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

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TABLE OF CONTENTS

[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 most common inherited disorder causing kidney disease. Current clinical management of ADPKD focuses primarily on symptom control and reducing associated complications, particularly hypertension. In recent years, improved understanding of molecular and cellular mechanisms involved in kidney cyst growth and disease progression has resulted in new pharmaceutical agents to target disease pathogenesis to prevent progressive disease.

Objectives

We aimed to evaluate the effects of interventions for preventing ADPKD progression on kidney function, kidney endpoints, kidney structure, patient-centred endpoints (such as cardiovascular events, sudden death, all-cause mortality, hospitalisations, BP control, quality of life, and kidney pain), as well as the general and specific adverse effects related to their use.

Search methods

We searched the Cochrane Renal Group's Specialised Register to 6 June 2015 using relevant search terms.

Selection criteria

Randomised controlled trials (RCTs) comparing any interventions for preventing the progression of ADPKD with other interventions or placebo were considered for inclusion without language restriction.

Data collection and analysis

Two authors independently assessed study risks of bias and extracted data. We summarised treatment effects on clinical outcomes, kidney function and structure and adverse events using random effects meta-analysis. We assessed heterogeneity in estimated treatment effects using the Cochran Q test and I^2 statistic. Summary treatment estimates were calculated as a mean difference (MD) or standardised mean difference (SMD) for continuous outcomes and a risk ratio (RR) for dichotomous outcomes together with their 95% confidence intervals.

Main results

We included 30 studies (2039 participants) that investigated 11 pharmacological interventions (angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), calcium channel blockers, beta blockers, vasopressin receptor 2 (V2R) antagonists, mammalian target of rapamycin (mTOR) inhibitors, somatostatin analogues, antiplatelet agents, eicosapentaenoic acids, statins and vitamin D compounds) in this review.

ACEi significantly reduced diastolic blood pressure (9 studies, 278 participants: MD -4.96 mm Hg, 95% CI -8.88 to -1.04), but had uncertain effects on kidney volumes (MD -42.50 mL, 95% CI -115.68 to 30.67), GFR (MD -3.41 mL/min/1.73 m^2, 95% CI -15.83 to 9.01), and SCr (MD -0.02 mg/dL, 95% CI -0.14 to 0.09), in data largely restricted to children. ACEi did not show different effects on GFR (MD -8.19 mL/min/1.73 m^2, 95% CI -29.46 to 13.07) and albuminuria (SMD -0.19, 95% CI -1.77 to 1.39) when compared with beta-blockers, or SCr (MD 0.00 mg/dL, 95% CI -0.09 to 0.10) when compared with ARBs.

Data for effects of V2R antagonists on kidney function and volumes compared to placebo were limited to narrative information within a single study while these agents increased thirst (1444 participants: RR 2.70, 95% CI 2.24 to 3.24) and dry mouth (1455 participants: RR 1.33, 95% CI 1.01 to 1.76).

Compared with no treatment, mTOR inhibitors had uncertain effects on kidney function (2 studies, 115 participants: MD 4.45 mL/min/1.73 m^2, 95% CI -3.20 to 12.11) and kidney volume (MD -0.08 L, 95% CI -0.75 to 0.59) but in three studies (560 participants) caused angioedema (RR 13.39, 95% CI 2.56 to 70.00), oral ulceration (RR 6.77, 95% CI 4.42 to 10.38), infections (RR 1.14, 95% CