data

Study	Narrative Results
Temmerman 2012	Quote: "In ADPKD pts, there was no significant difference in GFR between placebo and both treatment groups (LAN 90 or 120 mg) (Mann-Whitney Rank Sum test: P = 0.09)"

Analysis 5.5. Comparison 5: Somatostatin analogues versus control (placebo or standard therapy), Outcome 5: Kidney failure

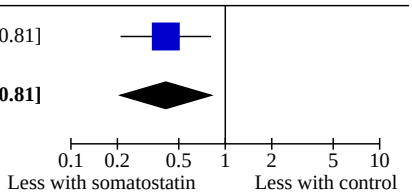
Study or Subgroup	Somatostatin Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
DIPAK 1 2014	3	153	2	152	40.0%	1.49 [0.25 , 8.79]
ALADIN 2 2019	3	51	8	49	60.0%	0.36 [0.10 , 1.28]
Total (Wald{fn})		**204**		**201**	**100.0%**	**0.64 [0.16 , 2.49]**
Total events:	6		10			
Test for overall effect: Z = 0.65 (P = 0.52)						
Test for subgroup differences: Not applicable						
Heterogeneity: Tau² = 0.39; Chi² = 1.63, df = 1 (P = 0.20); I² = 39%						



Analysis 5.6. Comparison 5: Somatostatin analogues versus control (placebo or standard therapy), Outcome 6: Kidney failure or doubling of serum creatinine

Study or Subgroup	Somatostatin Events	Somatostatin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
ALADIN 2 2019	9	51	21	49	100.0%	0.41 [0.21 , 0.81]
Total		**51**		**49**	**100.0%**	**0.41 [0.21 , 0.81]**
Total events:	9		21			

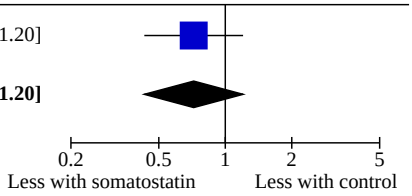
Test for overall effect: Z = 2.58 (P = 0.01)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 5.7. Comparison 5: Somatostatin analogues versus control (placebo or standard therapy), Outcome 7: 30% or more decrease in GFR or kidney failure

Study or Subgroup	Somatostatin Events	Somatostatin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
DIPAK 1 2014	21	153	29	152	100.0%	0.72 [0.43 , 1.20]
Total		**153**		**152**	**100.0%**	**0.72 [0.43 , 1.20]**
Total events:	21		29			

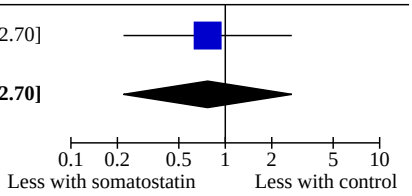
Test for overall effect: Z = 1.25 (P = 0.21)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 5.8. Comparison 5: Somatostatin analogues versus control (placebo or standard therapy), Outcome 8: Acute kidney injury

Study or Subgroup	Somatostatin Events	Somatostatin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
ALADIN 2 2019	4	51	5	49	100.0%	0.77 [0.22 , 2.70]
Total		**51**		**49**	**100.0%**	**0.77 [0.22 , 2.70]**
Total events:	4		5			

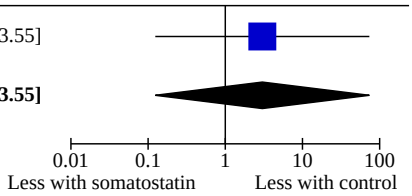
Test for overall effect: Z = 0.41 (P = 0.68)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 5.9. Comparison 5: Somatostatin analogues versus control (placebo or standard therapy), Outcome 9: Death

Study or Subgroup	Somatostatin Events	Somatostatin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
DIPAK 1 2014	1	154	0	155	100.0%	3.02 [0.12 , 73.55]
Total		**154**		**155**	**100.0%**	**3.02 [0.12 , 73.55]**
Total events:	1		0			

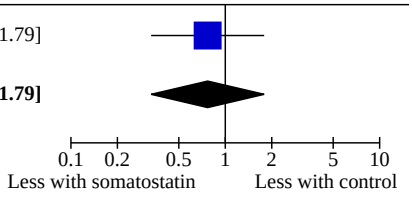
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 5.10. Comparison 5: Somatostatin analogues versus control (placebo or standard therapy), Outcome 10: Back or flank pain

Study or Subgroup	Somatostatin Events	Somatostatin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
ALADIN 2 2019	8	51	10	49	100.0%	0.77 [0.33 , 1.79]
Total		**51**		**49**	**100.0%**	**0.77 [0.33 , 1.79]**
Total events:	8		10			

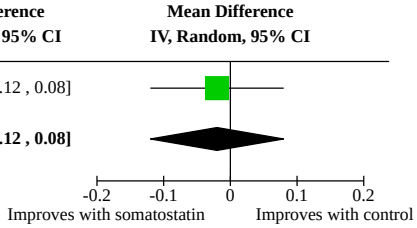
Test for overall effect: Z = 0.61 (P = 0.54)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 5.11. Comparison 5: Somatostatin analogues versus control (placebo or standard therapy), Outcome 11: Health-related quality of life

Study or Subgroup	Somatostatin Mean	Somatostatin SD	Somatostatin Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
DIPAK 1 2014	0.05	0.445	153	0.07	0.4455	152	100.0%	-0.02 [-0.12 , 0.08]
Total			**153**			**152**	**100.0%**	**-0.02 [-0.12 , 0.08]**

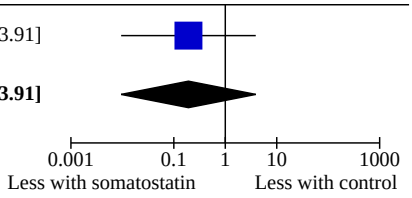
Test for overall effect: Z = 0.39 (P = 0.69)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 5.12. Comparison 5: Somatostatin analogues versus control (placebo or standard therapy), Outcome 12: Depression and anxiety

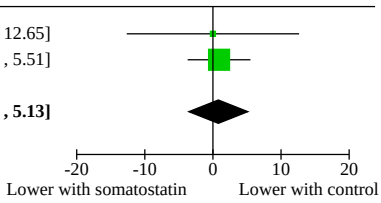
Study or Subgroup	Somatostatin Events	Somatostatin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
ALADIN 2 2019	0	51	2	49	100.0%	0.19 [0.01 , 3.91]
Total		**51**		**49**	**100.0%**	**0.19 [0.01 , 3.91]**
Total events:	0		2			

Test for overall effect: Z = 1.07 (P = 0.28)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 5.13. Comparison 5: Somatostatin analogues versus control (placebo or standard therapy), Outcome 13: Systolic blood pressure [mm Hg]

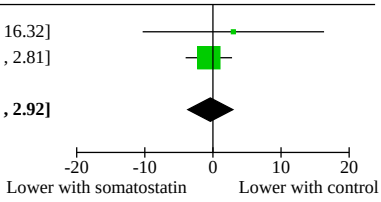
Study or Subgroup	Somatostatin Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Ruggenenti 2005	143	13	6	143	9	6	11.7%	0.00 [-12.65 , 12.65]
ALADIN 2013	123.8	9	40	122.9	11.7	39	88.3%	0.90 [-3.71 , 5.51]
Total (Wald{fn})			**46**			**45**	**100.0%**	**0.79 [-3.54 , 5.13]**



Test for overall effect: Z = 0.36 (P = 0.72)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.90); I² = 0%

Analysis 5.14. Comparison 5: Somatostatin analogues versus control (placebo or standard therapy), Outcome 14: Diastolic blood pressure [mm Hg]

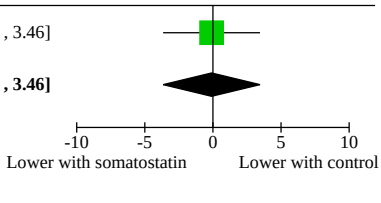
Study or Subgroup	Somatostatin Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Ruggenenti 2005	94	14	6	91	9	6	6.1%	3.00 [-10.32 , 16.32]
ALADIN 2013	77.3	7.2	40	77.9	8.2	39	93.9%	-0.60 [-4.01 , 2.81]
Total (Wald{fn})			**46**			**45**	**100.0%**	**-0.38 [-3.68 , 2.92]**



Test for overall effect: Z = 0.23 (P = 0.82)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 1 (P = 0.61); I² = 0%

Analysis 5.15. Comparison 5: Somatostatin analogues versus control (placebo or standard therapy), Outcome 15: Mean arterial pressure [mm Hg]

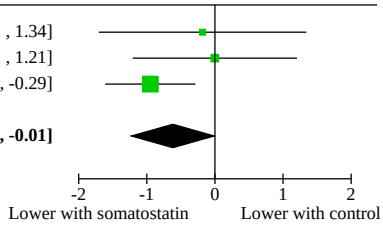
Study or Subgroup	Somatostatin Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
ALADIN 2013	92.8	7.1	40	92.9	8.9	39	100.0%	-0.10 [-3.66 , 3.46]
Total			**40**			**39**	**100.0%**	**-0.10 [-3.66 , 3.46]**



Test for overall effect: Z = 0.06 (P = 0.96)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable

Analysis 5.16. Comparison 5: Somatostatin analogues versus control (placebo or standard therapy), Outcome 16: Total kidney volume [L]

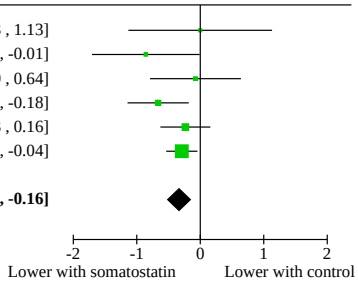
Study or Subgroup	Somatostatin Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
LOCKCYST 2009	0.983	1.737	12	1.165	2.657	20	14.9%	-0.18 [-1.71 , 1.34]
Ruggenenti 2005	2.622	1.11	6	2.623	1.02	6	22.9%	-0.00 [-1.21 , 1.21]
ALADIN 2013	1.672	1.195	35	2.621	1.603	35	62.2%	-0.95 [-1.61 , -0.29]
Total (Wald{fn})			**53**			**61**	**100.0%**	**-0.62 [-1.22 , -0.01]**



Test for overall effect: Z = 2.00 (P = 0.05)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.04; Chi² = 2.26, df = 2 (P = 0.32); I² = 11%

Analysis 5.17. Comparison 5: Somatostatin analogues versus control (placebo or standard therapy), Outcome 17: Total kidney volume (TKV), height-adjusted TKV and absolute change (pooled)

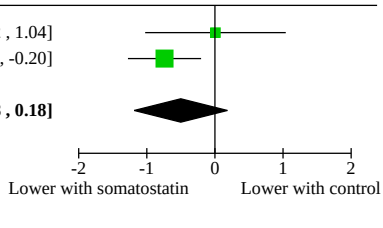
Study or Subgroup	Somatostatin Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Ruggenenti 2005	2.622	1.11	6	2.623	1.02	6	2.5%	-0.00 [-1.13 , 1.13]
Hogan 2010	0.25	7.53	8	8.61	10.07	21	4.4%	-0.86 [-1.71 , -0.01]
LOCKCYST 2009	0.983	1.737	12	1.165	2.657	20	6.2%	-0.08 [-0.79 , 0.64]
ALADIN 2013	1.672	1.195	35	2.621	1.603	35	13.7%	-0.66 [-1.15 , -0.18]
ALADIN 2 2019	604.2	1432.865799	51	939.1	1396.946904	49	20.6%	-0.23 [-0.63 , 0.16]
DIPAK 1 2014	4.15	4.688413	125	5.55	4.907553	132	52.6%	-0.29 [-0.54 , -0.04]
Total (Wald{fn})			**237**			**263**	**100.0%**	**-0.33 [-0.51 , -0.16]**



Test for overall effect: Z = 3.68 (P = 0.0002)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.00; Chi² = 4.46, df = 5 (P = 0.49); I² = 0%

Analysis 5.18. Comparison 5: Somatostatin analogues versus control (placebo or standard therapy), Outcome 18: Cyst volume [L]

Study or Subgroup	Somatostatin Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Ruggenenti 2005	1.77	0.941	6	1.762	0.882	6	31.9%	0.01 [-1.02 , 1.04]
ALADIN 2013	1.136	0.982	35	1.876	1.289	35	68.1%	-0.74 [-1.28 , -0.20]
Total (Wald{fn})			**41**			**41**	**100.0%**	**-0.50 [-1.18 , 0.18]**

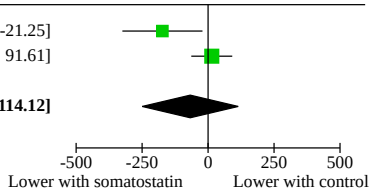


Test for overall effect: Z = 1.44 (P = 0.15)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.10; Chi² = 1.59, df = 1 (P = 0.21); I² = 37%

Analysis 5.19. Comparison 5: Somatostatin analogues versus control (placebo or standard therapy), Outcome 19: Parenchymal volume [mL]

Study or Subgroup	Somatostatin Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
ALADIN 2013	571	270	35	744	370	35	43.7%	-173.00 [-324.75 , -21.25]
Ruggenenti 2005	251	72	6	237	65	6	56.3%	14.00 [-63.61 , 91.61]
Total (Wald{fn})			**41**			**41**	**100.0%**	**-67.67 [-249.45 , 114.12]**

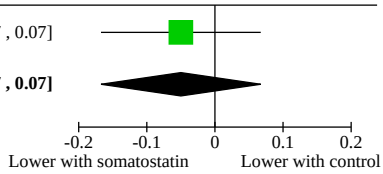
Test for overall effect: Z = 0.73 (P = 0.47)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 13703.27; Chi² = 4.62, df = 1 (P = 0.03); I² = 78%



Analysis 5.20. Comparison 5: Somatostatin analogues versus control (placebo or standard therapy), Outcome 20: Proteinuria [g/24 hours]

Study or Subgroup	Somatostatin Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
ALADIN 2013	0.2	0.29	40	0.25	0.24	39	100.0%	-0.05 [-0.17 , 0.07]
Total			**40**			**39**	**100.0%**	**-0.05 [-0.17 , 0.07]**

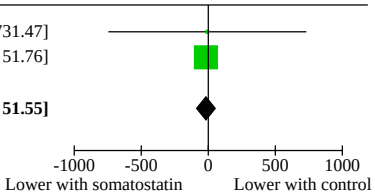
Test for overall effect: Z = 0.84 (P = 0.40)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 5.21. Comparison 5: Somatostatin analogues versus control (placebo or standard therapy), Outcome 21: Albuminuria [g/24 hours]

Study or Subgroup	Somatostatin Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Ruggenenti 2005	42	624	6	49	680	6	0.9%	-7.00 [-745.47 , 731.47]
ALADIN 2013	83.9	157.1	40	101.7	158.3	39	99.1%	-17.80 [-87.36 , 51.76]
Total (Wald{fn})			**46**			**45**	**100.0%**	**-17.71 [-86.96 , 51.55]**

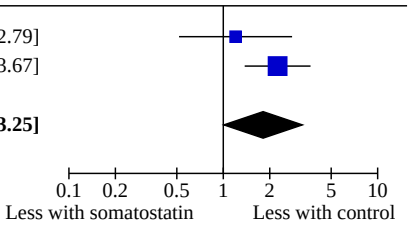
Test for overall effect: Z = 0.50 (P = 0.62)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%



Analysis 5.22. Comparison 5: Somatostatin analogues versus control (placebo or standard therapy), Outcome 22: Serious adverse events

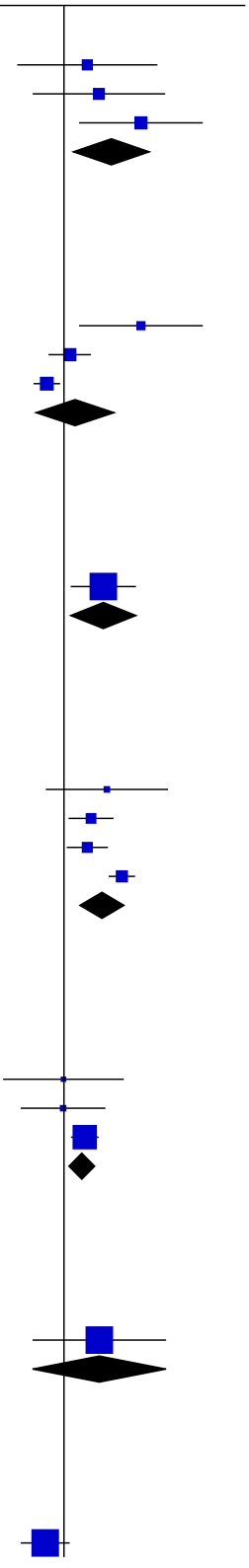
Study or Subgroup	Somatostatin Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ALADIN 2 2019	10	51	8	49	34.5%	1.20 [0.52 , 2.79]
DIPAK 1 2014	43	153	19	152	65.5%	2.25 [1.38 , 3.67]
Total (Wald{fn})		**204**		**201**	**100.0%**	**1.81 [1.01 , 3.25]**
Total events:	53		27			

Test for overall effect: Z = 1.99 (P = 0.05)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.07; Chi² = 1.59, df = 1 (P = 0.21); I² = 37%



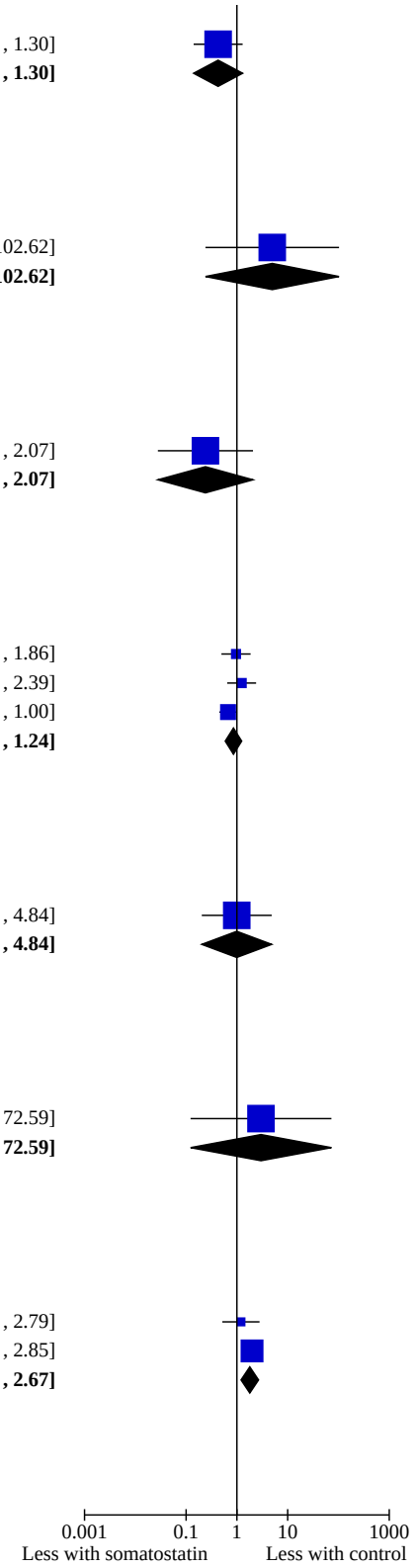
Analysis 5.23. Comparison 5: Somatostatin analogues versus control (placebo or standard therapy), Outcome 23: Adverse events

Study or Subgroup	Somatostatin Events	Somatostatin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
5.23.1 Alopecia						
ALADIN 2 2019	1	51	0	49	29.4%	2.88 [0.12 , 69.16]
ALADIN 2013	2	40	0	39	32.9%	4.88 [0.24 , 98.47]
DIPAK 1 2014	16	153	0	152	37.7%	32.79 [1.98 , 541.63]
Subtotal (Wald{fn})		**244**		**240**	**100.0%**	**8.58 [1.53 , 48.03]**
Total events:	19		0			
Test for overall effect: Z = 2.45 (P = 0.01)						
Heterogeneity: Tau² = 0.00; Chi² = 1.73, df = 2 (P = 0.42); I² = 0%						
5.23.2 Anaemia						
DIPAK 1 2014	16	153	0	152	20.7%	32.79 [1.98 , 541.63]
ALADIN 2013	8	40	6	39	38.2%	1.30 [0.50 , 3.40]
ALADIN 2 2019	11	51	23	49	41.1%	0.46 [0.25 , 0.84]
Subtotal (Wald{fn})		**244**		**240**	**100.0%**	**1.65 [0.28 , 9.72]**
Total events:	35		29			
Test for overall effect: Z = 0.56 (P = 0.58)						
Heterogeneity: Tau² = 1.89; Chi² = 14.72, df = 2 (P = 0.0006); I² = 86%						
5.23.3 Chest pain						
DIPAK 1 2014	12	153	2	152	100.0%	5.96 [1.36 , 26.19]
Subtotal		**153**		**152**	**100.0%**	**5.96 [1.36 , 26.19]**
Total events:	12		2			
Test for overall effect: Z = 2.36 (P = 0.02)						
Heterogeneity: Not applicable						
5.23.4 Diarrhoea or abnormal faeces						
Ruggenenti 2005	3	6	0	6	9.8%	7.00 [0.44 , 111.91]
ALADIN 2013	14	40	4	39	27.5%	3.41 [1.23 , 9.46]
ALADIN 2 2019	15	51	5	49	28.9%	2.88 [1.13 , 7.33]
DIPAK 1 2014	139	153	10	152	33.8%	13.81 [7.57 , 25.19]
Subtotal (Wald{fn})		**250**		**246**	**100.0%**	**5.59 [2.05 , 15.23]**
Total events:	171		19			
Test for overall effect: Z = 3.37 (P = 0.0008)						
Heterogeneity: Tau² = 0.68; Chi² = 10.88, df = 3 (P = 0.01); I² = 72%						
5.23.5 Dizziness						
ALADIN 2013	1	40	1	39	4.5%	0.97 [0.06 , 15.05]
ALADIN 2 2019	2	51	2	49	9.2%	0.96 [0.14 , 6.56]
DIPAK 1 2014	31	153	12	152	86.3%	2.57 [1.37 , 4.81]
Subtotal (Wald{fn})		**244**		**240**	**100.0%**	**2.24 [1.25 , 4.02]**
Total events:	34		15			
Test for overall effect: Z = 2.72 (P = 0.007)						
Heterogeneity: Tau² = 0.00; Chi² = 1.28, df = 2 (P = 0.53); I² = 0%						
5.23.6 Epigastric pain						
DIPAK 1 2014	2	153	0	152	100.0%	4.97 [0.24 , 102.62]
Subtotal		**153**		**152**	**100.0%**	**4.97 [0.24 , 102.62]**
Total events:	2		0			
Test for overall effect: Z = 1.04 (P = 0.30)						
Heterogeneity: Not applicable						
5.23.7 Gastrointestinal symptoms						
ALADIN 2 2019	4	51	9	49	100.0%	0.43 [0.14 , 1.30]



Analysis 5.23. (Continued)

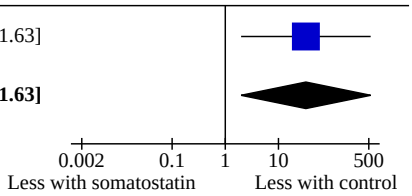
5.23.7 Gastrointestinal symptoms						
ALADIN 2 2019	4	51	9	49	100.0%	0.43 [0.14 , 1.30]
Subtotal		**51**		**49**	**100.0%**	**0.43 [0.14 , 1.30]**
Total events:	4		9			
Test for overall effect: Z = 1.50 (P = 0.13)						
Heterogeneity: Not applicable						
5.23.8 Fever						
DIPAK 1 2014	2	153	0	152	100.0%	4.97 [0.24 , 102.62]
Subtotal		**153**		**152**	**100.0%**	**4.97 [0.24 , 102.62]**
Total events:	2		0			
Test for overall effect: Z = 1.04 (P = 0.30)						
Heterogeneity: Not applicable						
5.23.9 Headache						
ALADIN 2 2019	1	51	4	49	100.0%	0.24 [0.03 , 2.07]
Subtotal		**51**		**49**	**100.0%**	**0.24 [0.03 , 2.07]**
Total events:	1		4			
Test for overall effect: Z = 1.30 (P = 0.19)						
Heterogeneity: Not applicable						
5.23.10 Infection						
ALADIN 2 2019	13	51	13	49	24.9%	0.96 [0.50 , 1.86]
ALADIN 2013	14	40	11	39	25.2%	1.24 [0.64 , 2.39]
DIPAK 1 2014	31	153	46	152	49.9%	0.67 [0.45 , 1.00]
Subtotal (Wald{fn})		**244**		**240**	**100.0%**	**0.86 [0.59 , 1.24]**
Total events:	58		70			
Test for overall effect: Z = 0.82 (P = 0.41)						
Heterogeneity: Tau² = 0.03; Chi² = 2.77, df = 2 (P = 0.25); I² = 28%						
5.23.11 Renal cyst infection						
DIPAK 1 2014	3	153	3	152	100.0%	0.99 [0.20 , 4.84]
Subtotal		**153**		**152**	**100.0%**	**0.99 [0.20 , 4.84]**
Total events:	3		3			
Test for overall effect: Z = 0.01 (P = 0.99)						
Heterogeneity: Not applicable						
5.23.12 Urinary tract infection						
DIPAK 1 2014	1	153	0	152	100.0%	2.98 [0.12 , 72.59]
Subtotal		**153**		**152**	**100.0%**	**2.98 [0.12 , 72.59]**
Total events:	1		0			
Test for overall effect: Z = 0.67 (P = 0.50)						
Heterogeneity: Not applicable						
5.23.13 Fatigue						
ALADIN 2 2019	10	51	8	49	20.2%	1.20 [0.52 , 2.79]
DIPAK 1 2014	64	153	32	152	79.8%	1.99 [1.39 , 2.85]
Subtotal (Wald{fn})		**204**		**201**	**100.0%**	**1.79 [1.21 , 2.67]**
Total events:	74		40			
Test for overall effect: Z = 2.89 (P = 0.004)						
Heterogeneity: Tau² = 0.02; Chi² = 1.16, df = 1 (P = 0.28); I² = 14%						



Analysis 5.24. Comparison 5: Somatostatin analogues versus control (placebo or standard therapy), Outcome 24: Withdrawal due to adverse events

Study or Subgroup	Somatostatin Events	Somatostatin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
DIPAK 1 2014	16	153	0	152	100.0%	32.79 [1.98 , 541.63]
Total		**153**		**152**	**100.0%**	**32.79 [1.98 , 541.63]**
Total events:	16		0			

Test for overall effect: Z = 2.44 (P = 0.01)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



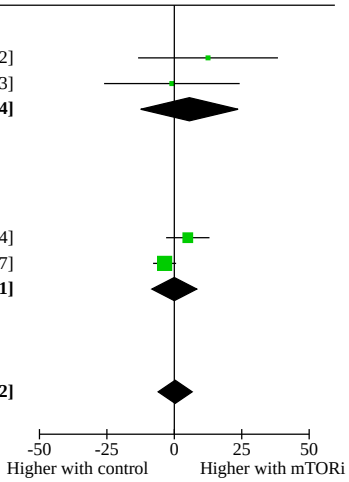
Comparison 6. mTOR inhibitors versus control (placebo, no treatment or standard therapy)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 GFR [mL/min/1.73 m^2]	4	165	Mean Difference (IV, Random, 95% CI)	0.32 [-5.98, 6.62]
6.1.1 Duration ≤ 1 year	2	32	Mean Difference (IV, Random, 95% CI)	5.59 [-12.45, 23.64]
6.1.2 Duration > 1 year	2	133	Mean Difference (IV, Random, 95% CI)	-0.00 [-8.32, 8.31]
6.2 GFR: descriptive data	0		Other data	No numeric data
6.3 Kidney failure	2	472	Risk Ratio (M-H, Random, 95% CI)	3.87 [0.44, 34.18]
6.4 Received transplantation	1	431	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.06, 16.11]
6.5 Death	1	431	Risk Ratio (M-H, Random, 95% CI)	2.03 [0.19, 22.20]
6.6 Systolic blood pressure [mm Hg]	2	112	Mean Difference (IV, Random, 95% CI)	2.48 [-2.07, 7.03]
6.7 Diastolic blood pressure [mm Hg]	2	112	Mean Difference (IV, Random, 95% CI)	0.27 [-3.30, 3.85]
6.8 Blood pressure: descriptive data	0		Other data	No numeric data
6.9 Total kidney volume [L]	4	151	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.59, 0.45]
6.10 Percent change in total kidney volume [L]	1	17	Mean Difference (IV, Random, 95% CI)	-3.00 [-7.83, 1.83]
6.11 Total kidney volume: descriptive data	0		Other data	No numeric data
6.12 Cyst volume [mL]	1	15	Mean Difference (IV, Random, 95% CI)	-55.00 [-862.98, 752.98]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.13 Cyst volume: descriptive data	0		Other data	No numeric data
6.14 Parenchymal volume [mL]	1	15	Mean Difference (IV, Random, 95% CI)	15.00 [-75.44, 105.44]
6.15 Parenchymal volume: descriptive data	0		Other data	No numeric data
6.16 Proteinuria	3	479	Std. Mean Difference (IV, Random, 95% CI)	-0.00 [-0.83, 0.83]
6.17 Proteinuria: descriptive data	0		Other data	No numeric data
6.18 Doubling of proteinuria	1	33	Risk Ratio (M-H, Random, 95% CI)	3.54 [1.19, 10.58]
6.19 Albuminuria	3	148	Std. Mean Difference (IV, Random, 95% CI)	0.01 [-0.64, 0.67]
6.20 Serious adverse events	2	71	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.43, 2.45]
6.21 Adverse events	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.21.1 Anaemia	1	431	Risk Ratio (M-H, Random, 95% CI)	3.41 [1.79, 6.51]
6.21.2 Angioedema	3	560	Risk Ratio (M-H, Random, 95% CI)	13.39 [2.56, 70.00]
6.21.3 Arrhythmias	1	41	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.27, 3.30]
6.21.4 Dermatitis	2	71	Risk Ratio (M-H, Random, 95% CI)	2.77 [0.48, 15.98]
6.21.5 Diarrhoea	4	601	Risk Ratio (M-H, Random, 95% CI)	1.73 [1.28, 2.33]
6.21.6 Dysmenorrhea	1	41	Risk Ratio (M-H, Random, 95% CI)	4.76 [0.61, 37.28]
6.21.7 Gastrointestinal symptoms	1	30	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.14, 1.17]
6.21.8 Haematuria	1	41	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.06, 1.16]
6.21.9 Hyperlipidaemia	1	431	Risk Ratio (M-H, Random, 95% CI)	5.68 [2.23, 14.43]
6.21.10 Infection	5	631	Risk Ratio (M-H, Random, 95% CI)	1.15 [1.02, 1.31]
6.21.11 Nausea	1	431	Risk Ratio (M-H, Random, 95% CI)	1.69 [0.85, 3.37]
6.21.12 Oral ulcers	4	590	Risk Ratio (M-H, Random, 95% CI)	6.82 [4.47, 10.39]
6.21.13 Peripheral oedema	2	71	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.15, 5.05]

Analysis 6.1. Comparison 6: mTOR inhibitors versus control (placebo, no treatment or standard therapy), Outcome 1: GFR [mL/min/1.73 m²]

Study or Subgroup	mTORi Mean	mTORi SD	mTORi Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
6.1.1 Duration ≤ 1 year								
Braun 2014	74.4	34.4	8	61.9	15.6	9	5.5%	12.50 [-13.42 , 38.42]
SIRENA 2010	73.4	25.1	7	74.3	24.4	8	5.8%	-0.90 [-26.03 , 24.23]
Subtotal (Wald{fn})			**15**			**17**	**11.3%**	**5.59 [-12.45 , 23.64]**
Test for overall effect: Z = 0.61 (P = 0.54)								
Heterogeneity: Tau² = 0.00; Chi² = 0.53, df = 1 (P = 0.47); I² = 0%								
6.1.2 Duration > 1 year								
SUISSE ADPKD 2007	92	21	50	87	20	50	33.5%	5.00 [-3.04 , 13.04]
SIRENA 2 2016	21.3	6.3	17	24.9	6.2	16	55.2%	-3.60 [-7.87 , 0.67]
Subtotal (Wald{fn})			**67**			**66**	**88.7%**	**-0.00 [-8.32 , 8.31]**
Test for overall effect: Z = 0.00 (P = 1.00)								
Heterogeneity: Tau² = 26.20; Chi² = 3.43, df = 1 (P = 0.06); I² = 71%								
Total (Wald{fn})			**82**			**83**	**100.0%**	**0.32 [-5.98 , 6.62]**
Test for overall effect: Z = 0.10 (P = 0.92)								
Test for subgroup differences: Chi² = 0.30, df = 1 (P = 0.58), I² = 0%								
Heterogeneity: Tau² = 13.98; Chi² = 4.56, df = 3 (P = 0.21); I² = 34%								



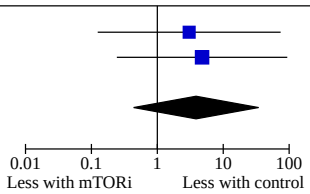
Analysis 6.2. Comparison 6: mTOR inhibitors versus control (placebo, no treatment or standard therapy), Outcome 2: GFR: descriptive data

GFR: descriptive data

Study	Description of outcome
Walz 2010	Quote: "The estimated GFR decreased by 8.9 ml per minute in the mTOR-inhibitors group and 7.7 ml per minute in the placebo group (P = 0.15) over the 2-year study period"

Analysis 6.3. Comparison 6: mTOR inhibitors versus control (placebo, no treatment or standard therapy), Outcome 3: Kidney failure

Study or Subgroup	mTORi Events	mTORi Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Walz 2010	1	214	0	217	46.5%	3.04 [0.12 , 74.26]	? + + ? + + ?
SIRENA 2 2016	2	21	0	20	53.5%	4.77 [0.24 , 93.67]	+ + − + + + +
Total (Wald{fn})		**235**		**237**	**100.0%**	**3.87 [0.44 , 34.18]**	
Total events:	3		0				
Test for overall effect: Z = 1.22 (P = 0.22)							
Test for subgroup differences: Not applicable							
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%							



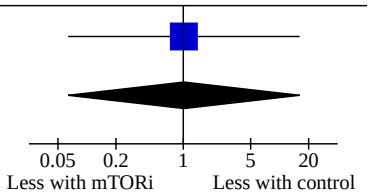
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 6.4. Comparison 6: mTOR inhibitors versus control (placebo, no treatment or standard therapy), Outcome 4: Received transplantation

Study or Subgroup	mTORi Events	mTORi Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Walz 2010	1	214	1	217	100.0%	1.01 [0.06 , 16.11]
Total		**214**		**217**	**100.0%**	**1.01 [0.06 , 16.11]**
Total events:	1		1			

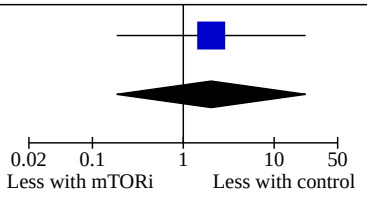
Test for overall effect: Z = 0.01 (P = 0.99)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 6.5. Comparison 6: mTOR inhibitors versus control (placebo, no treatment or standard therapy), Outcome 5: Death

Study or Subgroup	mTORi Events	mTORi Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Walz 2010	2	214	1	217	100.0%	2.03 [0.19 , 22.20]
Total		**214**		**217**	**100.0%**	**2.03 [0.19 , 22.20]**
Total events:	2		1			

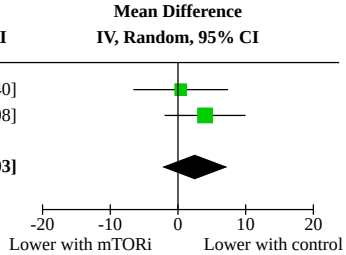
Test for overall effect: Z = 0.58 (P = 0.56)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 6.6. Comparison 6: mTOR inhibitors versus control (placebo, no treatment or standard therapy), Outcome 6: Systolic blood pressure [mm Hg]

Study or Subgroup	mTORi Mean	mTORi SD	mTORi Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
SIRENA 2010	133.3	6.9	7	132.9	6.9	8	42.2%	0.40 [-6.60 , 7.40]
SUISSE ADPKD 2007	130	14	48	126	16	49	57.8%	4.00 [-1.98 , 9.98]
Total (Wald{fn})			**55**			**57**	**100.0%**	**2.48 [-2.07 , 7.03]**

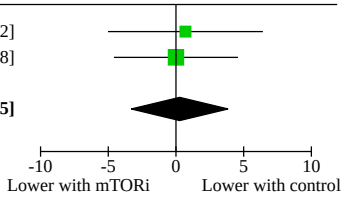
Test for overall effect: Z = 1.07 (P = 0.28)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.00; Chi² = 0.59, df = 1 (P = 0.44); I² = 0%



Analysis 6.7. Comparison 6: mTOR inhibitors versus control (placebo, no treatment or standard therapy), Outcome 7: Diastolic blood pressure [mm Hg]

Study or Subgroup	mTORi Mean	mTORi SD	mTORi Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
SIRENA 2010	87.1	5.3	7	86.4	6	8	39.1%	0.70 [-5.02 , 6.42]
SUISSE ADPKD 2007	82	11	48	82	12	49	60.9%	0.00 [-4.58 , 4.58]
Total (Wald{fn})			**55**			**57**	**100.0%**	**0.27 [-3.30 , 3.85]**

Test for overall effect: Z = 0.15 (P = 0.88)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.85); I² = 0%



Analysis 6.8. Comparison 6: mTOR inhibitors versus control (placebo, no treatment or standard therapy), Outcome 8: Blood pressure: descriptive data

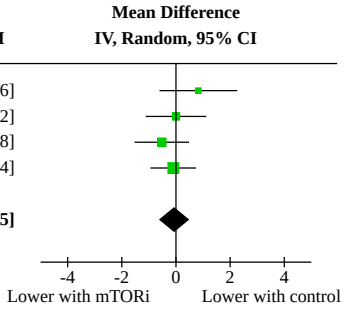
Blood pressure: descriptive data

Study	Description of outcome
SIRENA 2 2016	Baseline SBP treatment: 138.3 (9.5), final SBP treatment: 132.8 (12.7) Baseline SBP placebo: 134.1(13.3), final SBP placebo: 127.9 (11.6) Baseline DBP treatment: 87.1 (8.3), final DBP treatment: 84.8 (7.3) Baseline DBP placebo: 85.9 (7.2) n = 16, final DBP placebo: 81.9 (6.4) n = 17
Walz 2010	Quote: "The change from baseline in the systolic blood pressure at 24 months was −2.0 mm Hg in the mTOR-inhibitors group and −1.5 mm Hg in the placebo group (P = 0.76); the corresponding changes in diastolic blood pressure were −2.7 mm Hg and −2.6 mm Hg (P = 0.89)"

Analysis 6.9. Comparison 6: mTOR inhibitors versus control (placebo, no treatment or standard therapy), Outcome 9: Total kidney volume [L]

Study or Subgroup	mTORi Mean	mTORi SD	mTORi Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
SIRENA 2 2016	3.049	1.5195	8	2.2216	1.6514	11	13.2%	0.83 [-0.61 , 2.26]
SIRENA 2010	2	1.1	7	2	1.1	8	21.8%	0.00 [-1.12 , 1.12]
Braun 2014	1.537	0.863	8	2.059	1.236	9	26.9%	-0.52 [-1.53 , 0.48]
SUISSE ADPKD 2007	1	2.1	50	1.1	2.2	50	38.2%	-0.10 [-0.94 , 0.74]
Total (Wald{fn})			**73**			**78**	**100.0%**	**-0.07 [-0.59 , 0.45]**

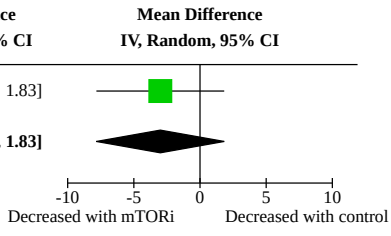
Test for overall effect: Z = 0.26 (P = 0.79)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.00; Chi² = 2.30, df = 3 (P = 0.51); I² = 0%



Analysis 6.10. Comparison 6: mTOR inhibitors versus control (placebo, no treatment or standard therapy), Outcome 10: Percent change in total kidney volume [L]

Study or Subgroup	mTORi Mean	mTORi SD	mTORi Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Braun 2014	4.8	5.3	8	7.8	4.8	9	100.0%	-3.00 [-7.83 , 1.83]
Total			**8**			**9**	**100.0%**	**-3.00 [-7.83 , 1.83]**

Test for overall effect: Z = 1.22 (P = 0.22)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



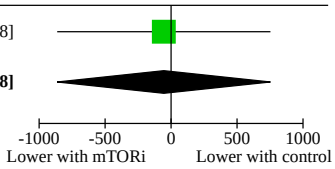
Analysis 6.11. Comparison 6: mTOR inhibitors versus control (placebo, no treatment or standard therapy), Outcome 11: Total kidney volume: descriptive data

Total kidney volume: descriptive data

Study	Description of outcome
Melemadathil 2013	Quote: "...there was a statistically significant reduction in total kidney volume when mTOR treatment was extended for 1 year"
Mora 2013	Quote: "...the mTOR group showed a kidney volume growth of 9,4 ±1,2mL/year compared with 11 ± 1.4 mL/year in control group"
Walz 2010	Quote: "...among patients receiving mTOR-inhibitors, the mean total kidney volume increased from 2028 ml to 2063 ml at 1 year and to 2176 ml at 2 years, and among those receiving placebo, it increased from 1911 ml to 2061 ml and to 2287 ml, respectively"

Analysis 6.12. Comparison 6: mTOR inhibitors versus control (placebo, no treatment or standard therapy), Outcome 12: Cyst volume [mL]

	mTORi			Control				Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**IV, Random, 95% CI**
SIRENA 2010	1112	780	7	1167	815	8	100.0%	-55.00 [-862.98 , 752.98]	
Total			**7**			**8**	**100.0%**	**-55.00 [-862.98 , 752.98]**	



Test for overall effect: Z = 0.13 (P = 0.89)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable

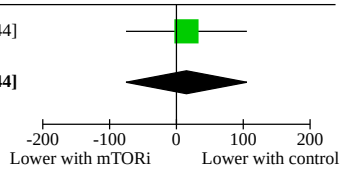
Analysis 6.13. Comparison 6: mTOR inhibitors versus control (placebo, no treatment or standard therapy), Outcome 13: Cyst volume: descriptive data

Cyst volume: descriptive data

Study	Description of outcome
Melemadathil 2013	Quote: "...there was a statistically significant reduction in total cyst volume when mTOR treatment was extended for 1 year"
Walz 2010	Quote: "The cyst volume increased by 76 ml at 1 year and 181 ml at 2 years in the mTOR-inhibitors group and by 98 ml and 215 ml, respectively, in the placebo group"

Analysis 6.14. Comparison 6: mTOR inhibitors versus control (placebo, no treatment or standard therapy), Outcome 14: Parenchymal volume [mL]

	mTORi			Control				Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**IV, Random, 95% CI**
SIRENA 2010	327	91	7	312	87	8	100.0%	15.00 [-75.44 , 105.44]	
Total			**7**			**8**	**100.0%**	**15.00 [-75.44 , 105.44]**	



Test for overall effect: Z = 0.33 (P = 0.75)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable

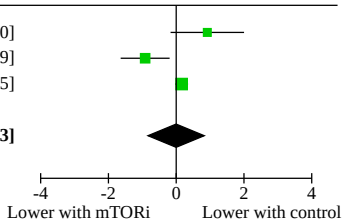
Analysis 6.15. Comparison 6: mTOR inhibitors versus control (placebo, no treatment or standard therapy), Outcome 15: Parenchymal volume: descriptive data

Parenchymal volume: descriptive data

Study	Description of outcome
Melemadathil 2013	Quote: "...there was a small but significant increase in renal parenchymal volume in patients receiving mTOR"
Walz 2010	Quote: "The parenchymal volume increased by 26 ml at 1 year and by 56 ml at 2 years in the mTOR-inhibitors group; the corresponding changes in the placebo group were 62 and 93 ml"

Analysis 6.16. Comparison 6: mTOR inhibitors versus control (placebo, no treatment or standard therapy), Outcome 16: Proteinuria

Study or Subgroup	mTORi Mean	mTORi SD	mTORi Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
SIRENA 2010	0.223	0.125	7	0.14	0.007	8	24.9%	0.92 [-0.17 , 2.00]
SIRENA 2 2016	0.3	0.2	16	0.6	0.4	17	32.7%	-0.92 [-1.64 , -0.19]
Walz 2010	564	1177	214	393	936	217	42.4%	0.16 [-0.03 , 0.35]
Total (Wald{fn})			**237**			**242**	**100.0%**	**-0.00 [-0.83 , 0.83]**



Test for overall effect: Z = 0.01 (P = 1.00)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.41; Chi² = 10.17, df = 2 (P = 0.006); I² = 80%

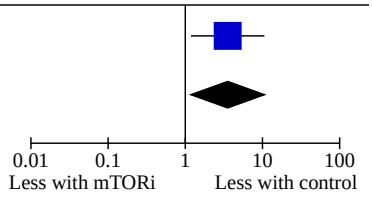
Analysis 6.17. Comparison 6: mTOR inhibitors versus control (placebo, no treatment or standard therapy), Outcome 17: Proteinuria: descriptive data

Proteinuria: descriptive data

Study	Description of outcome
Melemadathil 2013	Quote: "...there was a statistically significant increase in proteinuria in the mTOR arm as compared to the standard treatment group at the end of 6 months"

Analysis 6.18. Comparison 6: mTOR inhibitors versus control (placebo, no treatment or standard therapy), Outcome 18: Doubling of proteinuria

Study or Subgroup	mTORi Events	mTORi Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
SIRENA 2 2016	10	16	3	17	100.0%	3.54 [1.19 , 10.58]
Total		**16**		**17**	**100.0%**	**3.54 [1.19 , 10.58]**
Total events:	10		3			

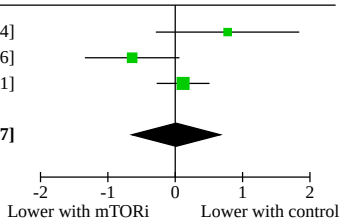


Test for overall effect: Z = 2.26 (P = 0.02)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable

Analysis 6.19. Comparison 6: mTOR inhibitors versus control (placebo, no treatment or standard therapy), Outcome 19: Albuminuria

Study or Subgroup	mTORi Mean	mTORi SD	mTORi Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
SIRENA 2010	76.3	57.3	7	39	31.3	8	22.2%	0.78 [-0.29 , 1.84]
SIRENA 2 2016	73.8	81.8	16	154.9	152.9	17	33.1%	-0.64 [-1.34 , 0.06]
SUISSE ADPKD 2007	3.4	12.9	50	2	10.8	50	44.7%	0.12 [-0.28 , 0.51]
Total (Wald{fn})			**73**			**75**	**100.0%**	**0.01 [-0.64 , 0.67]**

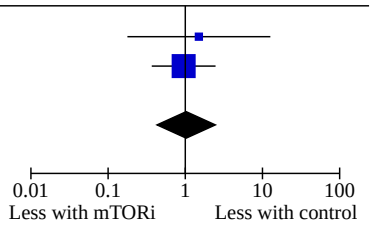
Test for overall effect: Z = 0.04 (P = 0.97)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.21; Chi² = 5.56, df = 2 (P = 0.06); I² = 64%



Analysis 6.20. Comparison 6: mTOR inhibitors versus control (placebo, no treatment or standard therapy), Outcome 20: Serious adverse events

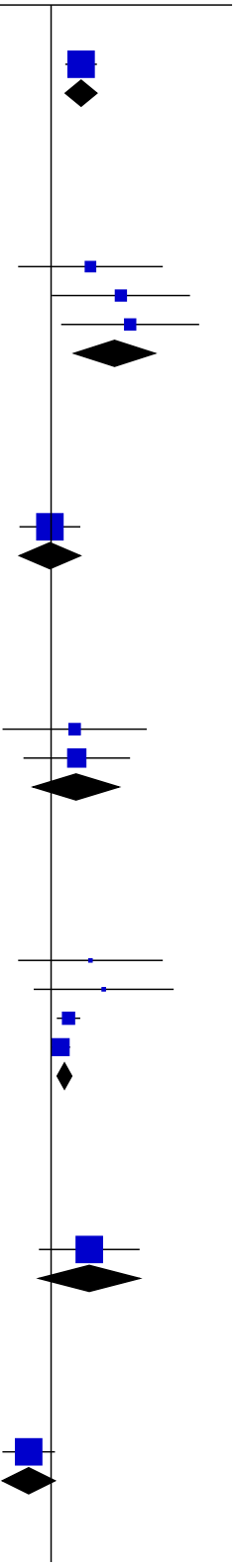
Study or Subgroup	mTORi Events	mTORi Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Braun 2014	3	20	1	10	16.6%	1.50 [0.18 , 12.65]
SIRENA 2 2016	6	21	6	20	83.4%	0.95 [0.37 , 2.47]
Total (Wald{fn})		**41**		**30**	**100.0%**	**1.03 [0.43 , 2.45]**
Total events:	9		7			

Test for overall effect: Z = 0.06 (P = 0.95)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.70); I² = 0%



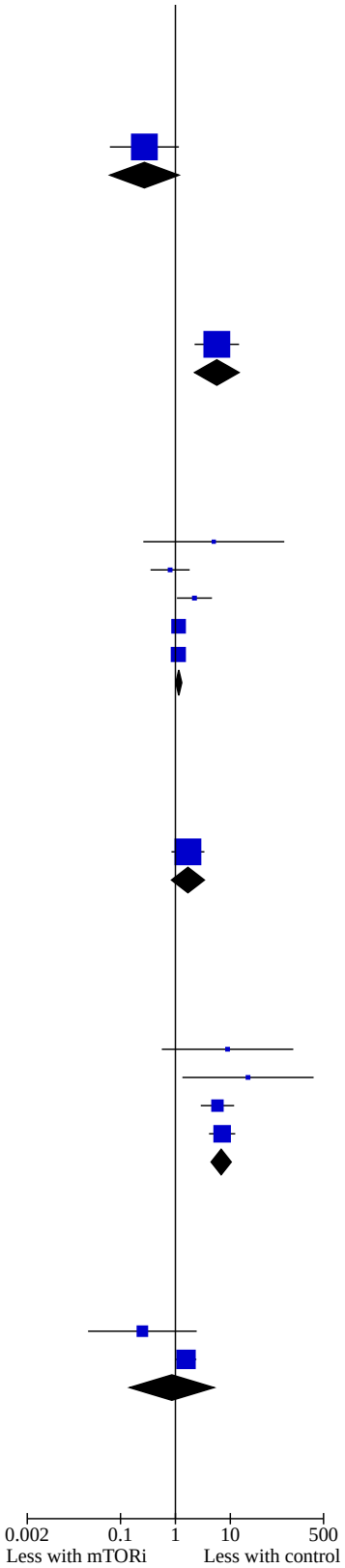
Analysis 6.21. Comparison 6: mTOR inhibitors versus control (placebo, no treatment or standard therapy), Outcome 21: Adverse events

Study or Subgroup	mTORi Events	mTORi Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
6.21.1 Anaemia						
Walz 2010	37	214	11	217	100.0%	3.41 [1.79 , 6.51]
Subtotal		**214**		**217**	**100.0%**	**3.41 [1.79 , 6.51]**
Total events:	37		11			
Test for overall effect: Z = 3.72 (P = 0.0002)						
Heterogeneity: Not applicable						
6.21.2 Angioedema						
SIRENA 2010	2	15	0	15	31.3%	5.00 [0.26 , 96.13]
SUISSE ADPKD 2007	8	49	0	50	34.3%	17.34 [1.03 , 292.48]
Walz 2010	12	214	0	217	34.4%	25.35 [1.51 , 425.45]
Subtotal (Wald{fn})		**278**		**282**	**100.0%**	**13.39 [2.56 , 70.00]**
Total events:	22		0			
Test for overall effect: Z = 3.07 (P = 0.002)						
Heterogeneity: Tau² = 0.00; Chi² = 0.70, df = 2 (P = 0.71); I² = 0%						
6.21.3 Arrhythmias						
SIRENA 2 2016	4	21	4	20	100.0%	0.95 [0.27 , 3.30]
Subtotal		**21**		**20**	**100.0%**	**0.95 [0.27 , 3.30]**
Total events:	4		4			
Test for overall effect: Z = 0.08 (P = 0.94)						
Heterogeneity: Not applicable						
6.21.4 Dermatitis						
Braun 2014	2	20	0	10	35.3%	2.62 [0.14 , 49.91]
SIRENA 2 2016	3	21	1	20	64.7%	2.86 [0.32 , 25.24]
Subtotal (Wald{fn})		**41**		**30**	**100.0%**	**2.77 [0.48 , 15.98]**
Total events:	5		1			
Test for overall effect: Z = 1.14 (P = 0.25)						
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.96); I² = 0%						
6.21.5 Diarrhoea						
SIRENA 2010	2	15	0	15	1.0%	5.00 [0.26 , 96.13]
SIRENA 2 2016	4	21	0	20	1.1%	8.59 [0.49 , 150.00]
SUISSE ADPKD 2007	30	49	15	50	38.7%	2.04 [1.26 , 3.29]
Walz 2010	51	214	35	217	59.2%	1.48 [1.00 , 2.17]
Subtotal (Wald{fn})		**299**		**302**	**100.0%**	**1.73 [1.28 , 2.33]**
Total events:	87		50			
Test for overall effect: Z = 3.60 (P = 0.0003)						
Heterogeneity: Tau² = 0.00; Chi² = 2.81, df = 3 (P = 0.42); I² = 0%						
6.21.6 Dysmenorrhea						
SIRENA 2 2016	5	21	1	20	100.0%	4.76 [0.61 , 37.28]
Subtotal		**21**		**20**	**100.0%**	**4.76 [0.61 , 37.28]**
Total events:	5		1			
Test for overall effect: Z = 1.49 (P = 0.14)						
Heterogeneity: Not applicable						
6.21.7 Gastrointestinal symptoms						
Braun 2014	4	20	5	10	100.0%	0.40 [0.14 , 1.17]
Subtotal		**20**		**10**	**100.0%**	**0.40 [0.14 , 1.17]**
Total events:	4		5			
Test for overall effect: Z = 1.67 (P = 0.09)						



Analysis 6.21. (Continued)

Total events:	4		3			
Test for overall effect: Z = 1.67 (P = 0.09)						
Heterogeneity: Not applicable						
6.21.8 Haematuria						
SIRENA 2 2016	2	21	7	20	100.0%	0.27 [0.06 , 1.16]
Subtotal		**21**		**20**	**100.0%**	**0.27 [0.06 , 1.16]**
Total events:	2		7			
Test for overall effect: Z = 1.76 (P = 0.08)						
Heterogeneity: Not applicable						
6.21.9 Hyperlipidaemia						
Walz 2010	28	214	5	217	100.0%	5.68 [2.23 , 14.43]
Subtotal		**214**		**217**	**100.0%**	**5.68 [2.23 , 14.43]**
Total events:	28		5			
Test for overall effect: Z = 3.65 (P = 0.0003)						
Heterogeneity: Not applicable						
6.21.10 Infection						
SIRENA 2010	2	15	0	15	0.2%	5.00 [0.26 , 96.13]
Braun 2014	8	20	5	10	2.3%	0.80 [0.35 , 1.82]
SIRENA 2 2016	14	21	6	20	2.8%	2.22 [1.07 , 4.63]
SUISSE ADPKD 2007	47	49	42	50	46.2%	1.14 [1.00 , 1.31]
Walz 2010	156	214	140	217	48.4%	1.13 [0.99 , 1.28]
Subtotal (Wald{fn})		**319**		**312**	**100.0%**	**1.15 [1.02 , 1.31]**
Total events:	227		193			
Test for overall effect: Z = 2.20 (P = 0.03)						
Heterogeneity: Tau² = 0.00; Chi² = 5.02, df = 4 (P = 0.28); I² = 20%						
6.21.11 Nausea						
Walz 2010	20	214	12	217	100.0%	1.69 [0.85 , 3.37]
Subtotal		**214**		**217**	**100.0%**	**1.69 [0.85 , 3.37]**
Total events:	20		12			
Test for overall effect: Z = 1.49 (P = 0.14)						
Heterogeneity: Not applicable						
6.21.12 Oral ulcers						
Braun 2014	8	20	0	10	2.3%	8.90 [0.57 , 140.31]
SIRENA 2010	10	15	0	15	2.4%	21.00 [1.34 , 328.86]
SUISSE ADPKD 2007	40	49	7	50	36.4%	5.83 [2.90 , 11.74]
Walz 2010	91	214	13	217	58.9%	7.10 [4.10 , 12.30]
Subtotal (Wald{fn})		**298**		**292**	**100.0%**	**6.82 [4.47 , 10.39]**
Total events:	149		20			
Test for overall effect: Z = 8.91 (P < 0.00001)						
Heterogeneity: Tau² = 0.00; Chi² = 0.92, df = 3 (P = 0.82); I² = 0%						
6.21.13 Peripheral oedema						
Braun 2014	1	20	2	10	32.5%	0.25 [0.03 , 2.44]
SIRENA 2 2016	18	21	11	20	67.5%	1.56 [1.01 , 2.40]
Subtotal (Wald{fn})		**41**		**30**	**100.0%**	**0.86 [0.15 , 5.05]**
Total events:	19		13			
Test for overall effect: Z = 0.17 (P = 0.87)						
Heterogeneity: Tau² = 1.16; Chi² = 2.66, df = 1 (P = 0.10); I² = 62%						



Comparison 7. mTOR inhibitors plus somatostatin analogues versus somatostatin analogues alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Total kidney volume: descriptive data	0		Other data	No numeric data

Analysis 7.1. Comparison 7: mTOR inhibitors plus somatostatin analogues versus somatostatin analogues alone, Outcome 1: Total kidney volume: descriptive data

Total kidney volume: descriptive data

Study	Description of outcome
ELATE 2011	Quote: "The median kidney volume was not affected by octreotide and did not change significantly in the 6 patients through the course of the trial (from 798 mL (IQR 675–1960 mL) at baseline to 811 mL (IQR 653–1960 mL) after 48 weeks, p=0.75). Likewise, octreotide-everolimus combination treatment (n=6) did not affect kidney volume over the course of 48 weeks (from 623 mL (IQR 483–1110 ml) to 602 mL (IQR 493–1259 mL), p=0.75). Change in kidney volume did not differ between treatment arms (p=1.00)"

Comparison 8. mTOR inhibitors (mTORi) plus renin-angiotensin system inhibitors (RAASi) versus RAASi alone

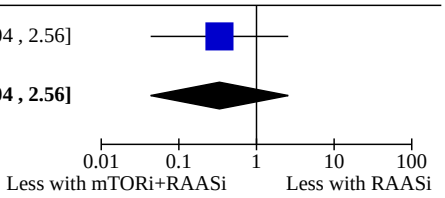
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Doubling of serum creatinine	1	16	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.04, 2.56]
8.2 GFR	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.2.1 High-dose mTORi	1	35	Mean Difference (IV, Random, 95% CI)	6.80 [-6.28, 19.88]
8.2.2 Low-dose mTORi	1	34	Mean Difference (IV, Random, 95% CI)	3.80 [-10.39, 17.99]
8.2.3 ARB + mTORi	1	16	Mean Difference (IV, Random, 95% CI)	9.60 [-8.98, 28.18]
8.3 Mean arterial pressure [mm Hg]	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.3.1 High-dose mTORi	1	35	Mean Difference (IV, Random, 95% CI)	3.00 [-2.89, 8.89]
8.3.2 Low-dose mTORi	1	36	Mean Difference (IV, Random, 95% CI)	-4.00 [-8.63, 0.63]
8.4 Blood pressure: descriptive data	0		Other data	No numeric data
8.5 Total kidney volume [L]	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.5.1 High-dose mTORi	1	35	Mean Difference (IV, Random, 95% CI)	-0.40 [-0.84, 0.04]
8.5.2 Low-dose mTORi	1	34	Mean Difference (IV, Random, 95% CI)	-0.18 [-0.61, 0.25]
8.5.3 ARB + mTORi	1	16	Mean Difference (IV, Random, 95% CI)	-0.73 [-1.06, -0.40]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.6 Cyst volume [mL]	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.6.1 High-dose mTORi	1	35	Mean Difference (IV, Random, 95% CI)	-44.00 [-104.07, 16.07]
8.6.2 Low-dose mTORi	1	34	Mean Difference (IV, Random, 95% CI)	-28.00 [-90.52, 34.52]
8.7 Proteinuria [g/24 hours]	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.7.1 High-dose mTORi	1	35	Mean Difference (IV, Random, 95% CI)	0.50 [0.09, 0.91]
8.7.2 Low-dose mTORi	1	37	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.29, 0.09]
8.8 Adverse events	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.8.1 Anaemia	1	53	Risk Ratio (M-H, Random, 95% CI)	2.24 [0.11, 44.13]
8.8.2 Hyperlipidaemia	1	53	Risk Ratio (M-H, Random, 95% CI)	10.29 [0.64, 164.71]
8.8.3 Infection	2	69	Risk Ratio (M-H, Random, 95% CI)	2.04 [0.58, 7.17]
8.8.4 Oral ulcers	1	53	Risk Ratio (M-H, Random, 95% CI)	7.61 [0.47, 124.35]

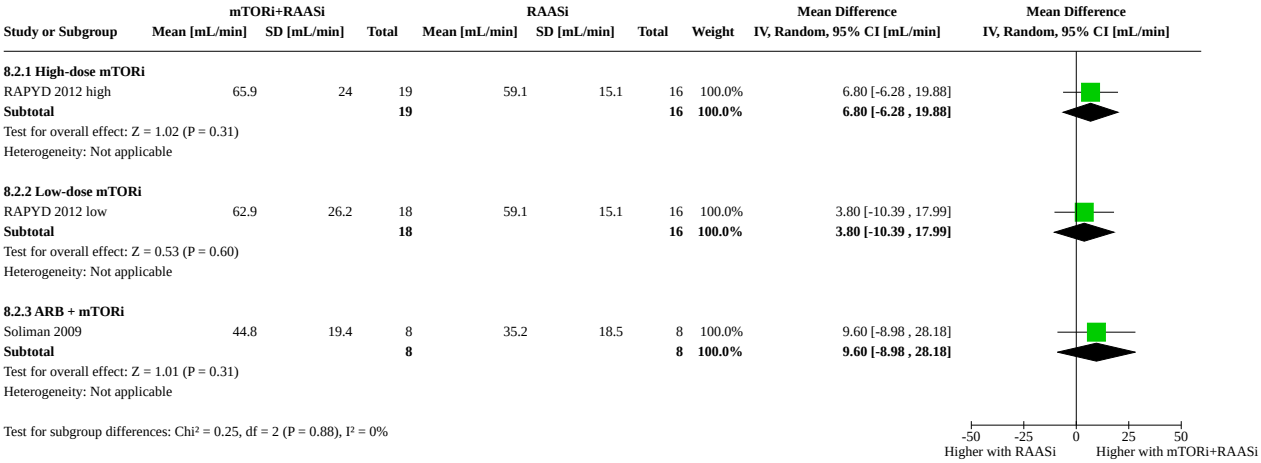
Analysis 8.1. Comparison 8: mTOR inhibitors (mTORi) plus renin-angiotensin system inhibitors (RAASi) versus RAASi alone, Outcome 1: Doubling of serum creatinine

Study or Subgroup	mTORi+RAASi Events	Total	RAASi Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Soliman 2009	1	8	3	8	100.0%	0.33 [0.04 , 2.56]
Total		**8**		**8**	**100.0%**	**0.33 [0.04 , 2.56]**
Total events:	1		3			

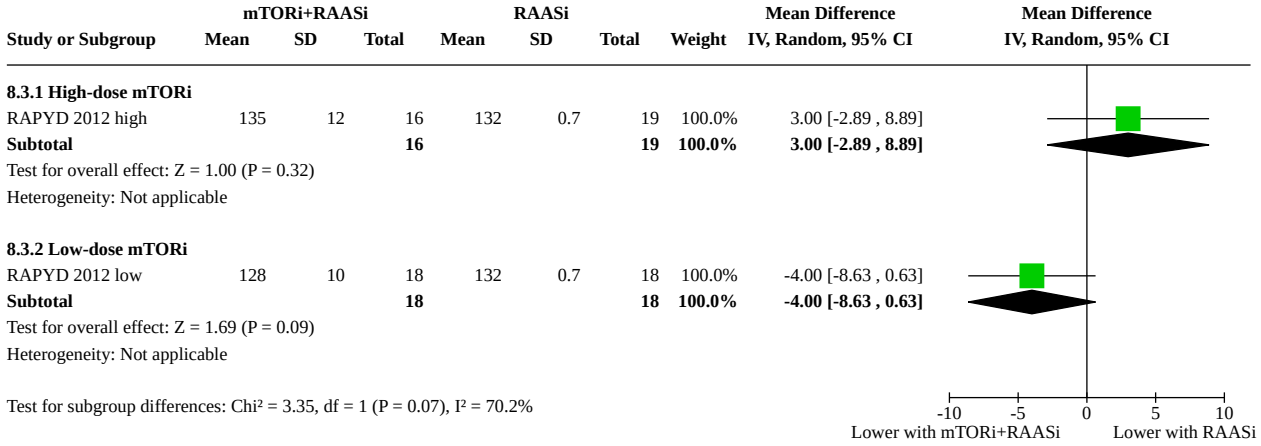
Test for overall effect: Z = 1.06 (P = 0.29)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 8.2. Comparison 8: mTOR inhibitors (mTORi) plus renin-angiotensin system inhibitors (RAASi) versus RAASi alone, Outcome 2: GFR



Analysis 8.3. Comparison 8: mTOR inhibitors (mTORi) plus renin-angiotensin system inhibitors (RAASi) versus RAASi alone, Outcome 3: Mean arterial pressure [mm Hg]



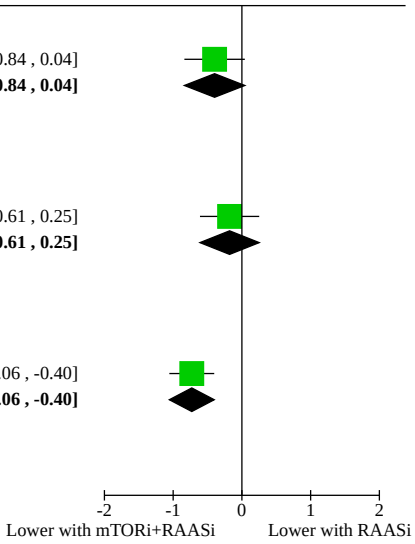
Analysis 8.4. Comparison 8: mTOR inhibitors (mTORi) plus renin-angiotensin system inhibitors (RAASi) versus RAASi alone, Outcome 4: Blood pressure: descriptive data

Blood pressure: descriptive data

Study	Description of outcome
Soliman 2009	The mean diastolic pressure decreased by 2.5 to 4.0 mm Hg in the ARB + mTOR group and increased by 0.5 to 1.5 mm Hg in the ARB alone group The mean systolic pressure decreased by 2.5 to 5.0 mm Hg in the ARB + mTOR group and increased by 1.0 to 2.5 mm Hg in the ARB alone group

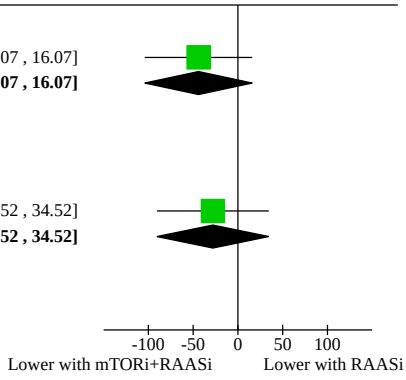
Analysis 8.5. Comparison 8: mTOR inhibitors (mTORi) plus renin-angiotensin system inhibitors (RAASi) versus RAASi alone, Outcome 5: Total kidney volume [L]

Study or Subgroup	mTORi+RAASi Mean	SD	Total	RAASi Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
8.5.1 High-dose mTORi								
RAPYD 2012 high	1.508	0.674	19	1.905	0.65	16	100.0%	-0.40 [-0.84 , 0.04]
Subtotal			**19**			**16**	**100.0%**	**-0.40 [-0.84 , 0.04]**
Test for overall effect: Z = 1.77 (P = 0.08)								
Heterogeneity: Not applicable								
8.5.2 Low-dose mTORi								
RAPYD 2012 low	1.726	0.628	18	1.905	0.65	16	100.0%	-0.18 [-0.61 , 0.25]
Subtotal			**18**			**16**	**100.0%**	**-0.18 [-0.61 , 0.25]**
Test for overall effect: Z = 0.81 (P = 0.42)								
Heterogeneity: Not applicable								
8.5.3 ARB + mTORi								
Soliman 2009	3.221	0.311	8	3.95	0.354	8	100.0%	-0.73 [-1.06 , -0.40]
Subtotal			**8**			**8**	**100.0%**	**-0.73 [-1.06 , -0.40]**
Test for overall effect: Z = 4.38 (P < 0.0001)								
Heterogeneity: Not applicable								
Test for subgroup differences: Chi² = 4.23, df = 2 (P = 0.12), I² = 52.7%								



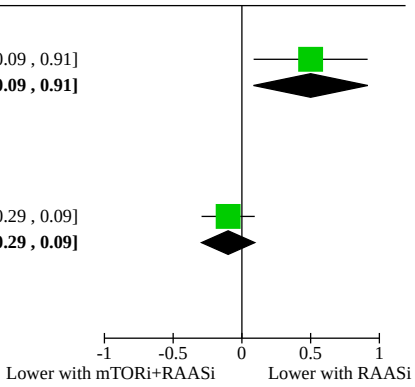
Analysis 8.6. Comparison 8: mTOR inhibitors (mTORi) plus renin-angiotensin system inhibitors (RAASi) versus RAASi alone, Outcome 6: Cyst volume [mL]

Study or Subgroup	mTORi+RAASi Mean	SD	Total	RAASi Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
8.6.1 High-dose mTORi								
RAPYD 2012 high	125	93	19	169	88	16	100.0%	-44.00 [-104.07 , 16.07]
Subtotal			**19**			**16**	**100.0%**	**-44.00 [-104.07 , 16.07]**
Test for overall effect: Z = 1.44 (P = 0.15)								
Heterogeneity: Not applicable								
8.6.2 Low-dose mTORi								
RAPYD 2012 low	141	98	18	169	88	16	100.0%	-28.00 [-90.52 , 34.52]
Subtotal			**18**			**16**	**100.0%**	**-28.00 [-90.52 , 34.52]**
Test for overall effect: Z = 0.88 (P = 0.38)								
Heterogeneity: Not applicable								
Test for subgroup differences: Chi² = 0.13, df = 1 (P = 0.72), I² = 0%								



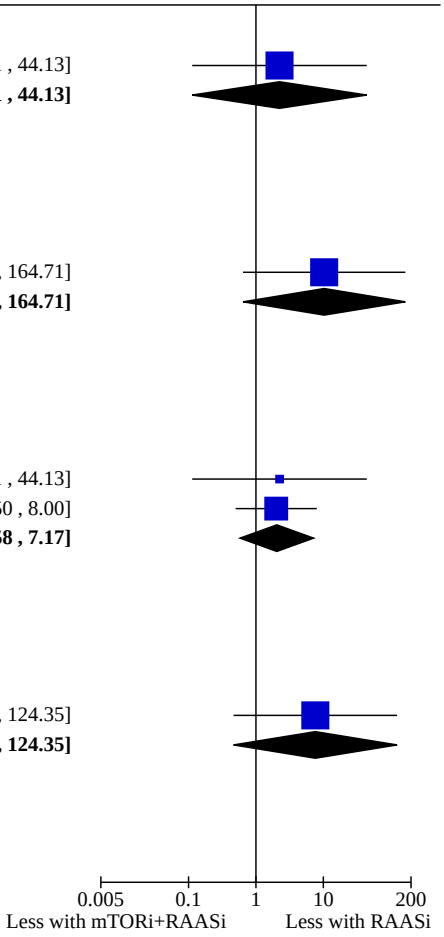
Analysis 8.7. Comparison 8: mTOR inhibitors (mTORi) plus renin-angiotensin system inhibitors (RAASi) versus RAASi alone, Outcome 7: Proteinuria [g/24 hours]

Study or Subgroup	mTORi+RAASi Mean	SD	Total	RAASi Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
8.7.1 High-dose mTORi								
RAPYD 2012 high	0.65	0.8	16	0.15	0.3	19	100.0%	0.50 [0.09 , 0.91]
Subtotal			**16**			**19**	**100.0%**	**0.50 [0.09 , 0.91]**
Test for overall effect: Z = 2.36 (P = 0.02)								
Heterogeneity: Not applicable								
8.7.2 Low-dose mTORi								
RAPYD 2012 low	0.15	0.3	19	0.25	0.3	18	100.0%	-0.10 [-0.29 , 0.09]
Subtotal			**19**			**18**	**100.0%**	**-0.10 [-0.29 , 0.09]**
Test for overall effect: Z = 1.01 (P = 0.31)								
Heterogeneity: Not applicable								
Test for subgroup differences: Chi² = 6.61, df = 1 (P = 0.01), I² = 84.9%								



Analysis 8.8. Comparison 8: mTOR inhibitors (mTORi) plus renin-angiotensin system inhibitors (RAASi) versus RAASi alone, Outcome 8: Adverse events

Study or Subgroup	mTORi+RAASi Events	Total	RAASi Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
8.8.1 Anaemia						
RAPYD 2012	2	37	0	16	100.0%	2.24 [0.11 , 44.13]
Subtotal		**37**		**16**	**100.0%**	**2.24 [0.11 , 44.13]**
Total events:	2		0			
Test for overall effect: Z = 0.53 (P = 0.60)						
Heterogeneity: Not applicable						
8.8.2 Hyperlipidaemia						
RAPYD 2012	11	37	0	16	100.0%	10.29 [0.64 , 164.71]
Subtotal		**37**		**16**	**100.0%**	**10.29 [0.64 , 164.71]**
Total events:	11		0			
Test for overall effect: Z = 1.65 (P = 0.10)						
Heterogeneity: Not applicable						
8.8.3 Infection						
RAPYD 2012	2	37	0	16	17.8%	2.24 [0.11 , 44.13]
Soliman 2009	4	8	2	8	82.2%	2.00 [0.50 , 8.00]
Subtotal (Wald{fn})		**45**		**24**	**100.0%**	**2.04 [0.58 , 7.17]**
Total events:	6		2			
Test for overall effect: Z = 1.11 (P = 0.27)						
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.95); I² = 0%						
8.8.4 Oral ulcers						
RAPYD 2012	8	37	0	16	100.0%	7.61 [0.47 , 124.35]
Subtotal		**37**		**16**	**100.0%**	**7.61 [0.47 , 124.35]**
Total events:	8		0			
Test for overall effect: Z = 1.42 (P = 0.15)						
Heterogeneity: Not applicable						
Test for subgroup differences: Chi² = 1.58, df = 3 (P = 0.66), I² = 0%						



Comparison 9. Metformin versus placebo

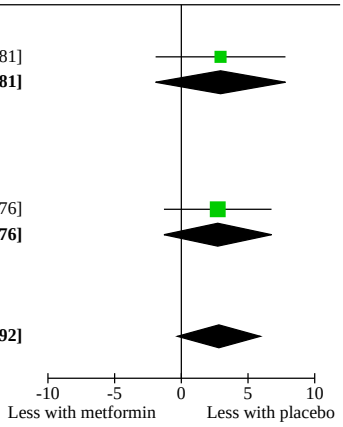
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Change in eGFR [mL/min/1.73 m^2]	2	142	Mean Difference (IV, Random, 95% CI)	2.82 [-0.29, 5.92]
9.1.1 Duration ≤ 1 year	1	45	Mean Difference (IV, Random, 95% CI)	2.94 [-1.93, 7.81]
9.1.2 Duration > 1 year	1	97	Mean Difference (IV, Random, 95% CI)	2.73 [-1.30, 6.76]
9.2 Rate of eGFR decline	1	45	Mean Difference (IV, Random, 95% CI)	2.94 [-1.93, 7.81]
9.3 Annual rate of eGFR decline	1	82	Mean Difference (IV, Random, 95% CI)	1.36 [-0.70, 3.42]
9.4 Kidney failure	1	97	Risk Ratio (M-H, Random, 95% CI)	Not estimable
9.5 Death	1	97	Risk Ratio (M-H, Random, 95% CI)	2.94 [0.12, 70.43]
9.6 Pain	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.6.1 Back pain	1	97	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.27, 2.50]
9.6.2 Abdominal fullness	1	97	Risk Ratio (M-H, Random, 95% CI)	2.94 [0.12, 70.43]
9.6.3 Pain interference on sleep	1	97	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.14, 6.68]
9.6.4 Pain during strenuous physical activity	1	97	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.17, 3.11]
9.7 Quality of life score	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
9.7.1 SF-36 physical component summary	1	84	Mean Difference (IV, Random, 95% CI)	-1.90 [-4.93, 1.13]
9.7.2 SF-36 mental component summary	1	84	Mean Difference (IV, Random, 95% CI)	0.30 [-2.67, 3.27]
9.8 Percent change in height-adjusted total kidney volume	2	140	Mean Difference (IV, Random, 95% CI)	1.05 [-1.73, 3.83]
9.9 Mean annual percent change in height-adjusted total kidney volume	1	73	Mean Difference (IV, Random, 95% CI)	1.71 [-2.34, 5.76]
9.10 Absolute change in height-adjusted total kidney volume	1	73	Mean Difference (IV, Random, 95% CI)	-146.90 [-381.70, 87.90]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.11 Height-adjusted liver volume	1	73	Mean Difference (IV, Random, 95% CI)	299.70 [65.36, 534.04]
9.12 Serious adverse events	2	148	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.26, 5.18]
9.13 Adverse events	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.13.1 Any adverse event	1	97	Risk Ratio (M-H, Random, 95% CI)	1.58 [0.90, 2.79]
9.13.2 Gastrointestinal tract symptoms	1	97	Risk Ratio (M-H, Random, 95% CI)	2.94 [0.12, 70.43]
9.13.3 Infection	2	148	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.50, 1.69]
9.13.4 Hypoglycaemia < 70 mg/dL	1	51	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.06, 14.55]
9.13.5 Sustained oedema refractory to diuretics	1	97	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.22, 2.74]
9.13.6 Urinary tract infection or cyst rupture	1	51	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.05, 4.98]
9.13.7 Diarrhoea	2	148	Risk Ratio (M-H, Random, 95% CI)	1.80 [1.16, 2.80]
9.13.8 Nausea	2	148	Risk Ratio (M-H, Random, 95% CI)	1.92 [1.10, 3.36]
9.14 Dose completion	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.14.1 Completed full dose	2	142	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.29, 2.52]
9.14.2 Completed 50% dose	1	45	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.67, 1.01]
9.15 C-reactive protein	1	73	Mean Difference (IV, Random, 95% CI)	0.05 [-0.05, 0.15]

Analysis 9.1. Comparison 9: Metformin versus placebo, Outcome 1: Change in eGFR [mL/min/1.73 m^2]

Study or Subgroup	Metformin Mean	Metformin SD	Metformin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
9.1.1 Duration ≤ 1 year								
Brosnahan 2022	-0.41	8.4897	22	-3.35	8.1529	23	40.7%	2.94 [-1.93 , 7.81]
Subtotal			**22**			**23**	**40.7%**	**2.94 [-1.93 , 7.81]**
Test for overall effect: Z = 1.18 (P = 0.24)								
Heterogeneity: Not applicable								
9.1.2 Duration > 1 year								
TAME-PKD 2018	-3.41	10.270388	49	-6.14	9.987267	48	59.3%	2.73 [-1.30 , 6.76]
Subtotal			**49**			**48**	**59.3%**	**2.73 [-1.30 , 6.76]**
Test for overall effect: Z = 1.33 (P = 0.18)								
Heterogeneity: Not applicable								
Total (Wald{fn})			**71**			**71**	**100.0%**	**2.82 [-0.29 , 5.92]**

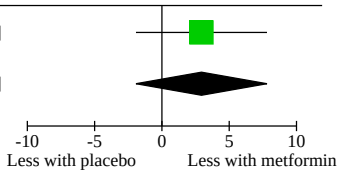
Test for overall effect: Z = 1.78 (P = 0.08)
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.95), I² = 0%
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.95); I² = 0%



Analysis 9.2. Comparison 9: Metformin versus placebo, Outcome 2: Rate of eGFR decline

Study or Subgroup	Metformin Mean	Metformin SD	Metformin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Brosnahan 2022	-0.41	8.4897	22	-3.35	8.1529	23	100.0%	2.94 [-1.93 , 7.81]
Total			**22**			**23**	**100.0%**	**2.94 [-1.93 , 7.81]**

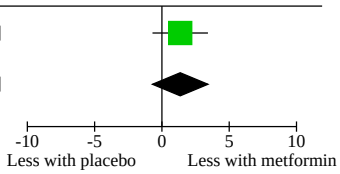
Test for overall effect: Z = 1.18 (P = 0.24)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 9.3. Comparison 9: Metformin versus placebo, Outcome 3: Annual rate of eGFR decline

Study or Subgroup	Metformin Mean	Metformin SD	Metformin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
TAME-PKD 2018	-1.71	4.7574	40	-3.07	4.7574	42	100.0%	1.36 [-0.70 , 3.42]
Total			**40**			**42**	**100.0%**	**1.36 [-0.70 , 3.42]**

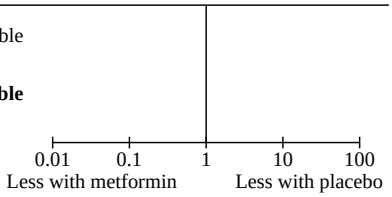
Test for overall effect: Z = 1.29 (P = 0.20)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 9.4. Comparison 9: Metformin versus placebo, Outcome 4: Kidney failure

Study or Subgroup	Metformin Events	Metformin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
TAME-PKD 2018	0	49	0	48		Not estimable
Total		**49**		**48**		**Not estimable**
Total events:	0		0			

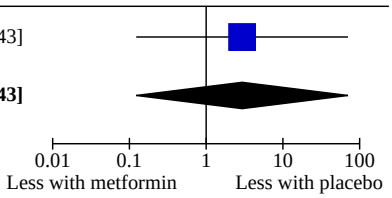
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 9.5. Comparison 9: Metformin versus placebo, Outcome 5: Death

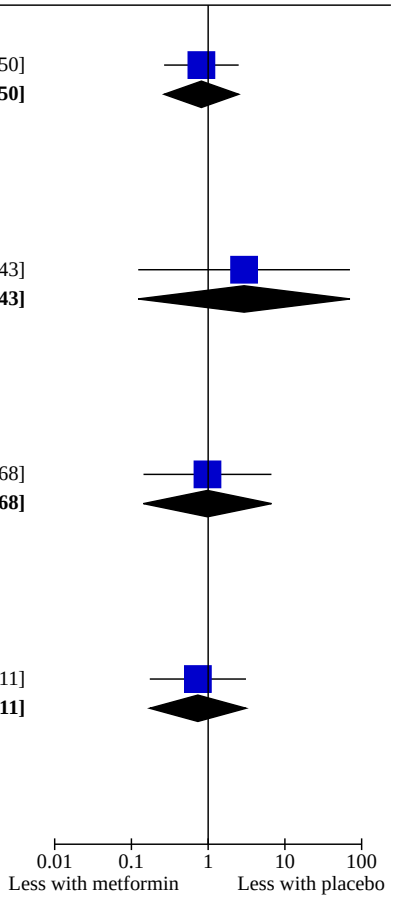
Study or Subgroup	Metformin Events	Metformin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
TAME-PKD 2018	1	49	0	48	100.0%	2.94 [0.12 , 70.43]
Total		**49**		**48**	**100.0%**	**2.94 [0.12 , 70.43]**
Total events:	1		0			

Test for overall effect: Z = 0.67 (P = 0.51)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



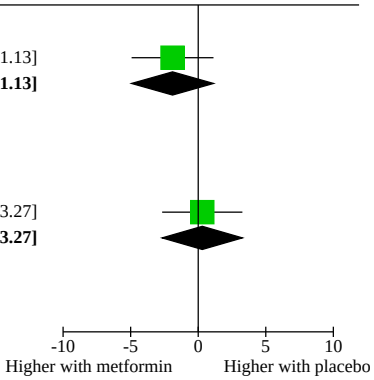
Analysis 9.6. Comparison 9: Metformin versus placebo, Outcome 6: Pain

Study or Subgroup	Metformin Events	Metformin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
9.6.1 Back pain						
TAME-PKD 2018	5	49	6	48	100.0%	0.82 [0.27 , 2.50]
Subtotal		**49**		**48**	**100.0%**	**0.82 [0.27 , 2.50]**
Total events:	5		6			
Test for overall effect: Z = 0.36 (P = 0.72)						
Heterogeneity: Not applicable						
9.6.2 Abdominal fullness						
TAME-PKD 2018	1	49	0	48	100.0%	2.94 [0.12 , 70.43]
Subtotal		**49**		**48**	**100.0%**	**2.94 [0.12 , 70.43]**
Total events:	1		0			
Test for overall effect: Z = 0.67 (P = 0.51)						
Heterogeneity: Not applicable						
9.6.3 Pain interference on sleep						
TAME-PKD 2018	2	49	2	48	100.0%	0.98 [0.14 , 6.68]
Subtotal		**49**		**48**	**100.0%**	**0.98 [0.14 , 6.68]**
Total events:	2		2			
Test for overall effect: Z = 0.02 (P = 0.98)						
Heterogeneity: Not applicable						
9.6.4 Pain during strenuous physical activity						
TAME-PKD 2018	3	49	4	48	100.0%	0.73 [0.17 , 3.11]
Subtotal		**49**		**48**	**100.0%**	**0.73 [0.17 , 3.11]**
Total events:	3		4			
Test for overall effect: Z = 0.42 (P = 0.68)						
Heterogeneity: Not applicable						
Test for subgroup differences: Chi² = 0.64, df = 3 (P = 0.89), I² = 0%						



Analysis 9.7. Comparison 9: Metformin versus placebo, Outcome 7: Quality of life score

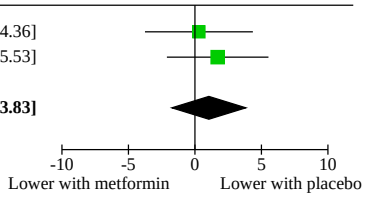
Study or Subgroup	Metformin Mean	Metformin SD	Metformin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
9.7.1 SF-36 physical component summary								
TAME-PKD 2018	51.4	7.4037	39	53.3	6.6571	45	100.0%	-1.90 [-4.93 , 1.13]
Subtotal			**39**			**45**	**100.0%**	**-1.90 [-4.93 , 1.13]**
Test for overall effect: Z = 1.23 (P = 0.22)								
Heterogeneity: Not applicable								
9.7.2 SF-36 mental component summary								
TAME-PKD 2018	53.5	7.4037	39	53.2	6.3242	45	100.0%	0.30 [-2.67 , 3.27]
Subtotal			**39**			**45**	**100.0%**	**0.30 [-2.67 , 3.27]**
Test for overall effect: Z = 0.20 (P = 0.84)								
Heterogeneity: Not applicable								
Test for subgroup differences: Chi² = 1.03, df = 1 (P = 0.31), I² = 3.2%								



Analysis 9.8. Comparison 9: Metformin versus placebo, Outcome 8: Percent change in height-adjusted total kidney volume

Study or Subgroup	Metformin Mean	Metformin SD	Metformin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Brosnahan 2022	3.45	5.957348	21	3.15	7.551569	22	47.0%	0.30 [-3.76 , 4.36]
TAME-PKD 2018	3.87	9.835203	49	2.16	9.350148	48	53.0%	1.71 [-2.11 , 5.53]
Total (Wald{fn})			**70**			**70**	**100.0%**	**1.05 [-1.73 , 3.83]**

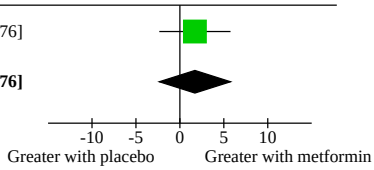
Test for overall effect: Z = 0.74 (P = 0.46)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 1 (P = 0.62); I² = 0%



Analysis 9.9. Comparison 9: Metformin versus placebo, Outcome 9: Mean annual percent change in height-adjusted total kidney volume

Study or Subgroup	Metformin Mean	Metformin SD	Metformin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
TAME-PKD 2018	3.87	8.8219	35	2.16	8.8219	38	100.0%	1.71 [-2.34 , 5.76]
Total			**35**			**38**	**100.0%**	**1.71 [-2.34 , 5.76]**

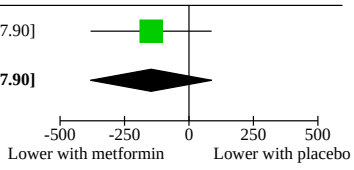
Test for overall effect: Z = 0.83 (P = 0.41)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 9.10. Comparison 9: Metformin versus placebo, Outcome 10: Absolute change in height-adjusted total kidney volume

Study or Subgroup	Metformin Mean	Metformin SD	Metformin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
TAME-PKD 2018	706.7	381.3549	35	853.6	622.4676	38	100.0%	-146.90 [-381.70 , 87.90]
Total			**35**			**38**	**100.0%**	**-146.90 [-381.70 , 87.90]**

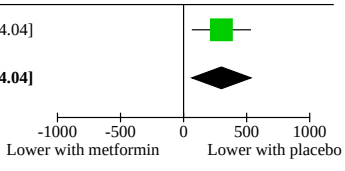
Test for overall effect: Z = 1.23 (P = 0.22)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 9.11. Comparison 9: Metformin versus placebo, Outcome 11: Height-adjusted liver volume

Study or Subgroup	Metformin Mean	Metformin SD	Metformin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
TAME-PKD 2018	1375.1	665.478899	35	1075.4	249.778044	38	100.0%	299.70 [65.36 , 534.04]
Total			**35**			**38**	**100.0%**	**299.70 [65.36 , 534.04]**

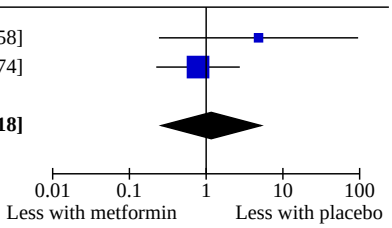
Test for overall effect: Z = 2.51 (P = 0.01)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 9.12. Comparison 9: Metformin versus placebo, Outcome 12: Serious adverse events

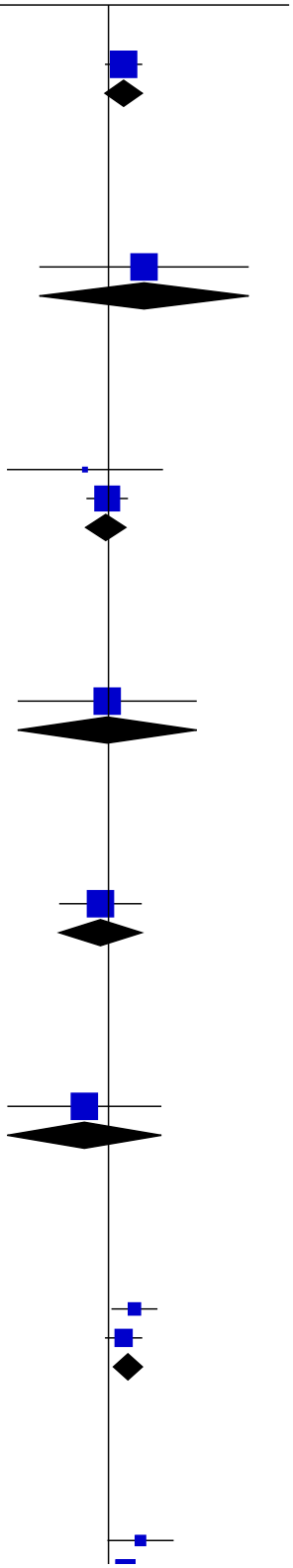
Study or Subgroup	Metformin Events	Metformin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Brosnahan 2022	2	26	0	25	21.8%	4.81 [0.24 , 95.58]
TAME-PKD 2018	4	49	5	48	78.2%	0.78 [0.22 , 2.74]
Total (Wald{fn})		**75**		**73**	**100.0%**	**1.16 [0.26 , 5.18]**
Total events:	6		5			

Test for overall effect: Z = 0.20 (P = 0.84)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.33; Chi² = 1.24, df = 1 (P = 0.26); I² = 20%



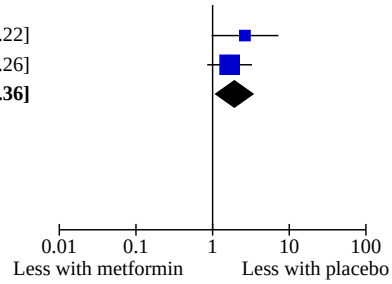
Analysis 9.13. Comparison 9: Metformin versus placebo, Outcome 13: Adverse events

Study or Subgroup	Metformin Events	Metformin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
9.13.1 Any adverse event						
TAME-PKD 2018	21	49	13	48	100.0%	1.58 [0.90 , 2.79]
Subtotal		**49**		**48**	**100.0%**	**1.58 [0.90 , 2.79]**
Total events:	21		13			
Test for overall effect: Z = 1.59 (P = 0.11)						
Heterogeneity: Not applicable						
9.13.2 Gastrointestinal tract symptoms						
TAME-PKD 2018	1	49	0	48	100.0%	2.94 [0.12 , 70.43]
Subtotal		**49**		**48**	**100.0%**	**2.94 [0.12 , 70.43]**
Total events:	1		0			
Test for overall effect: Z = 0.67 (P = 0.51)						
Heterogeneity: Not applicable						
9.13.3 Infection						
TAME-PKD 2018	1	49	2	48	6.6%	0.49 [0.05 , 5.23]
Brosnahan 2022	11	26	11	25	93.4%	0.96 [0.51 , 1.81]
Subtotal (Wald{fn})		**75**		**73**	**100.0%**	**0.92 [0.50 , 1.69]**
Total events:	12		13			
Test for overall effect: Z = 0.27 (P = 0.79)						
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.30, df = 1 (P = 0.58); I^2 = 0%						
9.13.4 Hypoglycaemia < 70 mg/dL						
TAME-PKD 2018	1	26	1	25	100.0%	0.96 [0.06 , 14.55]
Subtotal		**26**		**25**	**100.0%**	**0.96 [0.06 , 14.55]**
Total events:	1		1			
Test for overall effect: Z = 0.03 (P = 0.98)						
Heterogeneity: Not applicable						
9.13.5 Sustained oedema refractory to diuretics						
TAME-PKD 2018	4	49	5	48	100.0%	0.78 [0.22 , 2.74]
Subtotal		**49**		**48**	**100.0%**	**0.78 [0.22 , 2.74]**
Total events:	4		5			
Test for overall effect: Z = 0.38 (P = 0.70)						
Heterogeneity: Not applicable						
9.13.6 Urinary tract infection or cyst rupture						
TAME-PKD 2018	1	26	2	25	100.0%	0.48 [0.05 , 4.98]
Subtotal		**26**		**25**	**100.0%**	**0.48 [0.05 , 4.98]**
Total events:	1		2			
Test for overall effect: Z = 0.61 (P = 0.54)						
Heterogeneity: Not applicable						
9.13.7 Diarrhoea						
Brosnahan 2022	16	26	7	25	39.6%	2.20 [1.09 , 4.42]
TAME-PKD 2018	21	49	13	48	60.4%	1.58 [0.90 , 2.79]
Subtotal (Wald{fn})		**75**		**73**	**100.0%**	**1.80 [1.16 , 2.80]**
Total events:	37		20			
Test for overall effect: Z = 2.63 (P = 0.009)						
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.51, df = 1 (P = 0.47); I^2 = 0%						
9.13.8 Nausea						
Brosnahan 2022	11	26	4	25	30.9%	2.64 [0.97 , 7.22]



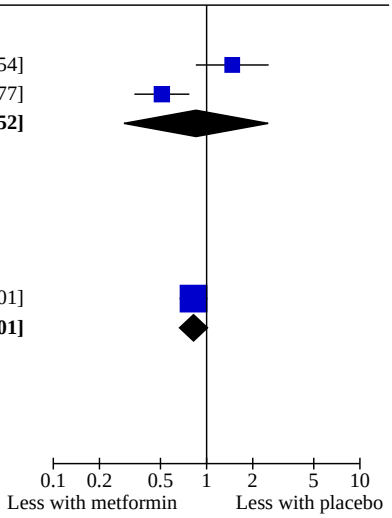
Analysis 9.13. (Continued)

9.13.8 Nausea						
Brosnahan 2022	11	26	4	25	30.9%	2.64 [0.97 , 7.22]
TAME-PKD 2018	17	49	10	48	69.1%	1.67 [0.85 , 3.26]
Subtotal (Wald{fn})		**75**		**73**	**100.0%**	**1.92 [1.10 , 3.36]**
Total events:	28		14			
Test for overall effect: Z = 2.29 (P = 0.02)						
Heterogeneity: Tau² = 0.00; Chi² = 0.56, df = 1 (P = 0.45); I² = 0%						
Test for subgroup differences: Chi² = 6.16, df = 7 (P = 0.52), I² = 0%						



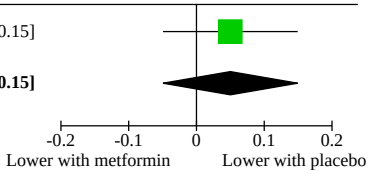
Analysis 9.14. Comparison 9: Metformin versus placebo, Outcome 14: Dose completion

	Metformin		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
9.14.1 Completed full dose							
TAME-PKD 2018	21	49	14	48	48.6%	1.47 [0.85 , 2.54]	
Brosnahan 2022	11	22	23	23	51.4%	0.51 [0.34 , 0.77]	
Subtotal (Wald{fn})		**71**		**71**	**100.0%**	**0.85 [0.29 , 2.52]**	
Total events:	32		37				
Test for overall effect: Z = 0.29 (P = 0.77)							
Heterogeneity: Tau² = 0.55; Chi² = 10.00, df = 1 (P = 0.002); I² = 90%							
9.14.2 Completed 50% dose							
Brosnahan 2022	18	22	23	23	100.0%	0.82 [0.67 , 1.01]	
Subtotal		**22**		**23**	**100.0%**	**0.82 [0.67 , 1.01]**	
Total events:	18		23				
Test for overall effect: Z = 1.84 (P = 0.07)							
Heterogeneity: Not applicable							
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.95), I² = 0%							



Analysis 9.15. Comparison 9: Metformin versus placebo, Outcome 15: C-reactive protein

	Metformin			Placebo				Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**IV, Random, 95% CI**
TAME-PKD 2018	0.14	0.262	35	0.09	0.1521	38	100.0%	0.05 [-0.05 , 0.15]	
Total			**35**			**38**	**100.0%**	**0.05 [-0.05 , 0.15]**	
Test for overall effect: Z = 0.99 (P = 0.32)									
Test for subgroup differences: Not applicable									
Heterogeneity: Not applicable									



Comparison 10. Metformin versus hydrochlorothiazide and placebo (cross-over results)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Quality of life: descriptive data	0		Other data	No numeric data

Analysis 10.1. Comparison 10: Metformin versus hydrochlorothiazide and placebo (cross-over results), Outcome 1: Quality of life: descriptive data

Quality of life: descriptive data

Study	Narrative Results
Kramers 2020	Seven (54%) participants experienced better quality of life during hydrochlorothiazide treatment as compared with baseline (P=0.001). Quality of life was not significantly different from baseline during metformin (P=0.90) or placebo treatment (P=0.50)

Comparison 11. Bosutinib versus placebo

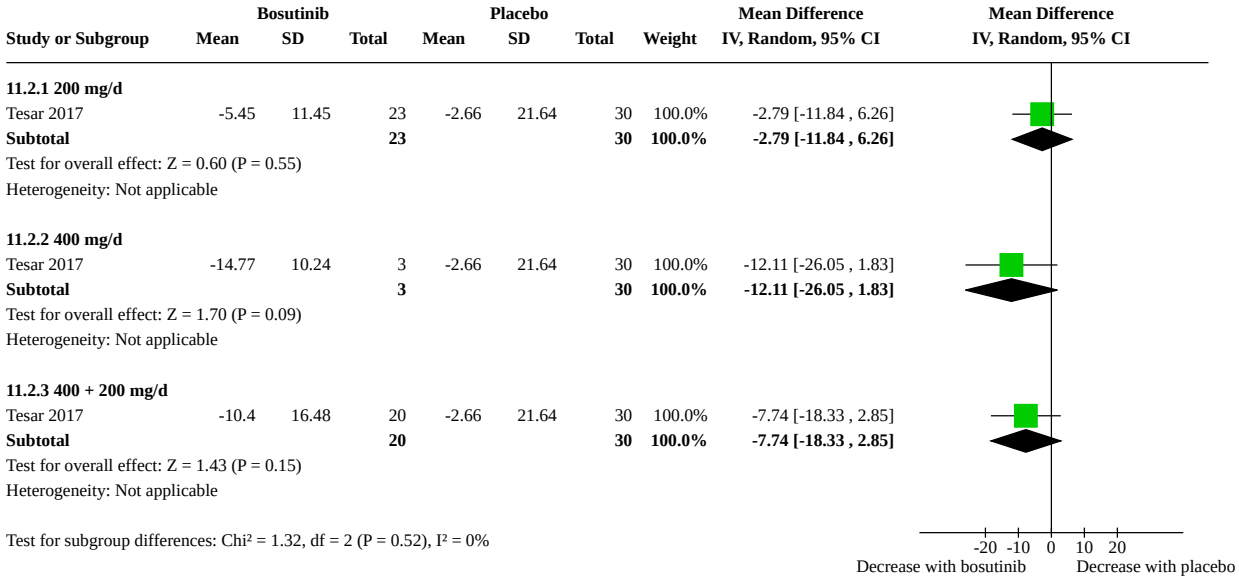
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Change in serum creatinine: descriptive data	0		Other data	No numeric data
11.2 eGFR change from baseline [%]	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
11.2.1 200 mg/d	1	53	Mean Difference (IV, Random, 95% CI)	-2.79 [-11.84, 6.26]
11.2.2 400 mg/d	1	33	Mean Difference (IV, Random, 95% CI)	-12.11 [-26.05, 1.83]
11.2.3 400 + 200 mg/d	1	50	Mean Difference (IV, Random, 95% CI)	-7.74 [-18.33, 2.85]
11.3 GFR: descriptive data	0		Other data	No numeric data
11.4 Total kidney volume: descriptive data	0		Other data	No numeric data
11.5 Serious adverse events	1	169	Risk Ratio (M-H, Random, 95% CI)	6.50 [0.37, 113.37]
11.6 Adverse events: descriptive data	0		Other data	No numeric data

Analysis 11.1. Comparison 11: Bosutinib versus placebo, Outcome 1: Change in serum creatinine: descriptive data

Change in serum creatinine: descriptive data

Study	Narrative results
Tesar 2017	Mean serum creatinine values were increased in all bosutinib groups at day 15; these remained stable over the 24- month initial treatment period and then returned close to baseline after a 30-day washout at the end of this period. Small increases in serum creatinine were also observed with bosutinib 200 and 400/200mg/d at month 26 during the extended treatment period; these levels again returned close to baseline after a 30-day washout at the end of this period.

Analysis 11.2. Comparison 11: Bosutinib versus placebo, Outcome 2: eGFR change from baseline [%]



Analysis 11.3. Comparison 11: Bosutinib versus placebo, Outcome 3: GFR: descriptive data

GFR: descriptive data

Study	Intervention	Control	Description
Tesar 2017	200 mg /d: 85.01 ± 18.36 mL/min/1.73 m^2 400 mg/d: 66.77 ± 10.63 mL/min/1.73 m^2 600 mg/d: 84.31 ± 24.76 mL/min/1.73 m^2	Control: median 84.95 IQR 21.29 mL/min/1.73m^2	Quote: "eGFR declined from baseline over time for all treatment groups; there was a general trend toward dose-dependent worsening of eGFR with increasing bosutinib dose that was partially reversible during the 30-day washout after the initial treatment period. However, differences in eGFR from baseline at month 24 or 25/end of initial treatment period were not significant"

Analysis 11.4. Comparison 11: Bosutinib versus placebo, Outcome 4: Total kidney volume: descriptive data

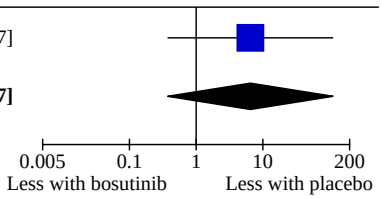
Total kidney volume: descriptive data

Study	Intervention group	Control group
Tesar 2017	200 mg/d (n=23): median 1403.45 (range 730.45 to 4819.55) 400 mg/d (n=3): median 849.10 (range 823.30 to 2546.50) 600 mg/d (n=20): median 1313.78 (range 707.20 to 2636.45)	Control (N=30): median 1727.30 (range 832.45 to 3945.35)

Analysis 11.5. Comparison 11: Bosutinib versus placebo, Outcome 5: Serious adverse events

Study or Subgroup	Bosutinib Events	Bosutinib Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Tesar 2017	6	113	0	56	100.0%	6.50 [0.37 , 113.37]
Total		**113**		**56**	**100.0%**	**6.50 [0.37 , 113.37]**
Total events:	6		0			

Test for overall effect: Z = 1.28 (P = 0.20)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 11.6. Comparison 11: Bosutinib versus placebo, Outcome 6: Adverse events: descriptive data

Adverse events: descriptive data

Study	Narrative results
Tesar 2017	Quote: "Treatment-emergent AEs (TEAEs; any causality) occurred more frequently with bosutinib 400 and 400/200 mg/d versus bosutinib 200 mg/d and placebo." Quote: "TEAEs (incidence ≥ 30% in any treatment group) were most commonly gastrointestinal, primarily diarrhea, which occurred more frequently with bosutinib versus placebo (200 mg/d, 45%; 400 mg/d, 84%; 400/200 mg/d, 75%; placebo, 20%). Liver-related TEAEs were also more common with bosutinib versus placebo; these were primarily events of increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and were generally of mild severity"

Comparison 12. Pioglitazone versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 Total kidney volume: cross-over descriptive results	0		Other data	No numeric data

Analysis 12.1. Comparison 12: Pioglitazone versus placebo, Outcome 1: Total kidney volume: cross-over descriptive results

Total kidney volume: cross-over descriptive results

Study	Narrative Results
Blazer-Yost 2021	The mean percent change in TKV with pioglitazone versus placebo was 4.3 ± 6.3% versus 7.85 ± 7.68%, respectively. The mean difference between the two periods was −3.5% (95% CI −8.4–1.4, P = 0.146).

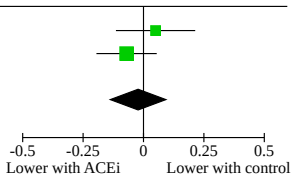
Comparison 13. Angiotenin-converting-enzyme inhibitors (ACEi) versus control (placebo or standard therapy)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 Serum creatinine [mg/dL]	2	42	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.14, 0.09]
13.2 GFR [mL/min/1.73 m^2]	3	103	Mean Difference (IV, Random, 95% CI)	-3.41 [-15.83, 9.01]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.3 Doubling of serum creatinine	1	64	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.45, 2.28]
13.4 Systolic blood pressure [mm Hg]	2	42	Mean Difference (IV, Random, 95% CI)	-5.44 [-14.26, 3.38]
13.5 Diastolic blood pressure [mm Hg]	2	42	Mean Difference (IV, Random, 95% CI)	-4.96 [-8.88, -1.04]
13.6 Mean arterial pressure [mm Hg]	1	61	Mean Difference (IV, Random, 95% CI)	-5.00 [-6.29, -3.71]
13.7 Total kidney volume [mL]	2	42	Mean Difference (IV, Random, 95% CI)	-42.50 [-115.68, 30.67]
13.8 Albuminuria	3	103	Std. Mean Difference (IV, Random, 95% CI)	-0.12 [-0.51, 0.26]

Analysis 13.1. Comparison 13: Angiotenin-converting-enzyme inhibitors (ACEi) versus control (placebo or standard therapy), Outcome 1: Serum creatinine [mg/dL]

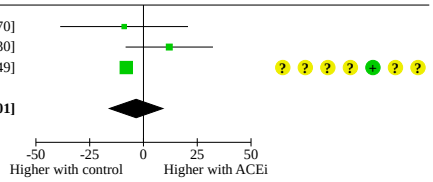
Study or Subgroup	ACEi Mean	ACEi SD	ACEi Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Cadnapaphornchai 2005 normotensive	0.73	0.11	13	0.68	0.27	12	39.7%	0.05 [-0.11 , 0.21]
Cadnapaphornchai 2005 borderline	0.73	0.12	9	0.8	0.14	8	60.3%	-0.07 [-0.19 , 0.05]
Total (Wald{fn})			**22**			**20**	**100.0%**	**-0.02 [-0.14 , 0.09]**



Test for overall effect: Z = 0.38 (P = 0.70)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.00; Chi² = 1.30, df = 1 (P = 0.25); I² = 23%

Analysis 13.2. Comparison 13: Angiotenin-converting-enzyme inhibitors (ACEi) versus control (placebo or standard therapy), Outcome 2: GFR [mL/min/1.73 m²]

Study or Subgroup	ACEi Mean	ACEi SD	ACEi Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Cadnapaphornchai 2005 normotensive	127	19.6	13	136	49	12	13.7%	-9.00 [-38.70 , 20.70]
Cadnapaphornchai 2005 borderline	126	21	9	114	21.6	8	23.6%	12.00 [-8.30 , 32.30]
van Dijk 2003	97	5	32	105	5	29	62.6%	-8.00 [-10.51 , -5.49]
Total (Wald{fn})			**54**			**49**	**100.0%**	**-3.41 [-15.83 , 9.01]**



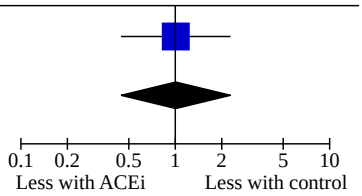
Test for overall effect: Z = 0.54 (P = 0.59)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 62.45; Chi² = 3.68, df = 2 (P = 0.16); I² = 46%

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 13.3. Comparison 13: Angiotenin-converting-enzyme inhibitors (ACEi) versus control (placebo or standard therapy), Outcome 3: Doubling of serum creatinine

Study or Subgroup	ACEi Events	ACEi Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
AIPRI 1996	8	30	9	34	100.0%	1.01 [0.45 , 2.28]
Total		**30**		**34**	**100.0%**	**1.01 [0.45 , 2.28]**
Total events:	8		9			

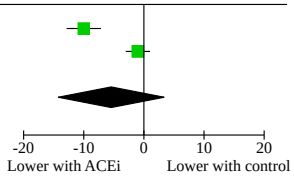
Test for overall effect: Z = 0.02 (P = 0.99)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 13.4. Comparison 13: Angiotenin-converting-enzyme inhibitors (ACEi) versus control (placebo or standard therapy), Outcome 4: Systolic blood pressure [mm Hg]

Study or Subgroup	ACEi Mean	ACEi SD	ACEi Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Cadnapaphornchai 2005 borderline	122	3	9	132	3	8	49.3%	-10.00 [-12.86 , -7.14]
Cadnapaphornchai 2005 normotensive	117	2	13	118	3	12	50.7%	-1.00 [-3.02 , 1.02]
Total (Wald{fn})			**22**			**20**	**100.0%**	**-5.44 [-14.26 , 3.38]**

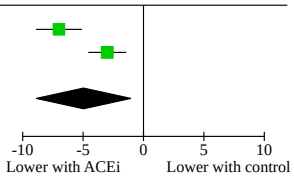
Test for overall effect: Z = 1.21 (P = 0.23)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 38.91; Chi² = 25.45, df = 1 (P < 0.00001); I² = 96%



Analysis 13.5. Comparison 13: Angiotenin-converting-enzyme inhibitors (ACEi) versus control (placebo or standard therapy), Outcome 5: Diastolic blood pressure [mm Hg]

Study or Subgroup	ACEi Mean	ACEi SD	ACEi Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Cadnapaphornchai 2005 borderline	71	2	9	78	2	8	49.1%	-7.00 [-8.90 , -5.10]
Cadnapaphornchai 2005 normotensive	68	2	13	71	2	12	50.9%	-3.00 [-4.57 , -1.43]
Total (Wald{fn})			**22**			**20**	**100.0%**	**-4.96 [-8.88 , -1.04]**

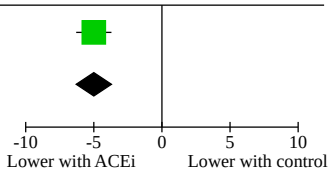
Test for overall effect: Z = 2.48 (P = 0.01)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 7.21; Chi² = 10.09, df = 1 (P = 0.001); I² = 90%



Analysis 13.6. Comparison 13: Angiotenin-converting-enzyme inhibitors (ACEi) versus control (placebo or standard therapy), Outcome 6: Mean arterial pressure [mm Hg]

Study or Subgroup	ACEi Mean	ACEi SD	ACEi Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
van Dijk 2003	100	2	32	105	3	29	100.0%	-5.00 [-6.29 , -3.71]
Total			**32**			**29**	**100.0%**	**-5.00 [-6.29 , -3.71]**

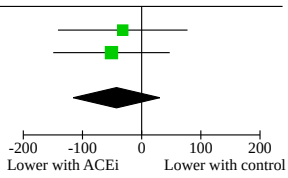
Test for overall effect: Z = 7.58 (P < 0.00001)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 13.7. Comparison 13: Angiotenin-converting-enzyme inhibitors (ACEi) versus control (placebo or standard therapy), Outcome 7: Total kidney volume [mL]

Study or Subgroup	ACEi Mean	ACEi SD	ACEi Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Cadnapaphornchai 2005 borderline	231	117	9	263	113	8	44.7%	-32.00 [-141.43 , 77.43]
Cadnapaphornchai 2005 normotensive	260	106	13	311	141	12	55.3%	-51.00 [-149.41 , 47.41]
Total (Wald{fn})			**22**			**20**	**100.0%**	**-42.50 [-115.68 , 30.67]**

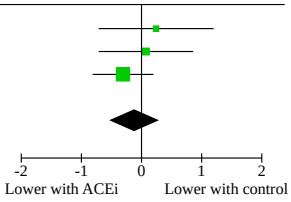
Test for overall effect: Z = 1.14 (P = 0.25)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.80); I² = 0%



Analysis 13.8. Comparison 13: Angiotenin-converting-enzyme inhibitors (ACEi) versus control (placebo or standard therapy), Outcome 8: Albuminuria

Study or Subgroup	ACEi Mean	ACEi SD	ACEi Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Cadnapaphornchai 2005 borderline	29	9.1	9	23	33	8	16.5%	0.24 [-0.71 , 1.20]
Cadnapaphornchai 2005 normotensive	22	25	13	20	28	12	24.5%	0.07 [-0.71 , 0.86]
van Dijk 2003	0.42	0.48	32	0.68	1.1	29	59.0%	-0.31 [-0.81 , 0.20]
Total (Wald{fn})			**54**			**49**	**100.0%**	**-0.12 [-0.51 , 0.26]**

Test for overall effect: Z = 0.62 (P = 0.53)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.00; Chi² = 1.31, df = 2 (P = 0.52); I² = 0%



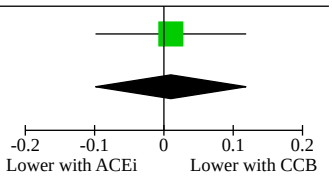
Comparison 14. Angiotensin-converting-enzyme inhibitors (ACEi) versus calcium channel blockers (CCB)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.1 Serum creatinine [mg/dL]	1	24	Mean Difference (IV, Random, 95% CI)	0.01 [-0.10, 0.12]
14.2 GFR [mL/min/1.73 m^2]	1	24	Mean Difference (IV, Random, 95% CI)	-13.00 [-17.56, -8.44]
14.3 Systolic blood pressure [mm Hg]	1	24	Mean Difference (IV, Random, 95% CI)	-5.00 [-8.62, -1.38]
14.4 Diastolic blood pressure [mm Hg]	1	24	Mean Difference (IV, Random, 95% CI)	-3.00 [-5.40, -0.60]
14.5 Mean arterial pressure [mm Hg]	1	24	Mean Difference (IV, Random, 95% CI)	-3.00 [-5.40, -0.60]
14.6 Albuminuria [mg/g]	1	24	Mean Difference (IV, Random, 95% CI)	-134.00 [-176.01, -91.99]

Analysis 14.1. Comparison 14: Angiotensin-converting-enzyme inhibitors (ACEi) versus calcium channel blockers (CCB), Outcome 1: Serum creatinine [mg/dL]

Study or Subgroup	ACEi Mean	ACEi SD	ACEi Total	CCB Mean	CCB SD	CCB Total	Weight	Mean Difference IV, Random, 95% CI
Ecder 1999	1.61	0.12	12	1.6	0.15	12	100.0%	0.01 [-0.10 , 0.12]
Total			**12**			**12**	**100.0%**	**0.01 [-0.10 , 0.12]**

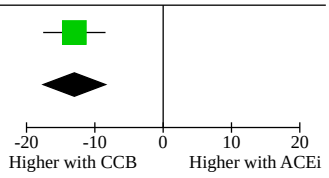
Test for overall effect: Z = 0.18 (P = 0.86)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 14.2. Comparison 14: Angiotensin-converting-enzyme inhibitors (ACEi) versus calcium channel blockers (CCB), Outcome 2: GFR [mL/min/1.73 m²]

Study or Subgroup	ACEi Mean	ACEi SD	ACEi Total	CCB Mean	CCB SD	CCB Total	Weight	Mean Difference IV, Random, 95% CI
Ecder 1999	56	4	12	69	7	12	100.0%	-13.00 [-17.56 , -8.44]
Total			**12**			**12**	**100.0%**	**-13.00 [-17.56 , -8.44]**

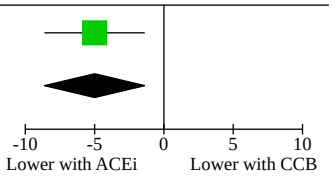
Test for overall effect: Z = 5.59 (P < 0.00001)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 14.3. Comparison 14: Angiotensin-converting-enzyme inhibitors (ACEi) versus calcium channel blockers (CCB), Outcome 3: Systolic blood pressure [mm Hg]

Study or Subgroup	ACEi Mean	ACEi SD	ACEi Total	CCB Mean	CCB SD	CCB Total	Weight	Mean Difference IV, Random, 95% CI
Ecder 1999	122	5	12	127	4	12	100.0%	-5.00 [-8.62 , -1.38]
Total			**12**			**12**	**100.0%**	**-5.00 [-8.62 , -1.38]**

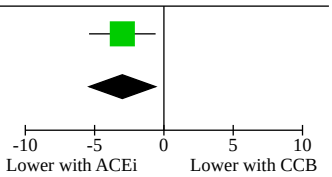
Test for overall effect: Z = 2.71 (P = 0.007)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 14.4. Comparison 14: Angiotensin-converting-enzyme inhibitors (ACEi) versus calcium channel blockers (CCB), Outcome 4: Diastolic blood pressure [mm Hg]

Study or Subgroup	ACEi Mean	ACEi SD	ACEi Total	CCB Mean	CCB SD	CCB Total	Weight	Mean Difference IV, Random, 95% CI
Ecder 1999	80	3	12	83	3	12	100.0%	-3.00 [-5.40 , -0.60]
Total			**12**			**12**	**100.0%**	**-3.00 [-5.40 , -0.60]**

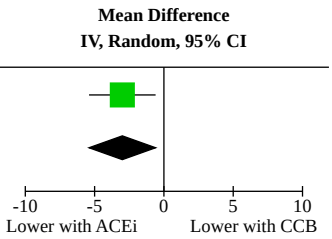
Test for overall effect: Z = 2.45 (P = 0.01)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 14.5. Comparison 14: Angiotensin-converting-enzyme inhibitors (ACEi) versus calcium channel blockers (CCB), Outcome 5: Mean arterial pressure [mm Hg]

Study or Subgroup	ACEi Mean	ACEi SD	ACEi Total	CCB Mean	CCB SD	CCB Total	Weight	Mean Difference IV, Random, 95% CI
Ecder 1999	94	3	12	97	3	12	100.0%	-3.00 [-5.40 , -0.60]
Total			**12**			**12**	**100.0%**	**-3.00 [-5.40 , -0.60]**

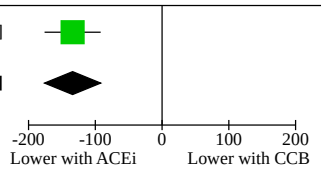
Test for overall effect: Z = 2.45 (P = 0.01)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 14.6. Comparison 14: Angiotensin-converting-enzyme inhibitors (ACEi) versus calcium channel blockers (CCB), Outcome 6: Albuminuria [mg/g]

Study or Subgroup	ACEi Mean	ACEi SD	ACEi Total	CCB Mean	CCB SD	CCB Total	Weight	Mean Difference IV, Random, 95% CI
Ecder 1999	14	6	12	148	74	12	100.0%	-134.00 [-176.01 , -91.99]
Total			**12**			**12**	**100.0%**	**-134.00 [-176.01 , -91.99]**

Test for overall effect: Z = 6.25 (P < 0.00001)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



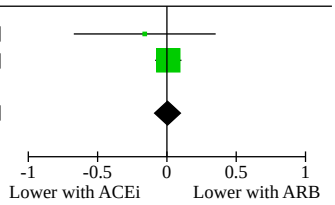
Comparison 15. Angiotensin-converting-enzyme inhibitors (ACEi) versus angiotensin receptor blockers (ARB)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.1 Serum creatinine [mg/dL]	2	52	Mean Difference (IV, Random, 95% CI)	0.00 [-0.09, 0.10]
15.2 GFR [mL/min/1.73 m^2]	1	32	Mean Difference (IV, Random, 95% CI)	-3.40 [-22.69, 15.89]
15.3 Systolic blood pressure [mm Hg]	1	32	Mean Difference (IV, Random, 95% CI)	-3.50 [-9.75, 2.75]
15.4 Diastolic blood pressure [mm Hg]	1	32	Mean Difference (IV, Random, 95% CI)	-1.80 [-5.23, 1.63]
15.5 Mean arterial pressure [mm Hg]	1	32	Mean Difference (IV, Random, 95% CI)	-2.20 [-6.41, 2.01]

Analysis 15.1. Comparison 15: Angiotensin-converting-enzyme inhibitors (ACEi) versus angiotensin receptor blockers (ARB), Outcome 1: Serum creatinine [mg/dL]

Study or Subgroup	ACEi Mean	ACEi SD	ACEi Total	ARB Mean	ARB SD	ARB Total	Weight	Mean Difference IV, Random, 95% CI
Ulusoy 2010	1.3	0.6	19	1.46	0.8	13	3.3%	-0.16 [-0.67 , 0.35]
Nakamura 2012a	0.79	0.08	10	0.78	0.13	10	96.7%	0.01 [-0.08 , 0.10]
Total (Wald{fn})			**29**			**23**	**100.0%**	**0.00 [-0.09 , 0.10]**

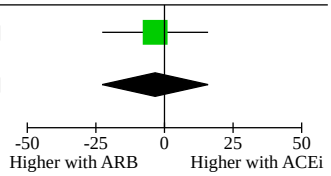
Test for overall effect: Z = 0.09 (P = 0.93)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.00; Chi² = 0.41, df = 1 (P = 0.52); I² = 0%



Analysis 15.2. Comparison 15: Angiotensin-converting-enzyme inhibitors (ACEi) versus angiotensin receptor blockers (ARB), Outcome 2: GFR [mL/min/1.73 m²]

Study or Subgroup	ACEi Mean	ACEi SD	ACEi Total	ARB Mean	ARB SD	ARB Total	Weight	Mean Difference IV, Random, 95% CI
Ulusoy 2010	73.8	27.7	19	77.2	27.1	13	100.0%	-3.40 [-22.69 , 15.89]
Total			**19**			**13**	**100.0%**	**-3.40 [-22.69 , 15.89]**

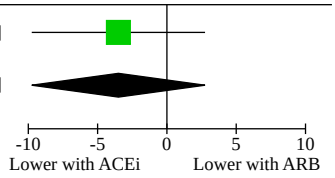
Test for overall effect: Z = 0.35 (P = 0.73)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 15.3. Comparison 15: Angiotensin-converting-enzyme inhibitors (ACEi) versus angiotensin receptor blockers (ARB), Outcome 3: Systolic blood pressure [mm Hg]

Study or Subgroup	ACEi Mean	ACEi SD	ACEi Total	ARB Mean	ARB SD	ARB Total	Weight	Mean Difference IV, Random, 95% CI
Ulusoy 2010	116.5	8.5	19	120	9.1	13	100.0%	-3.50 [-9.75 , 2.75]
Total			**19**			**13**	**100.0%**	**-3.50 [-9.75 , 2.75]**

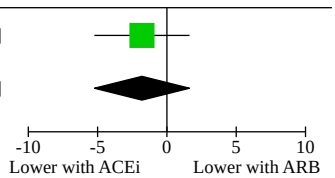
Test for overall effect: Z = 1.10 (P = 0.27)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



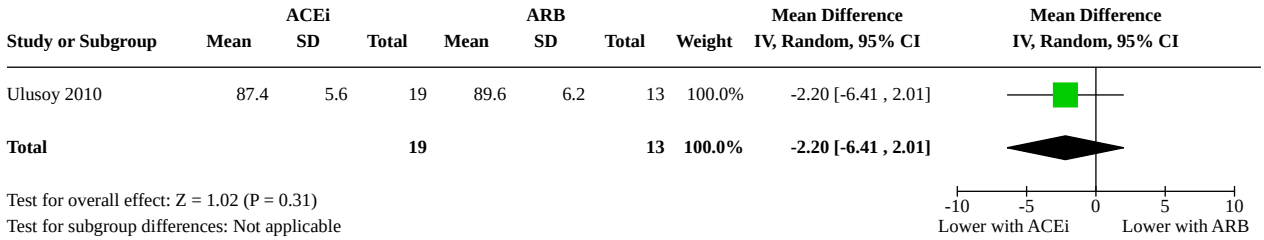
Analysis 15.4. Comparison 15: Angiotensin-converting-enzyme inhibitors (ACEi) versus angiotensin receptor blockers (ARB), Outcome 4: Diastolic blood pressure [mm Hg]

Study or Subgroup	ACEi Mean	ACEi SD	ACEi Total	ARB Mean	ARB SD	ARB Total	Weight	Mean Difference IV, Random, 95% CI
Ulusoy 2010	72.8	4.5	19	74.6	5.1	13	100.0%	-1.80 [-5.23 , 1.63]
Total			**19**			**13**	**100.0%**	**-1.80 [-5.23 , 1.63]**

Test for overall effect: Z = 1.03 (P = 0.30)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 15.5. Comparison 15: Angiotensin-converting-enzyme inhibitors (ACEi) versus angiotensin receptor blockers (ARB), Outcome 5: Mean arterial pressure [mm Hg]

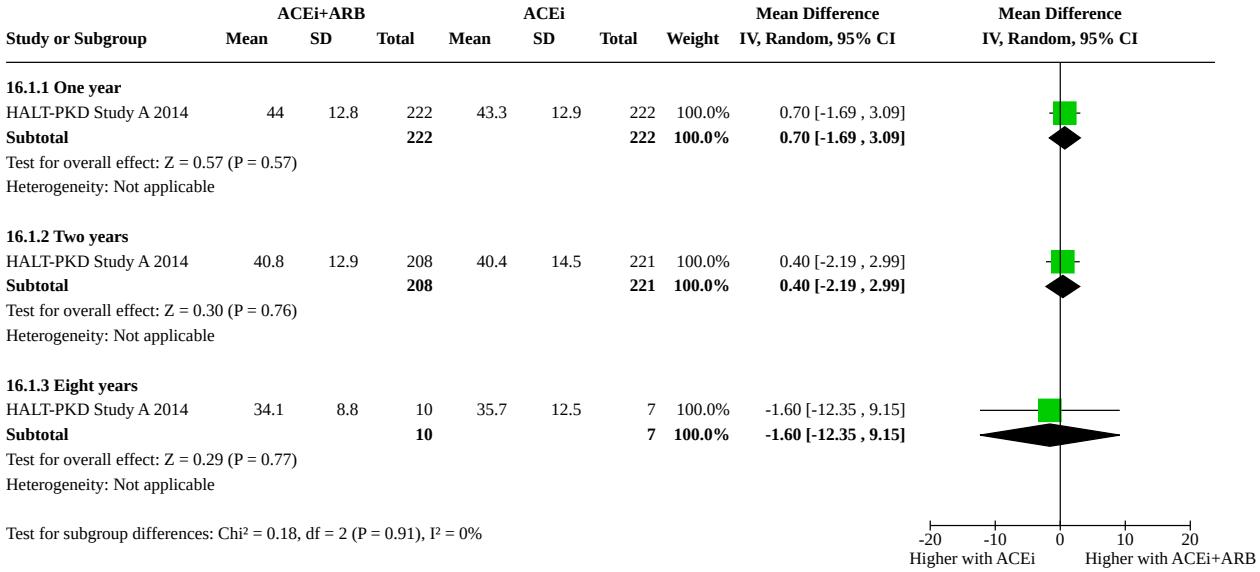


Comparison 16. Angiotensin-converting-enzyme inhibitors (ACEi) plus angiotensin receptor blockers (ARB) versus ACEi alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.1 eGFR [mL/min/1.73 m^2]	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
16.1.1 One year	1	444	Mean Difference (IV, Random, 95% CI)	0.70 [-1.69, 3.09]
16.1.2 Two years	1	429	Mean Difference (IV, Random, 95% CI)	0.40 [-2.19, 2.99]
16.1.3 Eight years	1	17	Mean Difference (IV, Random, 95% CI)	-1.60 [-12.35, 9.15]
16.2 Annual change in eGFR [mL/min/1.73 m^2]	2	1043	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.30, 0.26]
16.3 Death	2	1043	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.26, 2.72]
16.4 Back or flank pain	2	1044	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.05, 2.33]
16.5 Quality of life scores	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
16.5.1 SF-36 physical component summary	2	1043	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.16, 0.12]
16.5.2 SF-36 mental component summary	2	1043	Mean Difference (IV, Random, 95% CI)	0.10 [-0.19, 0.39]
16.6 Cardiovascular events	2	1044	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.41, 2.15]
16.7 Total kidney volume change [%]	1	553	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.87, 0.47]
16.8 Hospitalisations	1	485	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.68, 0.90]
16.9 Albuminuria	2	1042	Std. Mean Difference (IV, Random, 95% CI)	-0.04 [-0.16, 0.08]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.10 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
16.10.1 Acute kidney injury	1	486	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.41, 1.14]
16.10.2 Cancer	1	486	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.48, 3.37]
16.10.3 Cardiovascular disorder	1	486	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.38, 1.84]
16.10.4 Gastrointestinal disorder	1	486	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.32, 1.10]
16.10.5 Headache	1	486	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.14, 6.98]
16.10.6 Hyperkalaemia	1	486	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.76, 1.63]
16.10.7 Nephrolithiasis or renal colic	1	486	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.03, 2.20]
16.10.8 Renal haemorrhage or haematuria	1	486	Risk Ratio (M-H, Random, 95% CI)	2.48 [0.49, 12.66]
16.10.9 Stroke	1	486	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.30, 5.85]

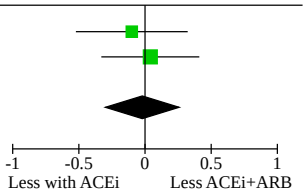
Analysis 16.1. Comparison 16: Angiotensin-converting-enzyme inhibitors (ACEi) plus angiotensin receptor blockers (ARB) versus ACEi alone, Outcome 1: eGFR [mL/min/1.73 m²]



Analysis 16.2. Comparison 16: Angiotensin-converting-enzyme inhibitors (ACEi) plus angiotensin receptor blockers (ARB) versus ACEi alone, Outcome 2: Annual change in eGFR [mL/min/1.73 m^2]

Study or Subgroup	ACEi+ARB Mean	ACEi+ARB SD	ACEi+ARB Total	ACEi Mean	ACEi SD	ACEi Total	Weight	Mean Difference IV, Random, 95% CI
HALT-PKD Study A 2014	-3	2.51778	273	-2.9	2.56845	284	43.4%	-0.10 [-0.52 , 0.32]
HALT-PKD Study B 2014	-3.87	2.220427	244	-3.91	1.934814	242	56.6%	0.04 [-0.33 , 0.41]
Total (Wald{fn})			**517**			**526**	**100.0%**	**-0.02 [-0.30 , 0.26]**

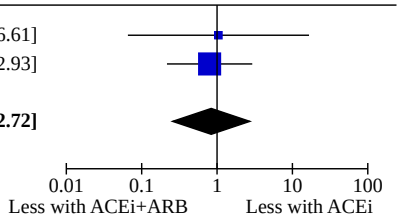
Test for overall effect: Z = 0.15 (P = 0.88)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 1 (P = 0.63); I² = 0%



Analysis 16.3. Comparison 16: Angiotensin-converting-enzyme inhibitors (ACEi) plus angiotensin receptor blockers (ARB) versus ACEi alone, Outcome 3: Death

Study or Subgroup	ACEi+ARB Events	ACEi+ARB Total	ACEi Events	ACEi Total	Weight	Risk Ratio M-H, Random, 95% CI
HALT-PKD Study A 2014	1	273	1	285	18.1%	1.04 [0.07 , 16.61]
HALT-PKD Study B 2014	4	243	5	242	81.9%	0.80 [0.22 , 2.93]
Total (Wald{fn})		**516**		**527**	**100.0%**	**0.84 [0.26 , 2.72]**
Total events:	5		6			

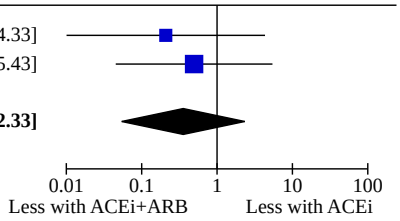
Test for overall effect: Z = 0.30 (P = 0.77)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.86); I² = 0%



Analysis 16.4. Comparison 16: Angiotensin-converting-enzyme inhibitors (ACEi) plus angiotensin receptor blockers (ARB) versus ACEi alone, Outcome 4: Back or flank pain

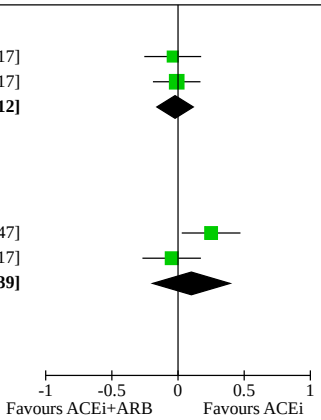
Study or Subgroup	ACEi+ARB Events	ACEi+ARB Total	ACEi Events	ACEi Total	Weight	Risk Ratio M-H, Random, 95% CI
HALT-PKD Study A 2014	0	273	2	285	38.4%	0.21 [0.01 , 4.33]
HALT-PKD Study B 2014	1	244	2	242	61.6%	0.50 [0.05 , 5.43]
Total (Wald{fn})		**517**		**527**	**100.0%**	**0.36 [0.05 , 2.33]**
Total events:	1		4			

Test for overall effect: Z = 1.08 (P = 0.28)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 1 (P = 0.66); I² = 0%



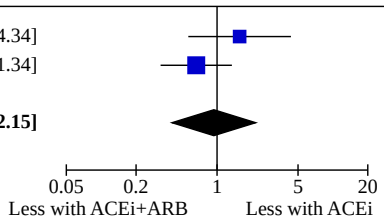
Analysis 16.5. Comparison 16: Angiotensin-converting-enzyme inhibitors (ACEi) plus angiotensin receptor blockers (ARB) versus ACEi alone, Outcome 5: Quality of life scores

Study or Subgroup	ACEi+ARB Mean	ACEi+ARB SD	ACEi+ARB Total	ACEi Mean	ACEi SD	ACEi Total	Weight	Mean Difference IV, Random, 95% CI
16.5.1 SF-36 physical component summary								
HALT-PKD Study B 2014	-0.68	1.266186	243	-0.64	1.145094	242	41.1%	-0.04 [-0.25 , 0.17]
HALT-PKD Study A 2014	-0.24	1.091038	273	-0.23	1.072086	285	58.9%	-0.01 [-0.19 , 0.17]
Subtotal (Wald{fn})			**516**			**527**	**100.0%**	**-0.02 [-0.16 , 0.12]**
Test for overall effect: Z = 0.32 (P = 0.75)								
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.83); I² = 0%								
16.5.2 SF-36 mental component summary								
HALT-PKD Study A 2014	0.19	1.342816	273	-0.06	1.329387	285	49.9%	0.25 [0.03 , 0.47]
HALT-PKD Study B 2014	-0.079	1.258267	243	-0.031	1.224066	242	50.1%	-0.05 [-0.27 , 0.17]
Subtotal (Wald{fn})			**516**			**527**	**100.0%**	**0.10 [-0.19 , 0.39]**
Test for overall effect: Z = 0.68 (P = 0.50)								
Heterogeneity: Tau² = 0.03; Chi² = 3.48, df = 1 (P = 0.06); I² = 71%								
Test for subgroup differences: Chi² = 0.56, df = 1 (P = 0.45), I² = 0%								



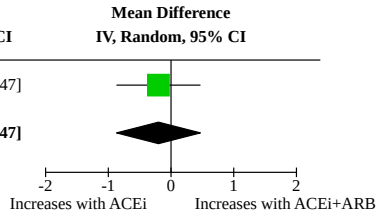
Analysis 16.6. Comparison 16: Angiotensin-converting-enzyme inhibitors (ACEi) plus angiotensin receptor blockers (ARB) versus ACEi alone, Outcome 6: Cardiovascular events

Study or Subgroup	ACEi+ARB Events	ACEi+ARB Total	ACEi Events	ACEi Total	Weight	Risk Ratio M-H, Random, 95% CI
HALT-PKD Study A 2014	9	273	6	285	40.6%	1.57 [0.56 , 4.34]
HALT-PKD Study B 2014	12	244	18	242	59.4%	0.66 [0.33 , 1.34]
Total (Wald{fn})		**517**		**527**	**100.0%**	**0.94 [0.41 , 2.15]**
Total events:	21		24			
Test for overall effect: Z = 0.15 (P = 0.88)						
Test for subgroup differences: Not applicable						
Heterogeneity: Tau² = 0.17; Chi² = 1.85, df = 1 (P = 0.17); I² = 46%						



Analysis 16.7. Comparison 16: Angiotensin-converting-enzyme inhibitors (ACEi) plus angiotensin receptor blockers (ARB) versus ACEi alone, Outcome 7: Total kidney volume change [%]

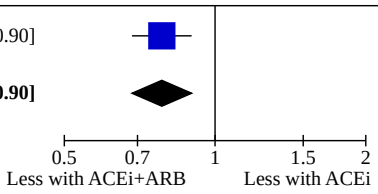
Study or Subgroup	ACEi+ARB Mean	ACEi+ARB SD	ACEi+ARB Total	ACEi Mean	ACEi SD	ACEi Total	Weight	Mean Difference IV, Random, 95% CI
HALT-PKD Study B 2014	6	3.762686	271	6.2	4.265519	282	100.0%	-0.20 [-0.87 , 0.47]
Total			**271**			**282**	**100.0%**	**-0.20 [-0.87 , 0.47]**
Test for overall effect: Z = 0.59 (P = 0.56)								
Test for subgroup differences: Not applicable								
Heterogeneity: Not applicable								



Analysis 16.8. Comparison 16: Angiotensin-converting-enzyme inhibitors (ACEi) plus angiotensin receptor blockers (ARB) versus ACEi alone, Outcome 8: Hospitalisations

Study or Subgroup	ACEi+ARB Events	ACEi+ARB Total	ACEi Events	ACEi Total	Weight	Risk Ratio M-H, Random, 95% CI
HALT-PKD Study B 2014	136	243	173	242	100.0%	0.78 [0.68 , 0.90]
Total		**243**		**242**	**100.0%**	**0.78 [0.68 , 0.90]**
Total events:	136		173			

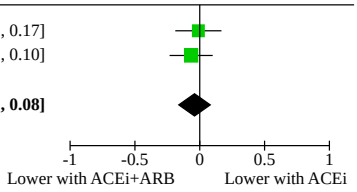
Test for overall effect: Z = 3.50 (P = 0.0005)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 16.9. Comparison 16: Angiotensin-converting-enzyme inhibitors (ACEi) plus angiotensin receptor blockers (ARB) versus ACEi alone, Outcome 9: Albuminuria

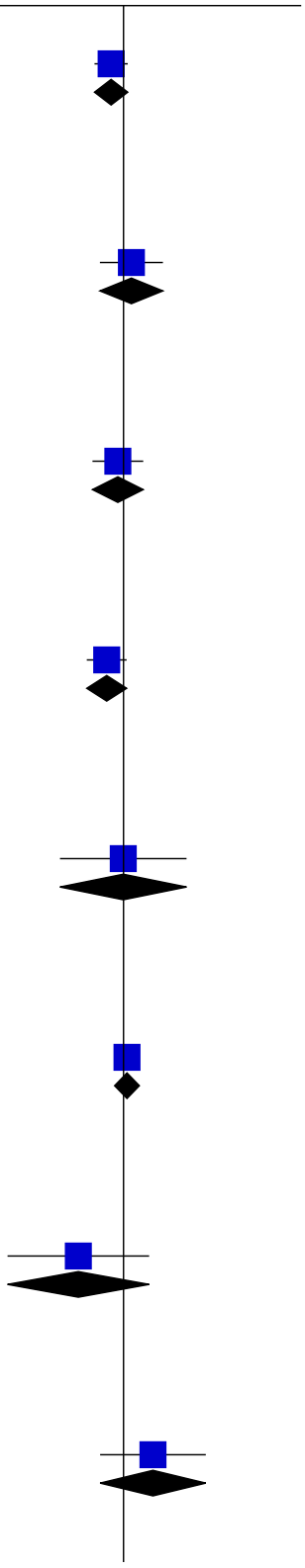
Study or Subgroup	ACEi+ARB Mean	ACEi+ARB SD	ACEi+ARB Total	ACEi Mean	ACEi SD	ACEi Total	Weight	Std. Mean Difference IV, Random, 95% CI
HALT-PKD Study B 2014	7.3	18.992796	243	7.5	18.558421	242	46.6%	-0.01 [-0.19 , 0.17]
HALT-PKD Study A 2014	-1.1	16.36557	273	0	16.694923	284	53.4%	-0.07 [-0.23 , 0.10]
Total (Wald{fn})			**516**			**526**	**100.0%**	**-0.04 [-0.16 , 0.08]**

Test for overall effect: Z = 0.65 (P = 0.51)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 1 (P = 0.65); I² = 0%



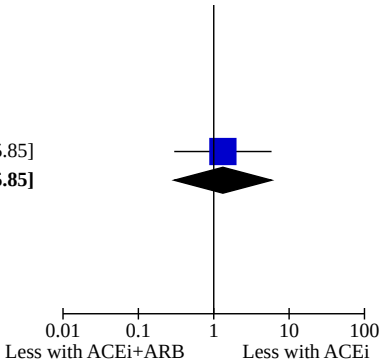
Analysis 16.10. Comparison 16: Angiotensin-converting-enzyme inhibitors (ACEi) plus angiotensin receptor blockers (ARB) versus ACEi alone, Outcome 10: Adverse events

Study or Subgroup	ACEi+ARB Events	ACEi+ARB Total	ACEi Events	ACEi Total	Weight	Risk Ratio M-H, Random, 95% CI
16.10.1 Acute kidney injury						
HALT-PKD Study A 2014	22	244	32	242	100.0%	0.68 [0.41 , 1.14]
Subtotal		**244**		**242**	**100.0%**	**0.68 [0.41 , 1.14]**
Total events:	22		32			
Test for overall effect: Z = 1.46 (P = 0.14)						
Heterogeneity: Not applicable						
16.10.2 Cancer						
HALT-PKD Study A 2014	9	244	7	242	100.0%	1.28 [0.48 , 3.37]
Subtotal		**244**		**242**	**100.0%**	**1.28 [0.48 , 3.37]**
Total events:	9		7			
Test for overall effect: Z = 0.49 (P = 0.62)						
Heterogeneity: Not applicable						
16.10.3 Cardiovascular disorder						
HALT-PKD Study A 2014	11	244	13	242	100.0%	0.84 [0.38 , 1.84]
Subtotal		**244**		**242**	**100.0%**	**0.84 [0.38 , 1.84]**
Total events:	11		13			
Test for overall effect: Z = 0.44 (P = 0.66)						
Heterogeneity: Not applicable						
16.10.4 Gastrointestinal disorder						
HALT-PKD Study A 2014	15	244	25	242	100.0%	0.60 [0.32 , 1.10]
Subtotal		**244**		**242**	**100.0%**	**0.60 [0.32 , 1.10]**
Total events:	15		25			
Test for overall effect: Z = 1.65 (P = 0.10)						
Heterogeneity: Not applicable						
16.10.5 Headache						
HALT-PKD Study A 2014	2	244	2	242	100.0%	0.99 [0.14 , 6.98]
Subtotal		**244**		**242**	**100.0%**	**0.99 [0.14 , 6.98]**
Total events:	2		2			
Test for overall effect: Z = 0.01 (P = 0.99)						
Heterogeneity: Not applicable						
16.10.6 Hyperkalaemia						
HALT-PKD Study A 2014	46	244	41	242	100.0%	1.11 [0.76 , 1.63]
Subtotal		**244**		**242**	**100.0%**	**1.11 [0.76 , 1.63]**
Total events:	46		41			
Test for overall effect: Z = 0.55 (P = 0.58)						
Heterogeneity: Not applicable						
16.10.7 Nephrolithiasis or renal colic						
HALT-PKD Study A 2014	1	244	4	242	100.0%	0.25 [0.03 , 2.20]
Subtotal		**244**		**242**	**100.0%**	**0.25 [0.03 , 2.20]**
Total events:	1		4			
Test for overall effect: Z = 1.25 (P = 0.21)						
Heterogeneity: Not applicable						
16.10.8 Renal haemorrhage or haematuria						
HALT-PKD Study A 2014	5	244	2	242	100.0%	2.48 [0.49 , 12.66]
Subtotal		**244**		**242**	**100.0%**	**2.48 [0.49 , 12.66]**
Total events:	5		2			
Test for overall effect: Z = 1.09 (P = 0.27)						



Analysis 16.10. (Continued)

Total events:	5		2			
Test for overall effect: Z = 1.09 (P = 0.27)						
Heterogeneity: Not applicable						
16.10.9 Stroke						
HALT-PKD Study A 2014	4	244	3	242	100.0%	1.32 [0.30 , 5.85]
Subtotal		**244**		**242**	**100.0%**	**1.32 [0.30 , 5.85]**
Total events:	4		3			
Test for overall effect: Z = 0.37 (P = 0.71)						
Heterogeneity: Not applicable						



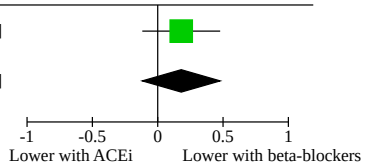
Comparison 17. Angiotensin-converting-enzyme inhibitors (ACEi) versus beta-blockers

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.1 Serum creatinine [mg/dL]	1	37	Mean Difference (IV, Random, 95% CI)	0.18 [-0.12, 0.48]
17.2 GFR [mL/min/1.73 m^2]	2	65	Mean Difference (IV, Random, 95% CI)	-8.06 [-29.62, 13.50]
17.3 GFR: descriptive data	0		Other data	No numeric data
17.4 Need for kidney replacement therapy	1	37	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.02, 8.97]
17.5 Cardiovascular events	1	37	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.08, 17.42]
17.6 Systolic blood pressure [mm Hg]	1	37	Mean Difference (IV, Random, 95% CI)	-1.00 [-2.29, 0.29]
17.7 Diastolic blood pressure [mm Hg]	1	37	Mean Difference (IV, Random, 95% CI)	1.00 [0.35, 1.65]
17.8 Mean arterial pressure [mm Hg]	1	28	Mean Difference (IV, Random, 95% CI)	-3.00 [-4.92, -1.08]
17.9 Blood pressure: descriptive data	0		Other data	No numeric data
17.10 Albuminuria	2	65	Std. Mean Difference (IV, Random, 95% CI)	-0.19 [-1.77, 1.39]

Analysis 17.1. Comparison 17: Angiotensin-converting-enzyme inhibitors (ACEi) versus beta-blockers, Outcome 1: Serum creatinine [mg/dL]

Study or Subgroup	ACEi Mean	ACEi SD	ACEi Total	Beta-blockers Mean	Beta-blockers SD	Beta-blockers Total	Weight	Mean Difference IV, Random, 95% CI
Zeltner 2008	1.88	0.5	17	1.7	0.41	20	100.0%	0.18 [-0.12 , 0.48]
Total			**17**			**20**	**100.0%**	**0.18 [-0.12 , 0.48]**

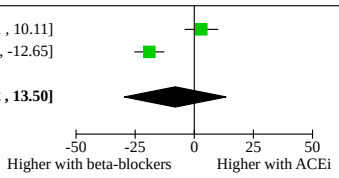
Test for overall effect: Z = 1.18 (P = 0.24)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 17.2. Comparison 17: Angiotensin-converting-enzyme inhibitors (ACEi) versus beta-blockers, Outcome 2: GFR [mL/min/1.73 m²]

Study or Subgroup	ACEi Mean	ACEi SD	ACEi Total	Beta-blockers Mean	Beta-blockers SD	Beta-blockers Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
Zeltner 2008	81	11	17	78	11	20	49.7%	3.00 [-4.11 , 10.11]	? ? + + − + ?
van Dijk 2003	64	9	13	83	8	15	50.3%	-19.00 [-25.35 , -12.65]	? ? ? ? + ? ?
Total (Wald{fn})			**30**			**35**	**100.0%**	**-8.06 [-29.62 , 13.50]**	

Test for overall effect: Z = 0.73 (P = 0.46)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 230.17; Chi² = 20.45, df = 1 (P < 0.00001); I² = 95%



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 17.3. Comparison 17: Angiotensin-converting-enzyme inhibitors (ACEi) versus beta-blockers, Outcome 3: GFR: descriptive data

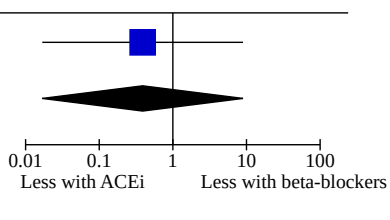
GFR: descriptive data

Study	Description of outcome
Watson 1999	eGFR (Cockcroft-Gault formula) significantly decreased in both groups over the 3 year period (ACEi: 19.3 mL/min/1.73 m^2; beta-blockers: 14.3 mL/min/1.73 m^2) but there was no difference in the rate of decline between groups.

Analysis 17.4. Comparison 17: Angiotensin-converting-enzyme inhibitors (ACEi) versus beta-blockers, Outcome 4: Need for kidney replacement therapy

Study or Subgroup	ACEi Events	ACEi Total	Beta-blockers Events	Beta-blockers Total	Weight	Risk Ratio M-H, Random, 95% CI
Zeltner 2008	0	17	1	20	100.0%	0.39 [0.02 , 8.97]
Total		**17**		**20**	**100.0%**	**0.39 [0.02 , 8.97]**
Total events:	0		1			

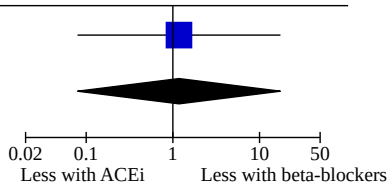
Test for overall effect: Z = 0.59 (P = 0.56)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 17.5. Comparison 17: Angiotensin-converting-enzyme inhibitors (ACEi) versus beta-blockers, Outcome 5: Cardiovascular events

Study or Subgroup	ACEi Events	ACEi Total	Beta-blockers Events	Beta-blockers Total	Weight	Risk Ratio M-H, Random, 95% CI
Zeltner 2008	1	17	1	20	100.0%	1.18 [0.08 , 17.42]
Total		**17**		**20**	**100.0%**	**1.18 [0.08 , 17.42]**
Total events:	1		1			

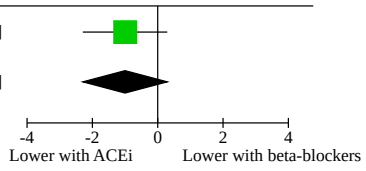
Test for overall effect: Z = 0.12 (P = 0.91)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 17.6. Comparison 17: Angiotensin-converting-enzyme inhibitors (ACEi) versus beta-blockers, Outcome 6: Systolic blood pressure [mm Hg]

Study or Subgroup	ACEi Mean	ACEi SD	ACEi Total	Beta-blockers Mean	Beta-blockers SD	Beta-blockers Total	Weight	Mean Difference IV, Random, 95% CI
Zeltner 2008	130	2	17	131	2	20	100.0%	-1.00 [-2.29 , 0.29]
Total			**17**			**20**	**100.0%**	**-1.00 [-2.29 , 0.29]**

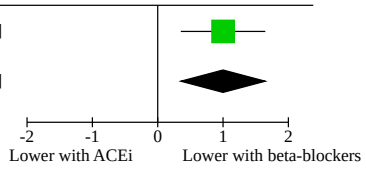
Test for overall effect: Z = 1.52 (P = 0.13)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 17.7. Comparison 17: Angiotensin-converting-enzyme inhibitors (ACEi) versus beta-blockers, Outcome 7: Diastolic blood pressure [mm Hg]

Study or Subgroup	ACEi Mean	ACEi SD	ACEi Total	Beta-blockers Mean	Beta-blockers SD	Beta-blockers Total	Weight	Mean Difference IV, Random, 95% CI
Zeltner 2008	83	1	17	82	1	20	100.0%	1.00 [0.35 , 1.65]
Total			**17**			**20**	**100.0%**	**1.00 [0.35 , 1.65]**

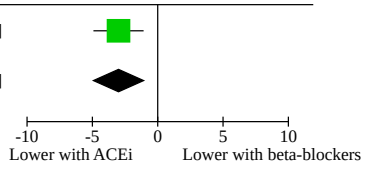
Test for overall effect: Z = 3.03 (P = 0.002)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 17.8. Comparison 17: Angiotensin-converting-enzyme inhibitors (ACEi) versus beta-blockers, Outcome 8: Mean arterial pressure [mm Hg]

Study or Subgroup	ACEi Mean	ACEi SD	ACEi Total	Beta-blockers Mean	Beta-blockers SD	Beta-blockers Total	Weight	Mean Difference IV, Random, 95% CI
van Dijk 2003	102	3	13	105	2	15	100.0%	-3.00 [-4.92 , -1.08]
Total			**13**			**15**	**100.0%**	**-3.00 [-4.92 , -1.08]**

Test for overall effect: Z = 3.06 (P = 0.002)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable

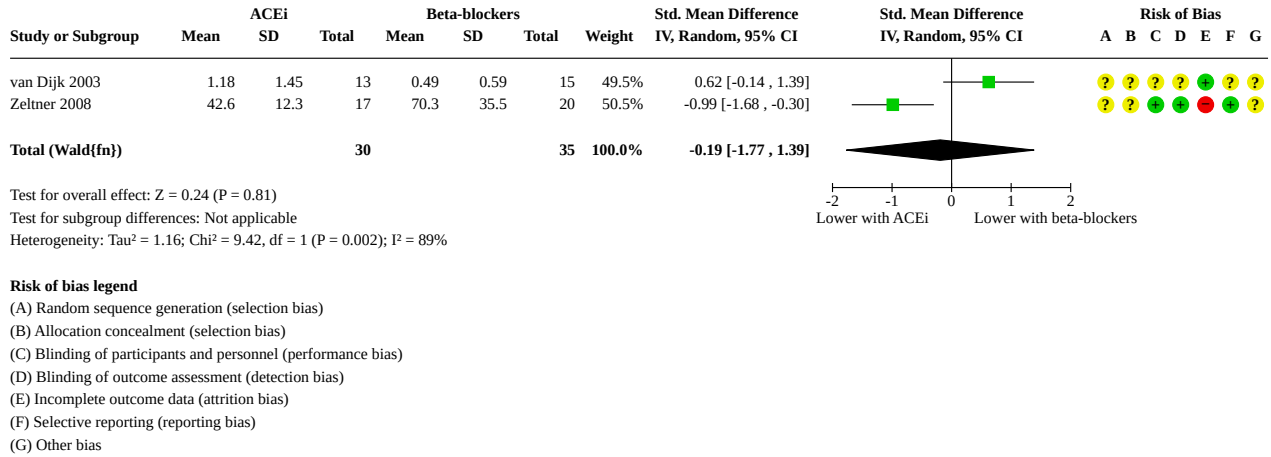


Analysis 17.9. Comparison 17: Angiotensin-converting-enzyme inhibitors (ACEi) versus beta-blockers, Outcome 9: Blood pressure: descriptive data

Blood pressure: descriptive data

Study	Description of outcome
Watson 1999	Good blood pressure control was achieved in both groups (ACEi: 132.6/84.6 mm Hg; beta-blockers: 130.9/84.5 mm Hg)

Analysis 17.10. Comparison 17: Angiotensin-converting-enzyme inhibitors (ACEi) versus beta-blockers, Outcome 10: Albuminuria



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

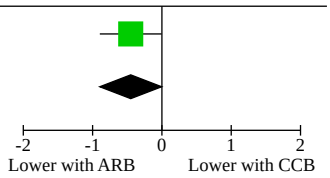
Comparison 18. Angiotensin receptor blockers (ARB) versus calcium channel blockers (CCB)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.1 Serum creatinine [mg/dL]	1	40	Mean Difference (IV, Random, 95% CI)	-0.45 [-0.90, -0.00]
18.2 GFR [mL/min/1.73 m^2]	1	31	Mean Difference (IV, Random, 95% CI)	6.30 [-8.49, 21.09]
18.3 Doubling of serum creatinine	1	49	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.02, 1.34]
18.4 Proteinuria [mg/day]	1	25	Mean Difference (IV, Random, 95% CI)	-304.00 [-578.54, -29.46]
18.5 Albuminuria [mg/day]	1	24	Mean Difference (IV, Random, 95% CI)	-238.00 [-394.61, -81.39]

Analysis 18.1. Comparison 18: Angiotensin receptor blockers (ARB) versus calcium channel blockers (CCB), Outcome 1: Serum creatinine [mg/dL]

Study or Subgroup	ARB Mean	ARB SD	ARB Total	CCB Mean	CCB SD	CCB Total	Weight	Mean Difference IV, Random, 95% CI
Nutahara 2005	1.26	0.46	21	1.71	0.89	19	100.0%	-0.45 [-0.90 , -0.00]
Total			**21**			**19**	**100.0%**	**-0.45 [-0.90 , -0.00]**

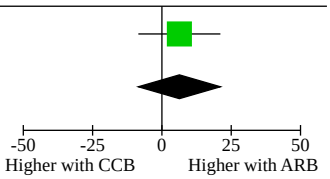
Test for overall effect: Z = 1.98 (P = 0.05)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 18.2. Comparison 18: Angiotensin receptor blockers (ARB) versus calcium channel blockers (CCB), Outcome 2: GFR [mL/min/1.73 m²]

Study or Subgroup	ARB Mean	ARB SD	ARB Total	CCB Mean	CCB SD	CCB Total	Weight	Mean Difference IV, Random, 95% CI
Nutahara 2005	64.8	27.8	20	58.5	14.2	11	100.0%	6.30 [-8.49 , 21.09]
Total			**20**			**11**	**100.0%**	**6.30 [-8.49 , 21.09]**

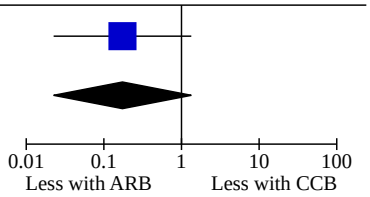
Test for overall effect: Z = 0.83 (P = 0.40)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 18.3. Comparison 18: Angiotensin receptor blockers (ARB) versus calcium channel blockers (CCB), Outcome 3: Doubling of serum creatinine

Study or Subgroup	ARB Events	ARB Total	CCB Events	CCB Total	Weight	Risk Ratio M-H, Random, 95% CI
Nutahara 2005	1	24	6	25	100.0%	0.17 [0.02 , 1.34]
Total		**24**		**25**	**100.0%**	**0.17 [0.02 , 1.34]**
Total events:	1		6			

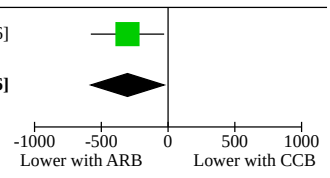
Test for overall effect: Z = 1.68 (P = 0.09)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



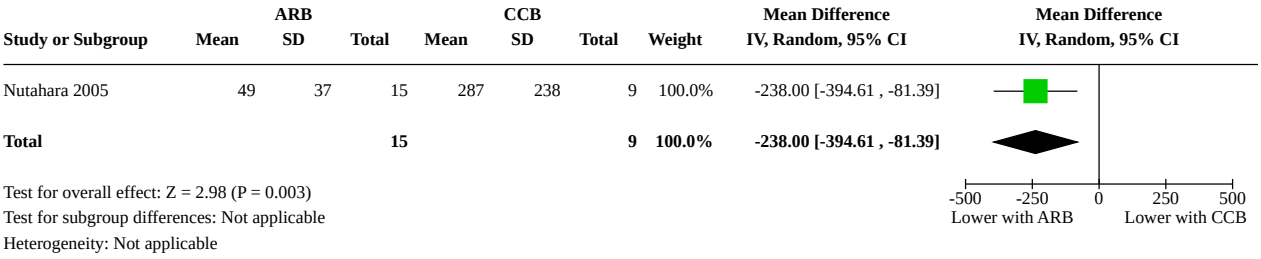
Analysis 18.4. Comparison 18: Angiotensin receptor blockers (ARB) versus calcium channel blockers (CCB), Outcome 4: Proteinuria [mg/day]

Study or Subgroup	ARB Mean	ARB SD	ARB Total	CCB Mean	CCB SD	CCB Total	Weight	Mean Difference IV, Random, 95% CI
Nutahara 2005	154	176	15	458	419	10	100.0%	-304.00 [-578.54 , -29.46]
Total			**15**			**10**	**100.0%**	**-304.00 [-578.54 , -29.46]**

Test for overall effect: Z = 2.17 (P = 0.03)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 18.5. Comparison 18: Angiotensin receptor blockers (ARB) versus calcium channel blockers (CCB), Outcome 5: Albuminuria [mg/day]



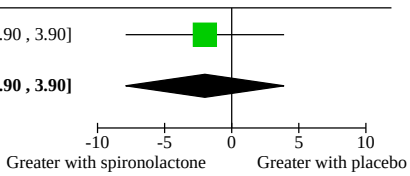
Comparison 19. Spironolactone versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19.1 Change in eGFR	1	60	Mean Difference (IV, Random, 95% CI)	-2.00 [-7.90, 3.90]
19.2 Systolic blood pressure: descriptive data	0		Other data	No numeric data
19.3 Diastolic blood pressure: descriptive data	0		Other data	No numeric data
19.4 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
19.4.1 Dizziness	1	61	Risk Ratio (M-H, Random, 95% CI)	0.16 [0.01, 2.92]
19.4.2 Muscle cramping/soreness	1	61	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.13, 4.10]
19.4.3 Vision changes	1	61	Risk Ratio (M-H, Random, 95% CI)	2.21 [0.21, 23.08]
19.4.4 Increased urination	1	61	Risk Ratio (M-H, Random, 95% CI)	5.50 [0.27, 110.01]
19.4.5 Hyperkalaemia	1	61	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.02, 8.66]
19.4.6 Fatigue	1	61	Risk Ratio (M-H, Random, 95% CI)	3.30 [0.14, 77.95]
19.4.7 Increased thirst	1	61	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.02, 8.66]
19.4.8 Nausea	1	61	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.02, 8.66]
19.4.9 Elevated AST/ALT	1	61	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.02, 8.66]

Analysis 19.1. Comparison 19: Spironolactone versus placebo, Outcome 1: Change in eGFR

Study or Subgroup	Spironolactone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Nowak 2019	-1.3	1.1	28	0.7	17	32	100.0%	-2.00 [-7.90 , 3.90]
Total			**28**			**32**	**100.0%**	**-2.00 [-7.90 , 3.90]**

Test for overall effect: Z = 0.66 (P = 0.51)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 19.2. Comparison 19: Spironolactone versus placebo, Outcome 2: Systolic blood pressure: descriptive data

Systolic blood pressure: descriptive data

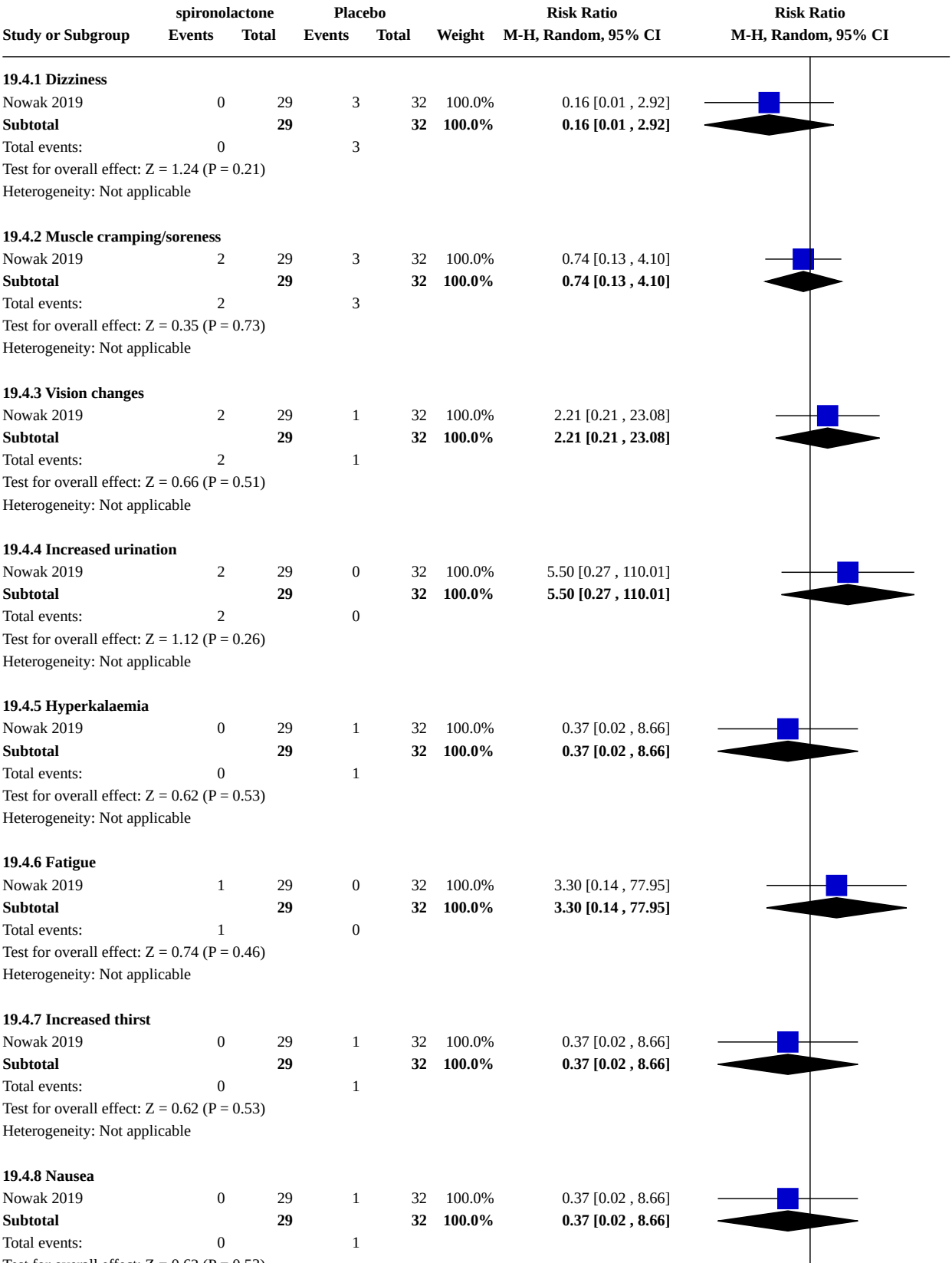
Study	Narrative Results
Nowak 2019	Change in brachial SBP at rest was −6 [IQR, −15, 1] mm Hg in the spironolactone group, compared with a change of 2 [IQR, −7, 10] mmHg in the placebo group

Analysis 19.3. Comparison 19: Spironolactone versus placebo, Outcome 3: Diastolic blood pressure: descriptive data

Diastolic blood pressure: descriptive data

Study	Narrative Results
Nowak 2019	Spironolactone brachial DBP median change -4 [IQR -10, 3] mmHg compared to placebo median change -1 [IQR -7, 9] mmHg, P=0.2 (low certainty evidence).

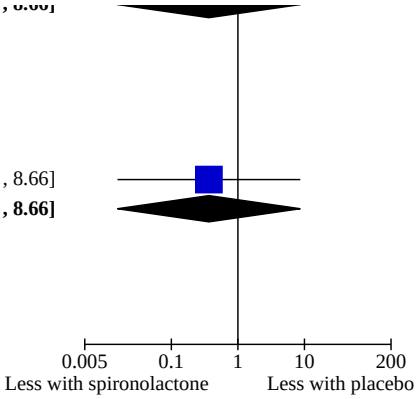
Analysis 19.4. Comparison 19: Spironolactone versus placebo, Outcome 4: Adverse events



Study or Subgroup	spironolactone Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
19.4.1 Dizziness						
Nowak 2019	0	29	3	32	100.0%	0.16 [0.01 , 2.92]
Subtotal		**29**		**32**	**100.0%**	**0.16 [0.01 , 2.92]**
Total events:	0		3			
Test for overall effect: Z = 1.24 (P = 0.21)						
Heterogeneity: Not applicable						
19.4.2 Muscle cramping/soreness						
Nowak 2019	2	29	3	32	100.0%	0.74 [0.13 , 4.10]
Subtotal		**29**		**32**	**100.0%**	**0.74 [0.13 , 4.10]**
Total events:	2		3			
Test for overall effect: Z = 0.35 (P = 0.73)						
Heterogeneity: Not applicable						
19.4.3 Vision changes						
Nowak 2019	2	29	1	32	100.0%	2.21 [0.21 , 23.08]
Subtotal		**29**		**32**	**100.0%**	**2.21 [0.21 , 23.08]**
Total events:	2		1			
Test for overall effect: Z = 0.66 (P = 0.51)						
Heterogeneity: Not applicable						
19.4.4 Increased urination						
Nowak 2019	2	29	0	32	100.0%	5.50 [0.27 , 110.01]
Subtotal		**29**		**32**	**100.0%**	**5.50 [0.27 , 110.01]**
Total events:	2		0			
Test for overall effect: Z = 1.12 (P = 0.26)						
Heterogeneity: Not applicable						
19.4.5 Hyperkalaemia						
Nowak 2019	0	29	1	32	100.0%	0.37 [0.02 , 8.66]
Subtotal		**29**		**32**	**100.0%**	**0.37 [0.02 , 8.66]**
Total events:	0		1			
Test for overall effect: Z = 0.62 (P = 0.53)						
Heterogeneity: Not applicable						
19.4.6 Fatigue						
Nowak 2019	1	29	0	32	100.0%	3.30 [0.14 , 77.95]
Subtotal		**29**		**32**	**100.0%**	**3.30 [0.14 , 77.95]**
Total events:	1		0			
Test for overall effect: Z = 0.74 (P = 0.46)						
Heterogeneity: Not applicable						
19.4.7 Increased thirst						
Nowak 2019	0	29	1	32	100.0%	0.37 [0.02 , 8.66]
Subtotal		**29**		**32**	**100.0%**	**0.37 [0.02 , 8.66]**
Total events:	0		1			
Test for overall effect: Z = 0.62 (P = 0.53)						
Heterogeneity: Not applicable						
19.4.8 Nausea						
Nowak 2019	0	29	1	32	100.0%	0.37 [0.02 , 8.66]
Subtotal		**29**		**32**	**100.0%**	**0.37 [0.02 , 8.66]**
Total events:	0		1			

Analysis 19.4. (Continued)

~~Subtotal~~		~~29~~		~~32~~	~~100.0%~~	~~0.37 [0.02 , 8.66]~~
Total events:	0		1			
Test for overall effect: Z = 0.62 (P = 0.53)						
Heterogeneity: Not applicable						
19.4.9 Elevated AST/ALT						
Nowak 2019	0	29	1	32	100.0%	0.37 [0.02 , 8.66]
Subtotal		**29**		**32**	**100.0%**	**0.37 [0.02 , 8.66]**
Total events:	0		1			
Test for overall effect: Z = 0.62 (P = 0.53)						
Heterogeneity: Not applicable						



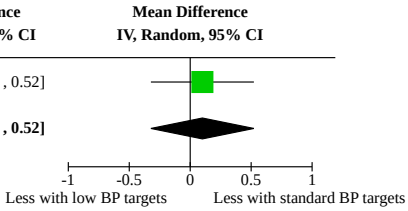
Comparison 20. Low blood pressure (BP) target (95/60 to 110/75 mm Hg) versus standard BP target (120/70 to 130/80 mm Hg)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20.1 Change in eGFR [mL/min/1.7 3 m2]	1	557	Mean Difference (IV, Random, 95% CI)	0.10 [-0.32, 0.52]
20.2 Acute kidney injury	1	558	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.54, 1.99]
20.3 Death	1	558	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.01, 4.30]
20.4 Quality of life scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
20.4.1 SF-36 physical component summary	1	558	Mean Difference (IV, Random, 95% CI)	0.13 [-0.06, 0.32]
20.4.2 SF-36 mental component summary	1	558	Mean Difference (IV, Random, 95% CI)	-0.23 [-0.45, -0.01]
20.5 Per cent annual change in total kidney volume [mL/cm]	1	558	Mean Difference (IV, Random, 95% CI)	-1.00 [-1.67, -0.33]
20.6 All cause hospitalisation	1	558	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.65, 0.99]
20.7 Albuminuria [mg/24 hours]	1	557	Mean Difference (IV, Random, 95% CI)	-6.20 [-8.95, -3.45]
20.8 Serious adverse events	1	558	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.69, 1.19]

Analysis 20.1. Comparison 20: Low blood pressure (BP) target (95/60 to 110/75 mm Hg) versus standard BP target (120/70 to 130/80 mm Hg), Outcome 1: Change in eGFR [mL/min/1.7 3 m^2]

Study or Subgroup	Low BP Mean	Low BP SD	Low BP Total	Standard BP Mean	Standard BP SD	Standard BP Total	Weight	Mean Difference IV, Random, 95% CI
HALT-PKD Study A 2014	-2.9	2.522428	274	-3	2.563885	283	100.0%	0.10 [-0.32 , 0.52]
Total			**274**			**283**	**100.0%**	**0.10 [-0.32 , 0.52]**

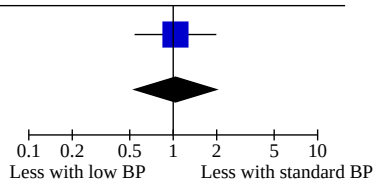
Test for overall effect: Z = 0.46 (P = 0.64)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 20.2. Comparison 20: Low blood pressure (BP) target (95/60 to 110/75 mm Hg) versus standard BP target (120/70 to 130/80 mm Hg), Outcome 2: Acute kidney injury

Study or Subgroup	Low BP Events	Low BP Total	Standard BP Events	Standard BP Total	Weight	Risk Ratio M-H, Random, 95% CI
HALT-PKD Study A 2014	17	274	17	284	100.0%	1.04 [0.54 , 1.99]
Total		**274**		**284**	**100.0%**	**1.04 [0.54 , 1.99]**
Total events:	17		17			

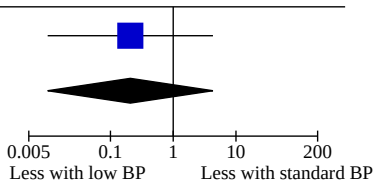
Test for overall effect: Z = 0.11 (P = 0.91)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 20.3. Comparison 20: Low blood pressure (BP) target (95/60 to 110/75 mm Hg) versus standard BP target (120/70 to 130/80 mm Hg), Outcome 3: Death

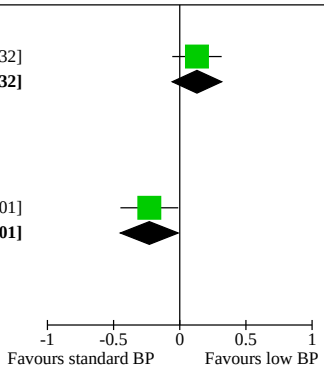
Study or Subgroup	Low BP Events	Low BP Total	Standard BP Events	Standard BP Total	Weight	Risk Ratio M-H, Random, 95% CI
HALT-PKD Study A 2014	0	274	2	284	100.0%	0.21 [0.01 , 4.30]
Total		**274**		**284**	**100.0%**	**0.21 [0.01 , 4.30]**
Total events:	0		2			

Test for overall effect: Z = 1.02 (P = 0.31)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



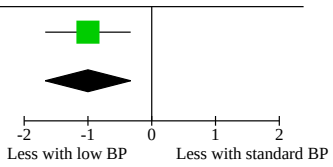
Analysis 20.4. Comparison 20: Low blood pressure (BP) target (95/60 to 110/75 mm Hg) versus standard BP target (120/70 to 130/80 mm Hg), Outcome 4: Quality of life scores

Study or Subgroup	Low BP Mean	Low BP SD	Low BP Total	Standard BP Mean	Standard BP SD	Standard BP Total	Weight	Mean Difference IV, Random, 95% CI
20.4.1 SF-36 physical component summary								
HALT-PKD Study A 2014	-0.17	1.135093	274	-0.3	1.112995	284	100.0%	0.13 [-0.06 , 0.32]
Subtotal			**274**			**284**	**100.0%**	**0.13 [-0.06 , 0.32]**
Test for overall effect: Z = 1.37 (P = 0.17)								
Heterogeneity: Not applicable								
20.4.2 SF-36 mental component summary								
HALT-PKD Study A 2014	-0.05	1.345295	274	0.18	1.284225	284	100.0%	-0.23 [-0.45 , -0.01]
Subtotal			**274**			**284**	**100.0%**	**-0.23 [-0.45 , -0.01]**
Test for overall effect: Z = 2.06 (P = 0.04)								
Heterogeneity: Not applicable								
Test for subgroup differences: Chi² = 6.03, df = 1 (P = 0.01), I² = 83.4%								



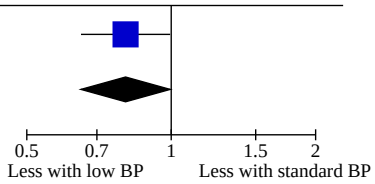
Analysis 20.5. Comparison 20: Low blood pressure (BP) target (95/60 to 110/75 mm Hg) versus standard BP target (120/70 to 130/80 mm Hg), Outcome 5: Per cent annual change in total kidney volume [mL/cm]

Study or Subgroup	Low BP Mean	Low BP SD	Low BP Total	Standard BP Mean	Standard BP SD	Standard BP Total	Weight	Mean Difference IV, Random, 95% CI
HALT-PKD Study A 2014	5.6	3.783643	274	6.6	4.280749	284	100.0%	-1.00 [-1.67 , -0.33]
Total			**274**			**284**	**100.0%**	**-1.00 [-1.67 , -0.33]**
Test for overall effect: Z = 2.93 (P = 0.003)								
Test for subgroup differences: Not applicable								
Heterogeneity: Not applicable								



Analysis 20.6. Comparison 20: Low blood pressure (BP) target (95/60 to 110/75 mm Hg) versus standard BP target (120/70 to 130/80 mm Hg), Outcome 6: All cause hospitalisation

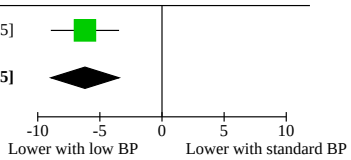
Study or Subgroup	Low BP Events	Low BP Total	Standard BP Events	Standard BP Total	Weight	Risk Ratio M-H, Random, 95% CI
HALT-PKD Study A 2014	93	274	120	284	100.0%	0.80 [0.65 , 0.99]
Total		**274**		**284**	**100.0%**	**0.80 [0.65 , 0.99]**
Total events:	93		120			
Test for overall effect: Z = 2.01 (P = 0.04)						
Test for subgroup differences: Not applicable						
Heterogeneity: Not applicable						



Analysis 20.7. Comparison 20: Low blood pressure (BP) target (95/60 to 110/75 mm Hg) versus standard BP target (120/70 to 130/80 mm Hg), Outcome 7: Albuminuria [mg/24 hours]

Study or Subgroup	Low BP Mean	Low BP SD	Low BP Total	Standard BP Mean	Standard BP SD	Standard BP Total	Weight	Mean Difference IV, Random, 95% CI
HALT-PKD Study A 2014	-3.8	16.395784	274	2.4	16.665251	283	100.0%	-6.20 [-8.95 , -3.45]
Total			**274**			**283**	**100.0%**	**-6.20 [-8.95 , -3.45]**

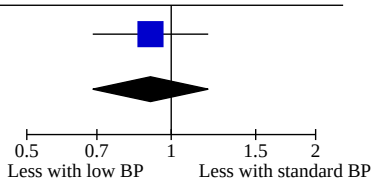
Test for overall effect: Z = 4.43 (P < 0.00001)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 20.8. Comparison 20: Low blood pressure (BP) target (95/60 to 110/75 mm Hg) versus standard BP target (120/70 to 130/80 mm Hg), Outcome 8: Serious adverse events

Study or Subgroup	Low BP Events	Low BP Total	Standard BP Events	Standard BP Total	Weight	Risk Ratio M-H, Random, 95% CI
HALT-PKD Study A 2014	69	274	79	284	100.0%	0.91 [0.69 , 1.19]
Total		**274**		**284**	**100.0%**	**0.91 [0.69 , 1.19]**
Total events:	69		79			

Test for overall effect: Z = 0.70 (P = 0.48)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



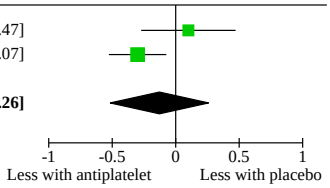
Comparison 21. Antiplatelet agents versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
21.1 Serum creatinine [mg/dL]	2	22	Mean Difference (IV, Random, 95% CI)	-0.13 [-0.52, 0.26]
21.2 GFR [mL/min/1.73 m^2]	2	22	Mean Difference (IV, Random, 95% CI)	2.24 [-8.05, 12.53]
21.3 Systolic blood pressure [mm Hg]	2	22	Mean Difference (IV, Random, 95% CI)	5.04 [-7.34, 17.43]
21.4 Diastolic blood pressure [mm Hg]	2	22	Mean Difference (IV, Random, 95% CI)	6.24 [-3.27, 15.74]
21.5 Albuminuria [µg/min]	2	22	Mean Difference (IV, Random, 95% CI)	-60.53 [-129.06, 8.01]

Analysis 21.1. Comparison 21: Antiplatelet agents versus placebo, Outcome 1: Serum creatinine [mg/dL]

Study or Subgroup	Antiplatelet agents Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Nakamura 2001d hypertensive	1	0.3	5	0.9	0.3	5	42.9%	0.10 [-0.27 , 0.47]
Nakamura 2001d normotensive	0.7	0.2	6	1	0.2	6	57.1%	-0.30 [-0.53 , -0.07]
Total (Wald{fn})			**11**			**11**	**100.0%**	**-0.13 [-0.52 , 0.26]**

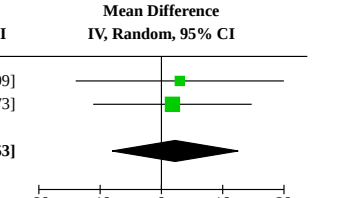
Test for overall effect: Z = 0.65 (P = 0.52)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.06; Chi² = 3.24, df = 1 (P = 0.07); I² = 69%



Analysis 21.2. Comparison 21: Antiplatelet agents versus placebo, Outcome 2: GFR [mL/min/1.73 m²]

Study or Subgroup	Antiplatelet agents Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Nakamura 2001d hypertensive	98.8	14	5	95.8	13.4	5	36.7%	3.00 [-13.99 , 19.99]
Nakamura 2001d normotensive	110.4	10.6	6	108.6	12.2	6	63.3%	1.80 [-11.13 , 14.73]
Total (Wald{fn})			**11**			**11**	**100.0%**	**2.24 [-8.05 , 12.53]**

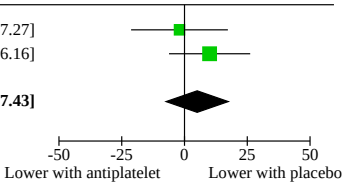
Test for overall effect: Z = 0.43 (P = 0.67)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%



Analysis 21.3. Comparison 21: Antiplatelet agents versus placebo, Outcome 3: Systolic blood pressure [mm Hg]

Study or Subgroup	Antiplatelet agents Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Nakamura 2001d normotensive	116	18	6	118	16	6	41.3%	-2.00 [-21.27 , 17.27]
Nakamura 2001d hypertensive	162	14	5	152	12	5	58.7%	10.00 [-6.16 , 26.16]
Total (Wald{fn})			**11**			**11**	**100.0%**	**5.04 [-7.34 , 17.43]**

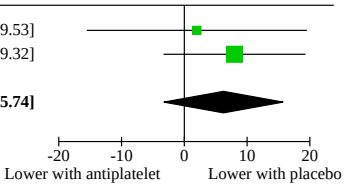
Test for overall effect: Z = 0.80 (P = 0.42)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.00; Chi² = 0.87, df = 1 (P = 0.35); I² = 0%



Analysis 21.4. Comparison 21: Antiplatelet agents versus placebo, Outcome 4: Diastolic blood pressure [mm Hg]

Study or Subgroup	Antiplatelet agents Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Nakamura 2001d hypertensive	98	12	5	96	16	5	29.4%	2.00 [-15.53 , 19.53]
Nakamura 2001d normotensive	78	10	6	70	10	6	70.6%	8.00 [-3.32 , 19.32]
Total (Wald{fn})			**11**			**11**	**100.0%**	**6.24 [-3.27 , 15.74]**

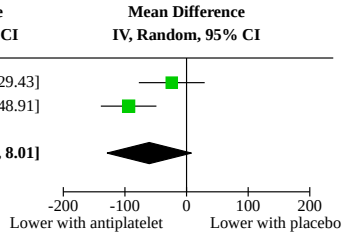
Test for overall effect: Z = 1.29 (P = 0.20)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.00; Chi² = 0.32, df = 1 (P = 0.57); I² = 0%



Analysis 21.5. Comparison 21: Antiplatelet agents versus placebo, Outcome 5: Albuminuria [µg/min]

Study or Subgroup	Antiplatelet agents Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Nakamura 2001d hypertensive	118	40	5	142	46	5	47.8%	-24.00 [-77.43 , 29.43]
Nakamura 2001d normotensive	46	26	6	140	50	6	52.2%	-94.00 [-139.09 , -48.91]
Total (Wald{fn})			**11**			**11**	**100.0%**	**-60.53 [-129.06 , 8.01]**

Test for overall effect: Z = 1.73 (P = 0.08)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 1813.73; Chi² = 3.85, df = 1 (P = 0.05); I² = 74%

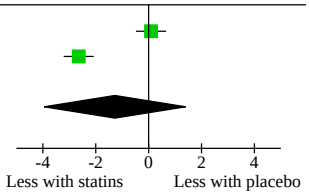


Comparison 22. Statins versus control (placebo, standard therapy or no treatment)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22.1 Change in eGFR	2	140	Std. Mean Difference (IV, Random, 95% CI)	-1.28 [-3.96, 1.40]
22.2 GFR: descriptive data	0		Other data	No numeric data
22.3 Creatinine clearance [mL/min/1.73 m^2]	1	91	Mean Difference (IV, Random, 95% CI)	0.00 [-10.12, 10.12]
22.4 Systolic blood pressure [mm Hg]	2	140	Mean Difference (IV, Random, 95% CI)	0.32 [-3.20, 3.84]
22.5 Diastolic blood pressure [mm Hg]	2	140	Mean Difference (IV, Random, 95% CI)	-1.17 [-3.84, 1.50]
22.6 Change in height-adjusted total kidney volume	1	91	Mean Difference (IV, Random, 95% CI)	-8.00 [-9.24, -6.76]
22.7 Proteinuria: descriptive data	0		Other data	No numeric data
22.8 Urinary albumin excretion: > 20% increase	1	91	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.76, 1.93]
22.9 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
22.9.1 Elevated AST	1	91	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.06, 13.29]

Analysis 22.1. Comparison 22: Statins versus control (placebo, standard therapy or no treatment), Outcome 1: Change in eGFR

Study or Subgroup	Statins Mean	Statins SD	Statins Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
AIPRI 1996	-0.31	10.4	29	-1.34	12.2	20	50.0%	0.09 [-0.48 , 0.66]
Cadnapaphornchai 2011	23	3	49	31	3	42	50.0%	-2.64 [-3.21 , -2.07]
Total (Wald{fn})			**78**			**62**	**100.0%**	**-1.28 [-3.96 , 1.40]**



Test for overall effect: Z = 0.93 (P = 0.35)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 3.66; Chi² = 44.27, df = 1 (P < 0.00001); I² = 98%

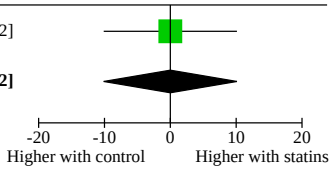
Analysis 22.2. Comparison 22: Statins versus control (placebo, standard therapy or no treatment), Outcome 2: GFR: descriptive data

GFR: descriptive data

Study	Description of outcome
Fassett 2010	There was a 23% reduction in the rate of GFR change in statins-treated patients compared with controls, although not statistically significant
van Dijk 2001	Compared to placebo, treatment with statins significantly increased GFR from 124 ± 4 mL/min to 132 ± 6 mL/min (p < 0.05) (cross-over study)

Analysis 22.3. Comparison 22: Statins versus control (placebo, standard therapy or no treatment), Outcome 3: Creatinine clearance [mL/min/1.73 m²]

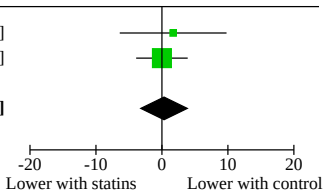
Study or Subgroup	Statins Mean	Statins SD	Statins Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Cadnapaphornchai 2011	126	24	49	126	25	42	100.0%	0.00 [-10.12 , 10.12]
Total			**49**			**42**	**100.0%**	**0.00 [-10.12 , 10.12]**



Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable

Analysis 22.4. Comparison 22: Statins versus control (placebo, standard therapy or no treatment), Outcome 4: Systolic blood pressure [mm Hg]

Study or Subgroup	Statins Mean	Statins SD	Statins Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Fassett 2010	130.1	13.3	29	128.4	14.8	20	18.9%	1.70 [-6.39 , 9.79]
Cadnapaphornchai 2011	123	10	49	123	9	42	81.1%	0.00 [-3.90 , 3.90]
Total (Wald{fn})			**78**			**62**	**100.0%**	**0.32 [-3.20 , 3.84]**

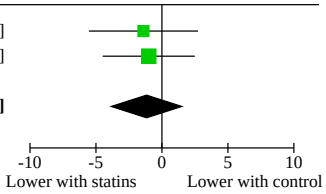


Test for overall effect: Z = 0.18 (P = 0.86)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 1 (P = 0.71); I² = 0%

Analysis 22.5. Comparison 22: Statins versus control (placebo, standard therapy or no treatment), Outcome 5: Diastolic blood pressure [mm Hg]

Study or Subgroup	Statins Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Fassett 2010	81.8	6.4	29	83.2	7.8	20	41.6%	-1.40 [-5.54 , 2.74]
Cadnapaphornchai 2011	74	9	49	75	8	42	58.4%	-1.00 [-4.49 , 2.49]
Total (Wald{fn})			**78**			**62**	**100.0%**	**-1.17 [-3.84 , 1.50]**

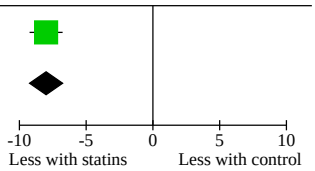
Test for overall effect: Z = 0.86 (P = 0.39)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%



Analysis 22.6. Comparison 22: Statins versus control (placebo, standard therapy or no treatment), Outcome 6: Change in height-adjusted total kidney volume

Study or Subgroup	Statins Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Cadnapaphornchai 2011	23	3	49	31	3	42	100.0%	-8.00 [-9.24 , -6.76]
Total			**49**			**42**	**100.0%**	**-8.00 [-9.24 , -6.76]**

Test for overall effect: Z = 12.68 (P < 0.00001)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 22.7. Comparison 22: Statins versus control (placebo, standard therapy or no treatment), Outcome 7: Proteinuria: descriptive data

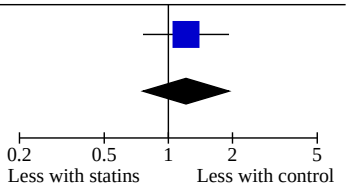
Proteinuria: descriptive data

Study	Description of outcome
Fassett 2010	Urinary protein excretion decreased by 2.8% in statins-treated patients and increased by 21.2% in controls

Analysis 22.8. Comparison 22: Statins versus control (placebo, standard therapy or no treatment), Outcome 8: Urinary albumin excretion: > 20% increase

Study or Subgroup	Statins Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Cadnapaphornchai 2011	24	49	17	42	100.0%	1.21 [0.76 , 1.93]
Total		**49**		**42**	**100.0%**	**1.21 [0.76 , 1.93]**
Total events:	24		17			

Test for overall effect: Z = 0.80 (P = 0.42)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable

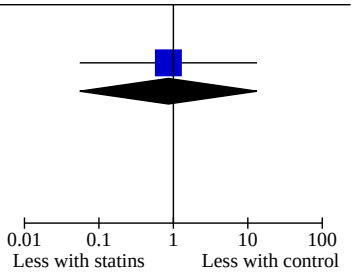


Analysis 22.9. Comparison 22: Statins versus control (placebo, standard therapy or no treatment), Outcome 9: Adverse events

Study or Subgroup	Statins Events	Statins Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
22.9.1 Elevated AST						
Cadnapaphornchai 2011	1	49	1	42	100.0%	0.86 [0.06 , 13.29]
Subtotal		**49**		**42**	**100.0%**	**0.86 [0.06 , 13.29]**
Total events:	1		1			

Test for overall effect: Z = 0.11 (P = 0.91)
Heterogeneity: Not applicable

Test for subgroup differences: Not applicable



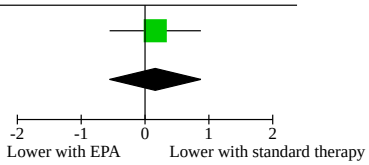
Comparison 23. Eicosapentaenoic acids (EPA) versus standard therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
23.1 Serum creatinine [mg/dL]	1	41	Mean Difference (IV, Random, 95% CI)	0.16 [-0.55, 0.87]
23.2 GFR [mL/min/1.73 m^2]	1	41	Mean Difference (IV, Random, 95% CI)	6.10 [-11.16, 23.36]
23.3 Total kidney volume [mL]	1	41	Mean Difference (IV, Random, 95% CI)	-209.00 [-729.06, 311.06]
23.4 Albuminuria [mg/day]	1	41	Mean Difference (IV, Random, 95% CI)	82.40 [-162.09, 326.89]

Analysis 23.1. Comparison 23: Eicosapentaenoic acids (EPA) versus standard therapy, Outcome 1: Serum creatinine [mg/dL]

Study or Subgroup	EPA Mean	EPA SD	EPA Total	Standard therapy Mean	Standard therapy SD	Standard therapy Total	Weight	Mean Difference IV, Random, 95% CI
Higashihara 2008	2.27	1.27	21	2.11	1.06	20	100.0%	0.16 [-0.55 , 0.87]
Total			**21**			**20**	**100.0%**	**0.16 [-0.55 , 0.87]**

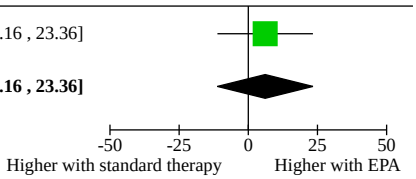
Test for overall effect: Z = 0.44 (P = 0.66)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 23.2. Comparison 23: Eicosapentaenoic acids (EPA) versus standard therapy, Outcome 2: GFR [mL/min/1.73 m²]

Study or Subgroup	EPA Mean	EPA SD	EPA Total	Standard therapy Mean	Standard therapy SD	Standard therapy Total	Weight	Mean Difference IV, Random, 95% CI
Higashihara 2008	54.7	32.9	21	48.6	22.8	20	100.0%	6.10 [-11.16 , 23.36]
Total			**21**			**20**	**100.0%**	**6.10 [-11.16 , 23.36]**

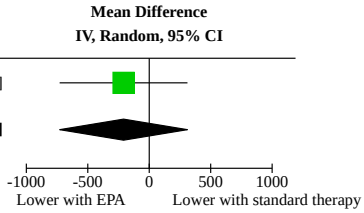
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 23.3. Comparison 23: Eicosapentaenoic acids (EPA) versus standard therapy, Outcome 3: Total kidney volume [mL]

Study or Subgroup	EPA Mean	EPA SD	EPA Total	Standard therapy Mean	Standard therapy SD	Standard therapy Total	Weight	Mean Difference IV, Random, 95% CI
Higashihara 2008	1708	868	21	1917	831	20	100.0%	-209.00 [-729.06 , 311.06]
Total			**21**			**20**	**100.0%**	**-209.00 [-729.06 , 311.06]**

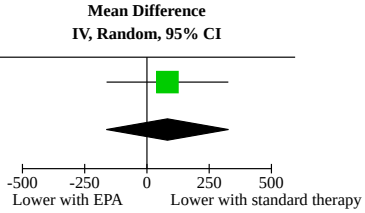
Test for overall effect: Z = 0.79 (P = 0.43)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 23.4. Comparison 23: Eicosapentaenoic acids (EPA) versus standard therapy, Outcome 4: Albuminuria [mg/day]

Study or Subgroup	EPA Mean	EPA SD	EPA Total	Standard therapy Mean	Standard therapy SD	Standard therapy Total	Weight	Mean Difference IV, Random, 95% CI
Higashihara 2008	275.9	459.4	21	193.5	332	20	100.0%	82.40 [-162.09 , 326.89]
Total			**21**			**20**	**100.0%**	**82.40 [-162.09 , 326.89]**

Test for overall effect: Z = 0.66 (P = 0.51)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Comparison 24. Prescribed versus ad libitum water intake

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
24.1 Serum creatinine: descriptive data	0		Other data	No numeric data
24.2 Doubling of serum creatinine	1	184	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.31, 5.79]
24.3 Change in eGFR	2	226	Mean Difference (IV, Random, 95% CI)	0.07 [-0.96, 1.10]
24.3.1 Duration ≤ 1 year	1	42	Mean Difference (IV, Random, 95% CI)	0.10 [-5.11, 5.31]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
24.3.2 Duration > 1 year	1	184	Mean Difference (IV, Random, 95% CI)	0.07 [-0.98, 1.12]
24.4 Annual rate of eGFR	1	184	Mean Difference (IV, Random, 95% CI)	0.07 [-0.98, 1.12]
24.5 Decrease in eGFR: > 25%	1	184	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.27, 2.08]
24.6 Kidney failure	1	184	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.14, 6.95]
24.7 ADPKD disease progression	1	184	Hazard Ratio (IV, Random, 95% CI)	0.91 [0.73, 1.13]
24.8 Pain	1	184	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.81, 1.19]
24.9 Systolic blood pressure [mm Hg]	1	184	Mean Difference (IV, Random, 95% CI)	-1.40 [-5.96, 3.16]
24.10 Diastolic blood pressure [mm Hg]	1	184	Mean Difference (IV, Random, 95% CI)	-1.65 [-4.68, 1.38]
24.11 Mean arterial pressure: descriptive data	0		Other data	No numeric data
24.12 Height-adjusted total kidney volume [mL]	1	184	Mean Difference (IV, Random, 95% CI)	-16.00 [-60.71, 28.71]
24.13 Annual rate of height-adjusted total kidney volume [%]	1	184	Mean Difference (IV, Random, 95% CI)	-1.00 [-2.51, 0.51]
24.14 UACR [mg/g]	1	184	Mean Difference (IV, Random, 95% CI)	-8.94 [-56.79, 38.91]
24.15 Urine volume [mL]	1	184	Mean Difference (IV, Random, 95% CI)	633.00 [369.00, 897.00]
24.16 Urine osmolality [mOsmol/Kg]	2	226	Mean Difference (IV, Random, 95% CI)	-129.23 [-220.20, -38.26]
24.17 Serious adverse events	1	184	Risk Ratio (M-H, Random, 95% CI)	1.61 [1.04, 2.48]
24.18 Adverse events	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
24.18.1 Urinary tract infection	2	226	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.55, 2.15]
24.18.2 Hyponatraemia	2	226	Risk Ratio (M-H, Random, 95% CI)	4.19 [1.08, 16.25]
24.18.3 Cyst rupture	1	184	Risk Ratio (M-H, Random, 95% CI)	2.50 [0.50, 12.56]
24.18.4 Cyst infection	2	226	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.11, 9.52]
24.18.5 Nephrolithiasis	1	184	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.07, 1.61]
24.18.6 Dysuria	1	184	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.30, 2.45]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
24.19 Adherence	1	184	Risk Ratio (M-H, Random, 95% CI)	3.00 [1.84, 4.88]

Analysis 24.1. Comparison 24: Prescribed versus ad libitum water intake, Outcome 1: Serum creatinine: descriptive data

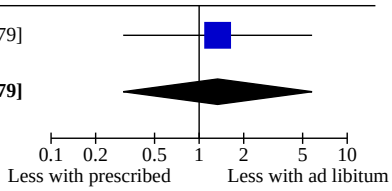
Serum creatinine: descriptive data

Study	Narrative Results
DRINK 2018	SCr (mmol/L) Week 0: AW group= 91 (62–115) versus HW group = 94 (66–149) Week 8: AW group= 97 (61–124) versus HW group = 85 (65–135) P=0.65

Analysis 24.2. Comparison 24: Prescribed versus ad libitum water intake, Outcome 2: Doubling of serum creatinine

Study or Subgroup	Prescribed Events	Prescribed Total	Ad libitum Events	Ad libitum Total	Weight	Risk Ratio M-H, Random, 95% CI
PREVENT-ADPKD 2018	4	92	3	92	100.0%	1.33 [0.31 , 5.79]
Total		**92**		**92**	**100.0%**	**1.33 [0.31 , 5.79]**
Total events:	4		3			

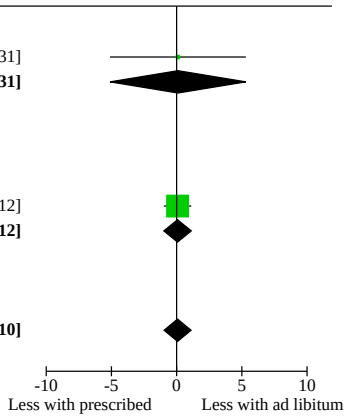
Test for overall effect: Z = 0.38 (P = 0.70)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 24.3. Comparison 24: Prescribed versus ad libitum water intake, Outcome 3: Change in eGFR

Study or Subgroup	Prescribed Mean	Prescribed SD	Prescribed Total	Ad libitum Mean	Ad libitum SD	Ad libitum Total	Weight	Mean Difference IV, Random, 95% CI
24.3.1 Duration ≤ 1 year								
DRINK 2018	0.7	7.68902	21	0.6	9.44651	21	3.9%	0.10 [-5.11 , 5.31]
Subtotal			**21**			**21**	**3.9%**	**0.10 [-5.11 , 5.31]**
Test for overall effect: Z = 0.04 (P = 0.97)								
Heterogeneity: Not applicable								
24.3.2 Duration > 1 year								
PREVENT-ADPKD 2018	-2.31	3.669829	92	-2.38	3.621541	92	96.1%	0.07 [-0.98 , 1.12]
Subtotal			**92**			**92**	**96.1%**	**0.07 [-0.98 , 1.12]**
Test for overall effect: Z = 0.13 (P = 0.90)								
Heterogeneity: Not applicable								
Total (Wald{fn})			**113**			**113**	**100.0%**	**0.07 [-0.96 , 1.10]**

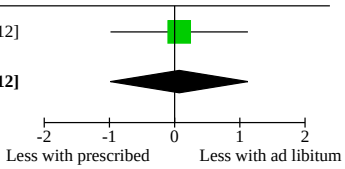
Test for overall effect: Z = 0.14 (P = 0.89)
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.99), I² = 0%
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0%



Analysis 24.4. Comparison 24: Prescribed versus ad libitum water intake, Outcome 4: Annual rate of eGFR

Study or Subgroup	Prescribed Mean	Prescribed SD	Prescribed Total	Ad libitum Mean	Ad libitum SD	Ad libitum Total	Weight	Mean Difference IV, Random, 95% CI
PREVENT-ADPKD 2018	-2.31	3.669829	92	-2.38	3.621541	92	100.0%	0.07 [-0.98 , 1.12]
Total			**92**			**92**	**100.0%**	**0.07 [-0.98 , 1.12]**

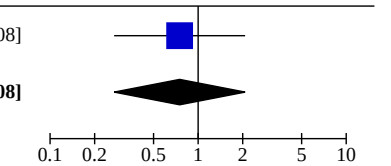
Test for overall effect: Z = 0.13 (P = 0.90)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 24.5. Comparison 24: Prescribed versus ad libitum water intake, Outcome 5: Decrease in eGFR: > 25%

Study or Subgroup	Prescribed Events	Prescribed Total	Ad libitum Events	Ad libitum Total	Weight	Risk Ratio M-H, Random, 95% CI
PREVENT-ADPKD 2018	6	92	8	92	100.0%	0.75 [0.27 , 2.08]
Total		**92**		**92**	**100.0%**	**0.75 [0.27 , 2.08]**
Total events:	6		8			

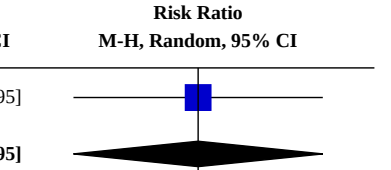
Test for overall effect: Z = 0.55 (P = 0.58)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 24.6. Comparison 24: Prescribed versus ad libitum water intake, Outcome 6: Kidney failure

Study or Subgroup	Prescribed Events	Prescribed Total	Ad libitum Events	Ad libitum Total	Weight	Risk Ratio M-H, Random, 95% CI
PREVENT-ADPKD 2018	2	92	2	92	100.0%	1.00 [0.14 , 6.95]
Total		**92**		**92**	**100.0%**	**1.00 [0.14 , 6.95]**
Total events:	2		2			

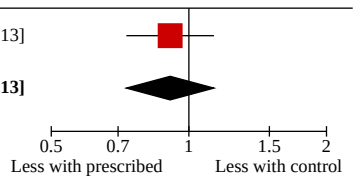
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 24.7. Comparison 24: Prescribed versus ad libitum water intake, Outcome 7: ADPKD disease progression

Study or Subgroup	log[Hazard Ratio]	SE	Prescribed Total	Ad libitum Total	Weight	Hazard Ratio IV, Random, 95% CI
PREVENT-ADPKD 2018	-0.0943	0.1125	92	92	100.0%	0.91 [0.73 , 1.13]
Total			**92**	**92**	**100.0%**	**0.91 [0.73 , 1.13]**

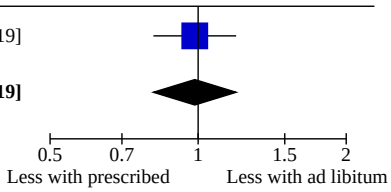
Test for overall effect: Z = 0.84 (P = 0.40)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 24.8. Comparison 24: Prescribed versus ad libitum water intake, Outcome 8: Pain

Study or Subgroup	Prescribed Events	Prescribed Total	Ad libitum Events	Ad libitum Total	Weight	Risk Ratio M-H, Random, 95% CI
PREVENT-ADPKD 2018	63	92	64	92	100.0%	0.98 [0.81 , 1.19]
Total		**92**		**92**	**100.0%**	**0.98 [0.81 , 1.19]**
Total events:	63		64			

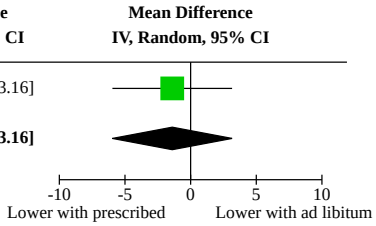
Test for overall effect: Z = 0.16 (P = 0.87)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 24.9. Comparison 24: Prescribed versus ad libitum water intake, Outcome 9: Systolic blood pressure [mm Hg]

Study or Subgroup	Prescribed Mean	Prescribed SD	Prescribed Total	Ad libitum Mean	Ad libitum SD	Ad libitum Total	Weight	Mean Difference IV, Random, 95% CI
PREVENT-ADPKD 2018	131.5	16.3	92	132.9	15.22	92	100.0%	-1.40 [-5.96 , 3.16]
Total			**92**			**92**	**100.0%**	**-1.40 [-5.96 , 3.16]**

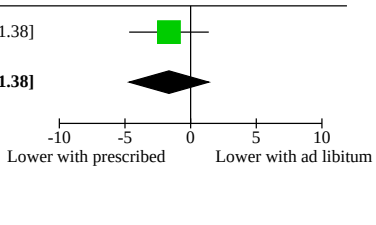
Test for overall effect: Z = 0.60 (P = 0.55)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 24.10. Comparison 24: Prescribed versus ad libitum water intake, Outcome 10: Diastolic blood pressure [mm Hg]

Study or Subgroup	Prescribed Mean	Prescribed SD	Prescribed Total	Ad libitum Mean	Ad libitum SD	Ad libitum Total	Weight	Mean Difference IV, Random, 95% CI
PREVENT-ADPKD 2018	82.84	10.5	92	84.49	10.48	92	100.0%	-1.65 [-4.68 , 1.38]
Total			**92**			**92**	**100.0%**	**-1.65 [-4.68 , 1.38]**

Test for overall effect: Z = 1.07 (P = 0.29)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 24.11. Comparison 24: Prescribed versus ad libitum water intake, Outcome 11: Mean arterial pressure: descriptive data

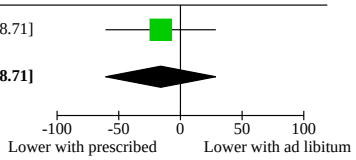
Mean arterial pressure: descriptive data

Study	Narrative Results
DRINK 2018	MAP, median (IQR) (mm Hg) Week 0: control= 95 (91–104) treatmet =102 (92–107) Week 8: control = 94 (88–102) treatment = 95 (90–111) P=0.33

Analysis 24.12. Comparison 24: Prescribed versus ad libitum water intake, Outcome 12: Height-adjusted total kidney volume [mL]

Study or Subgroup	Prescribed Mean	Prescribed SD	Prescribed Total	Ad libitum Mean	Ad libitum SD	Ad libitum Total	Weight	Mean Difference IV, Random, 95% CI
PREVENT-ADPKD 2018	39	139.550066	92	55	168.522397	92	100.0%	-16.00 [-60.71 , 28.71]
Total			**92**			**92**	**100.0%**	**-16.00 [-60.71 , 28.71]**

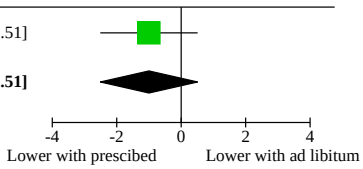
Test for overall effect: Z = 0.70 (P = 0.48)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 24.13. Comparison 24: Prescribed versus ad libitum water intake, Outcome 13: Annual rate of height-adjusted total kidney volume [%]

Study or Subgroup	Prescribed Mean	Prescribed SD	Prescribed Total	Ad libitum Mean	Ad libitum SD	Ad libitum Total	Weight	Mean Difference IV, Random, 95% CI
PREVENT-ADPKD 2018	6.8	4.587286	92	7.8	5.794466	92	100.0%	-1.00 [-2.51 , 0.51]
Total			**92**			**92**	**100.0%**	**-1.00 [-2.51 , 0.51]**

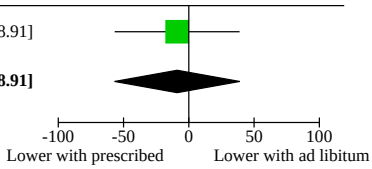
Test for overall effect: Z = 1.30 (P = 0.19)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 24.14. Comparison 24: Prescribed versus ad libitum water intake, Outcome 14: UACR [mg/g]

Study or Subgroup	Prescribed Mean	Prescribed SD	Prescribed Total	Ad libitum Mean	Ad libitum SD	Ad libitum Total	Weight	Mean Difference IV, Random, 95% CI
PREVENT-ADPKD 2018	82.21	173.72	92	91.15	156.99	92	100.0%	-8.94 [-56.79 , 38.91]
Total			**92**			**92**	**100.0%**	**-8.94 [-56.79 , 38.91]**

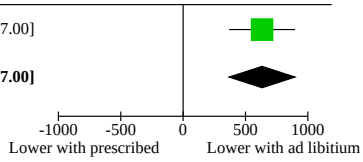
Test for overall effect: Z = 0.37 (P = 0.71)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 24.15. Comparison 24: Prescribed versus ad libitum water intake, Outcome 15: Urine volume [mL]

Study or Subgroup	Prescribed Mean	Prescribed SD	Prescribed Total	Ad libitum Mean	Ad libitum SD	Ad libitum Total	Weight	Mean Difference IV, Random, 95% CI
PREVENT-ADPKD 2018	2997	913.5551	92	2364	913.5551	92	100.0%	633.00 [369.00 , 897.00]
Total			**92**			**92**	**100.0%**	**633.00 [369.00 , 897.00]**

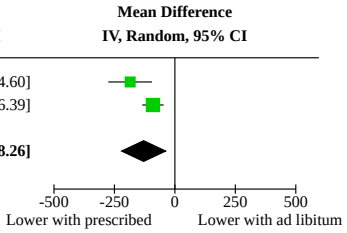
Test for overall effect: Z = 4.70 (P < 0.00001)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 24.16. Comparison 24: Prescribed versus ad libitum water intake, Outcome 16: Urine osmolality [mOsmol/Kg]

Study or Subgroup	Prescribed Mean	Prescribed SD	Prescribed Total	Ad libitum Mean	Ad libitum SD	Ad libitum Total	Weight	Mean Difference IV, Random, 95% CI
DRINK 2018	194	72.6	21	379	198.5	21	40.9%	-185.00 [-275.40 , -94.60]
PREVENT-ADPKD 2018	328	153.466609	92	418.6	152.507442	92	59.1%	-90.60 [-134.81 , -46.39]
Total (Wald{fn})			**113**			**113**	**100.0%**	**-129.23 [-220.20 , -38.26]**

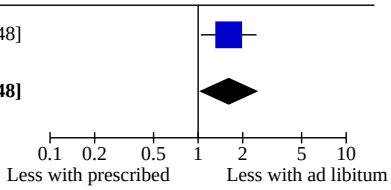
Test for overall effect: Z = 2.78 (P = 0.005)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 3137.63; Chi² = 3.38, df = 1 (P = 0.07); I² = 70%



Analysis 24.17. Comparison 24: Prescribed versus ad libitum water intake, Outcome 17: Serious adverse events

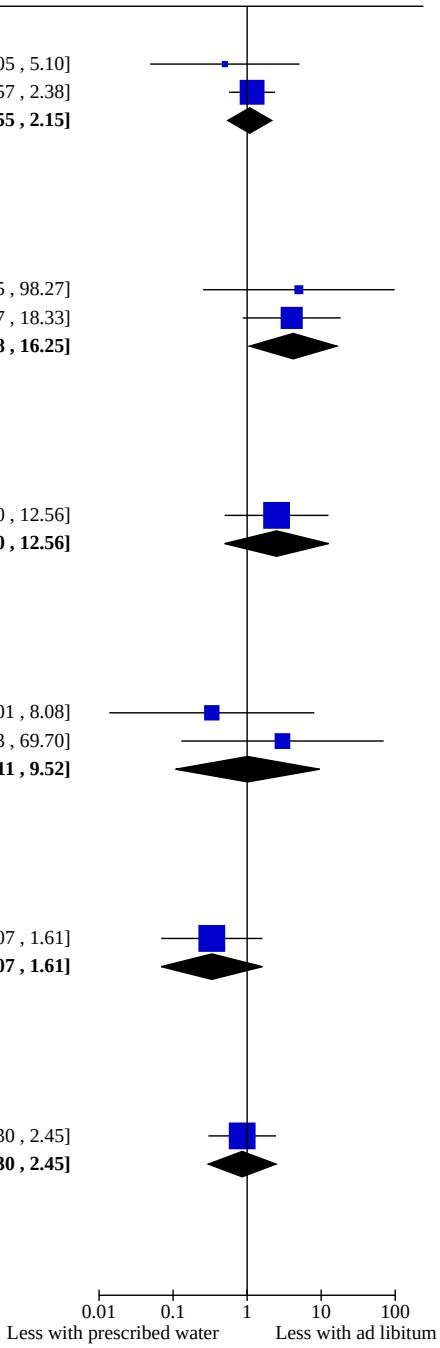
Study or Subgroup	Prescribed Events	Prescribed Total	Ad libitum Events	Ad libitum Total	Weight	Risk Ratio M-H, Random, 95% CI
PREVENT-ADPKD 2018	37	92	23	92	100.0%	1.61 [1.04 , 2.48]
Total		**92**		**92**	**100.0%**	**1.61 [1.04 , 2.48]**
Total events:	37		23			

Test for overall effect: Z = 2.15 (P = 0.03)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 24.18. Comparison 24: Prescribed versus ad libitum water intake, Outcome 18: Adverse events

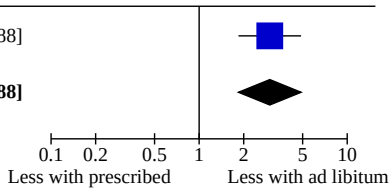
Study or Subgroup	Prescribed Events	Prescribed Total	Ad libitum Events	Ad libitum Total	Weight	Risk Ratio M-H, Random, 95% CI
24.18.1 Urinary tract infection						
DRINK 2018	1	21	2	21	8.7%	0.50 [0.05 , 5.10]
PREVENT-ADPKD 2018	14	92	12	92	91.3%	1.17 [0.57 , 2.38]
Subtotal (Wald{fn})		**113**		**113**	**100.0%**	**1.08 [0.55 , 2.15]**
Total events:	15		14			
Test for overall effect: Z = 0.23 (P = 0.82)						
Heterogeneity: Tau² = 0.00; Chi² = 0.47, df = 1 (P = 0.49); I² = 0%						
24.18.2 Hyponatraemia						
DRINK 2018	2	21	0	21	20.7%	5.00 [0.25 , 98.27]
PREVENT-ADPKD 2018	8	92	2	92	79.3%	4.00 [0.87 , 18.33]
Subtotal (Wald{fn})		**113**		**113**	**100.0%**	**4.19 [1.08 , 16.25]**
Total events:	10		2			
Test for overall effect: Z = 2.07 (P = 0.04)						
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.90); I² = 0%						
24.18.3 Cyst rupture						
PREVENT-ADPKD 2018	5	92	2	92	100.0%	2.50 [0.50 , 12.56]
Subtotal		**92**		**92**	**100.0%**	**2.50 [0.50 , 12.56]**
Total events:	5		2			
Test for overall effect: Z = 1.11 (P = 0.27)						
Heterogeneity: Not applicable						
24.18.4 Cyst infection						
PREVENT-ADPKD 2018	0	92	1	92	49.3%	0.33 [0.01 , 8.08]
DRINK 2018	1	21	0	21	50.7%	3.00 [0.13 , 69.70]
Subtotal (Wald{fn})		**113**		**113**	**100.0%**	**1.01 [0.11 , 9.52]**
Total events:	1		1			
Test for overall effect: Z = 0.01 (P = 0.99)						
Heterogeneity: Tau² = 0.00; Chi² = 0.92, df = 1 (P = 0.34); I² = 0%						
24.18.5 Nephrolithiasis						
PREVENT-ADPKD 2018	2	92	6	92	100.0%	0.33 [0.07 , 1.61]
Subtotal		**92**		**92**	**100.0%**	**0.33 [0.07 , 1.61]**
Total events:	2		6			
Test for overall effect: Z = 1.37 (P = 0.17)						
Heterogeneity: Not applicable						
24.18.6 Dysuria						
PREVENT-ADPKD 2018	6	92	7	92	100.0%	0.86 [0.30 , 2.45]
Subtotal		**92**		**92**	**100.0%**	**0.86 [0.30 , 2.45]**
Total events:	6		7			
Test for overall effect: Z = 0.29 (P = 0.77)						
Heterogeneity: Not applicable						
Test for subgroup differences: Chi² = 7.10, df = 5 (P = 0.21), I² = 29.5%						



Analysis 24.19. Comparison 24: Prescribed versus ad libitum water intake, Outcome 19: Adherence

Study or Subgroup	Prescribed Events	Prescribed Total	Ad libitum Events	Ad libitum Total	Weight	Risk Ratio M-H, Random, 95% CI
PREVENT-ADPKD 2018	48	92	16	92	100.0%	3.00 [1.84 , 4.88]
Total		**92**		**92**	**100.0%**	**3.00 [1.84 , 4.88]**
Total events:	48		16			

Test for overall effect: Z = 4.43 (P < 0.00001)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



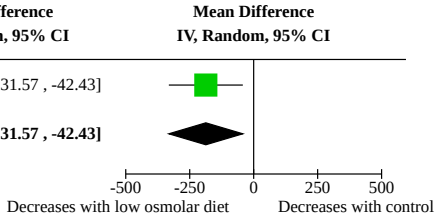
Comparison 25. Low osmolar diet versus control (no intervention)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
25.1 Change in urine osmolality [mOsm/kg]	1	34	Mean Difference (IV, Random, 95% CI)	-187.00 [-331.57, -42.43]

Analysis 25.1. Comparison 25: Low osmolar diet versus control (no intervention), Outcome 1: Change in urine osmolality [mOsm/kg]

Study or Subgroup	Low osmolar diet Mean	Low osmolar diet SD	Low osmolar diet Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Amro 2016	-167	264	17	20	151	17	100.0%	-187.00 [-331.57 , -42.43]
Total			**17**			**17**	**100.0%**	**-187.00 [-331.57 , -42.43]**

Test for overall effect: Z = 2.54 (P = 0.01)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Comparison 26. Curcumin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
26.1 eGFR: descriptive data	0		Other data	No numeric data
26.2 Total kidney volume [mL]	1	57	Mean Difference (IV, Random, 95% CI)	66.00 [-141.35, 273.35]
26.3 Adverse events	1	68	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.39, 2.03]

Analysis 26.1. Comparison 26: Curcumin versus placebo, Outcome 1: eGFR: descriptive data

eGFR: descriptive data

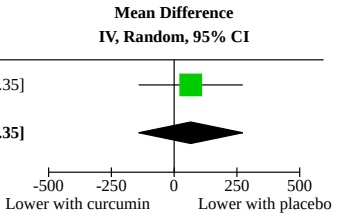
Study	Narrative Results
Nowak 2020	There was no difference in change in eGFR at 12 months

Baseline Treatment: 109±16
Final Treatment: 109±18
Baseline Control: 115±18
Final Control: 111±17

Analysis 26.2. Comparison 26: Curcumin versus placebo, Outcome 2: Total kidney volume [mL]

Study or Subgroup	Curcumin Mean	Curcumin SD	Curcumin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Nowak 2020	397	352.022305	28	331	442.978474	29	100.0%	66.00 [-141.35 , 273.35]
Total			**28**			**29**	**100.0%**	**66.00 [-141.35 , 273.35]**

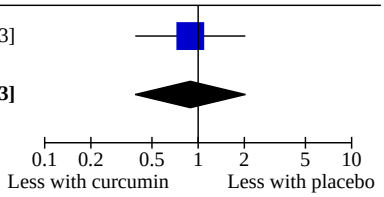
Test for overall effect: Z = 0.62 (P = 0.53)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 26.3. Comparison 26: Curcumin versus placebo, Outcome 3: Adverse events

Study or Subgroup	Curcumin Events	Curcumin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Nowak 2020	8	34	9	34	100.0%	0.89 [0.39 , 2.03]
Total		**34**		**34**	**100.0%**	**0.89 [0.39 , 2.03]**
Total events:	8		9			

Test for overall effect: Z = 0.28 (P = 0.78)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



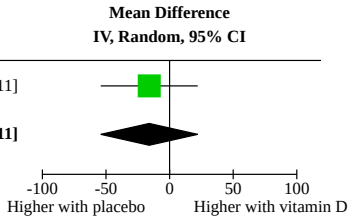
Comparison 27. Vitamin D versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
27.1 eGFR [mL/min/1.73 m^2]	1	42	Mean Difference (IV, Random, 95% CI)	-16.00 [-54.11, 22.11]
27.2 Systolic blood pressure [mm Hg]	1	42	Mean Difference (IV, Random, 95% CI)	5.00 [-2.96, 12.96]
27.3 Diastolic blood pressure [mm Hg]	1	42	Mean Difference (IV, Random, 95% CI)	1.00 [-4.48, 6.48]

Analysis 27.1. Comparison 27: Vitamin D versus placebo, Outcome 1: eGFR [mL/min/1.73 m^2]

Study or Subgroup	Vitamin D Mean	Vitamin D SD	Vitamin D Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Vendramini 2021	58	76.890201	21	74	45.035689	21	100.0%	-16.00 [-54.11 , 22.11]
Total			**21**			**21**	**100.0%**	**-16.00 [-54.11 , 22.11]**

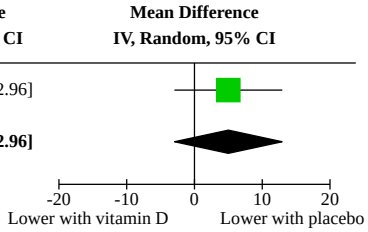
Test for overall effect: Z = 0.82 (P = 0.41)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 27.2. Comparison 27: Vitamin D versus placebo, Outcome 2: Systolic blood pressure [mm Hg]

Study or Subgroup	Vitamin D Mean	Vitamin D SD	Vitamin D Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Vendramini 2021	126	11	21	121	15	21	100.0%	5.00 [-2.96 , 12.96]
Total			**21**			**21**	**100.0%**	**5.00 [-2.96 , 12.96]**

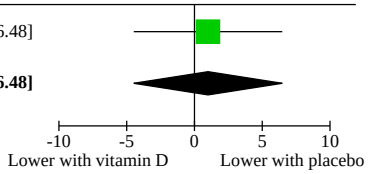
Test for overall effect: Z = 1.23 (P = 0.22)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 27.3. Comparison 27: Vitamin D versus placebo, Outcome 3: Diastolic blood pressure [mm Hg]

Study or Subgroup	Vitamin D Mean	Vitamin D SD	Vitamin D Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Vendramini 2021	81	8	21	80	10	21	100.0%	1.00 [-4.48 , 6.48]
Total			**21**			**21**	**100.0%**	**1.00 [-4.48 , 6.48]**

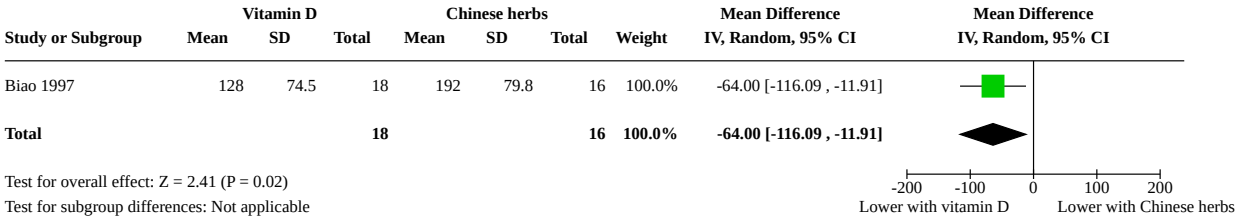
Test for overall effect: Z = 0.36 (P = 0.72)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Comparison 28. Vitamin D versus traditional Chinese herbal medicine

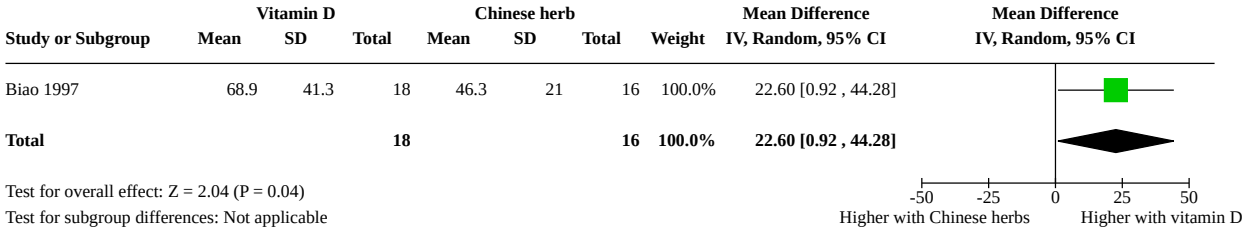
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
28.1 Serum creatinine [µmol/L]	1	34	Mean Difference (IV, Random, 95% CI)	-64.00 [-116.09, -11.91]
28.2 GFR [mL/min]	1	34	Mean Difference (IV, Random, 95% CI)	22.60 [0.92, 44.28]

Analysis 28.1. Comparison 28: Vitamin D versus traditional Chinese herbal medicine, Outcome 1: Serum creatinine [µmol/L]



Test for overall effect: Z = 2.41 (P = 0.02)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable

Analysis 28.2. Comparison 28: Vitamin D versus traditional Chinese herbal medicine, Outcome 2: GFR [mL/min]



Test for overall effect: Z = 2.04 (P = 0.04)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable

Comparison 29. Niacinamide versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
29.1 eGFR: descriptive data	0		Other data	No numeric data
29.2 Frequency scale of back or abdominal pain	1	36	Mean Difference (IV, Random, 95% CI)	-0.20 [-1.38, 0.98]
29.3 Quality of life score	1	36	Mean Difference (IV, Random, 95% CI)	-3.20 [-9.35, 2.95]
29.4 Total kidney volume change [%]	1	36	Mean Difference (IV, Random, 95% CI)	-1.50 [-6.05, 3.05]
29.5 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
29.5.1 Diarrhea	1	36	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.42, 9.58]
29.5.2 Nausea	1	36	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.26, 2.50]
29.5.3 Headache	1	36	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.23, 4.31]

Analysis 29.1. Comparison 29: Niacinamide versus placebo, Outcome 1: eGFR: descriptive data

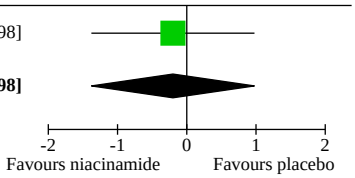
eGFR: descriptive data

Study	Narrative Results
El Ters 2020	Placebo: eGFR annual change 0.032 Niacinamide: eGFR annual change -1.589

P=0.55

Analysis 29.2. Comparison 29: Niacinamide versus placebo, Outcome 2: Frequency scale of back or abdominal pain

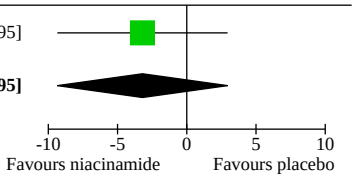
Study or Subgroup	Niacinamide Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
El Ters 2020	2.2	1.7	18	2.4	1.9	18	100.0%	-0.20 [-1.38 , 0.98]
Total			**18**			**18**	**100.0%**	**-0.20 [-1.38 , 0.98]**



Test for overall effect: Z = 0.33 (P = 0.74)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable

Analysis 29.3. Comparison 29: Niacinamide versus placebo, Outcome 3: Quality of life score

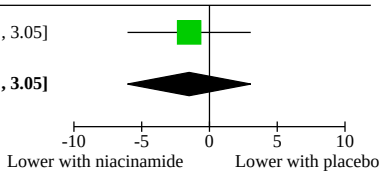
Study or Subgroup	Niacinamide Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
El Ters 2020	21.4	9	18	24.6	9.8	18	100.0%	-3.20 [-9.35 , 2.95]
Total			**18**			**18**	**100.0%**	**-3.20 [-9.35 , 2.95]**



Test for overall effect: Z = 1.02 (P = 0.31)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable

Analysis 29.4. Comparison 29: Niacinamide versus placebo, Outcome 4: Total kidney volume change [%]

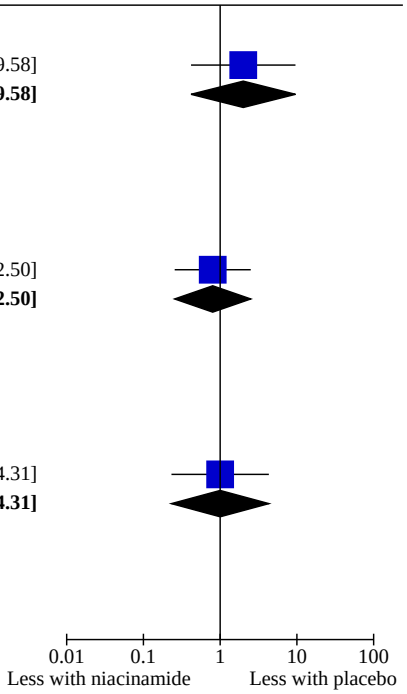
Study or Subgroup	Niacinamide Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
El Ters 2020	3	7.8	18	4.5	6	18	100.0%	-1.50 [-6.05 , 3.05]
Total			**18**			**18**	**100.0%**	**-1.50 [-6.05 , 3.05]**



Test for overall effect: Z = 0.65 (P = 0.52)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable

Analysis 29.5. Comparison 29: Niacinamide versus placebo, Outcome 5: Adverse events

Study or Subgroup	Niacinamide Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
29.5.1 Diarrhea						
El Ters 2020	4	18	2	18	100.0%	2.00 [0.42 , 9.58]
Subtotal		**18**		**18**	**100.0%**	**2.00 [0.42 , 9.58]**
Total events:	4		2			
Test for overall effect: Z = 0.87 (P = 0.39)						
Heterogeneity: Not applicable						
29.5.2 Nausea						
El Ters 2020	4	18	5	18	100.0%	0.80 [0.26 , 2.50]
Subtotal		**18**		**18**	**100.0%**	**0.80 [0.26 , 2.50]**
Total events:	4		5			
Test for overall effect: Z = 0.38 (P = 0.70)						
Heterogeneity: Not applicable						
29.5.3 Headache						
El Ters 2020	3	18	3	18	100.0%	1.00 [0.23 , 4.31]
Subtotal		**18**		**18**	**100.0%**	**1.00 [0.23 , 4.31]**
Total events:	3		3			
Test for overall effect: Z = 0.00 (P = 1.00)						
Heterogeneity: Not applicable						
Test for subgroup differences: $Chi^2 = 0.87$, df = 2 (P = 0.65), $I^2 = 0\%$						



APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. (polycystic next kidney next disease*):ti,ab,kw 2. (kidney next polycystic next disease*):ti,ab,kw 3. ADPKD:ti,ab,kw 4. PKD:ti,ab,kw 5. (#1 OR #2 OR #3 OR #4)
MEDLINE	1. Polycystic Kidney Diseases/ 2. Polycystic Kidney, Autosomal Dominant/ 3. polycystic kidney disease*.tw. 4. ADPKD.tw. 5. PKD.tw. 6. or/1-5
EMBASE	1. Kidney Polycystic Disease/ 2. polycystic kidney disease*.tw. 3. ADPKD.tw. 4. PKD.tw. 5. or/1-4

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.
	Unclear: Insufficient information about the sequence generation process to permit judgement.
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear: Randomisation stated but no information on method used is available.
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.

(Continued)

	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

FEEDBACK

Ongoing studies now complete,

Summary

For the review, 'Interventions for preventing the progression of autosomal dominant polycystic kidney disease' I was just extracting the research recommendations at the end of the review so they can be promoted for research funding. Part of extracting the research uncertainties or recommendations is to list any on-going studies which might address the uncertainty, so that research funders know to wait for any on-going research to complete. Going form this review, it lists several ongoing studies which are completed. Shouldn't these now be listed in the awaiting assessment section of the review

Reply

Thank you for your feedback. The ongoing studies have now been moved to "Studies awaiting classification" and the authors will assess these studies in a future update of this review.

Contributors

Mark Fenton - Database of Uncertainties about the Effects of Treatments (DUETs); National Institute for Health and Clinical Excellence

Narelle Willis - Managing Editor, Cochrane Kidney and Transplant

WHAT'S NEW

Date	Event	Description
2 October 2024	New search has been performed	New studies added
2 October 2024	New citation required and conclusions have changed	New interventions added

HISTORY

Protocol first published: Issue 1, 2013
Review first published: Issue 7, 2015

Date	Event	Description
3 September 2015	Feedback has been incorporated	Ongoing studies now completed
3 September 2015	Amended	Two ongoing studies moved to studies awaiting assessment; one ongoing study move to excluded studies
31 August 2015	Amended	Correction of search dates

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: DB, JC, GS
2. Study selection: DB, MR, KSP, DT, BC
3. Extract data from studies: DB, MR, KSP, DT, BC
4. Enter data into RevMan: DB, MR, KSP, DT, BC
5. Carry out the analysis: DB, MR, SG, GS, KSP, DT, BC
6. Interpret the analysis: DB, SG, GS, KSP, DT, BC
7. Draft the final review: DB, CZ, JC, SG, GS, KSP, DT, BC, AM
8. Disagreement resolution: SG, BC
9. Update the review: KSP, DT, BC, AM, SG

DECLARATIONS OF INTEREST

- Kitty St Pierre: no relevant interests were disclosed
- Brydee A Cashmore: no relevant interests were disclosed
- Davide Bolignano: no relevant interests were disclosed
- Carmine Zoccali: no relevant interests were disclosed
- Marinella Ruospo: no relevant interests were disclosed
- Jonathan C Craig: no relevant interests were disclosed
- Giovanni FM Strippoli: no relevant interests were disclosed
- Andrew J Mallett: no relevant interests were disclosed
- Suetonia C Green: no relevant interests were disclosed
- David J Tunnicliffe: no relevant interests were disclosed

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- No sources of support provided

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

No differences

INDEX TERMS

Medical Subject Headings (MeSH)

Antidiuretic Hormone Receptor Antagonists [therapeutic use]; *Disease Progression; Glomerular Filtration Rate; *Polycystic Kidney, Autosomal Dominant [drug therapy] [mortality]; Randomized Controlled Trials as Topic; Tolvaptan [therapeutic use]

MeSH check words

Humans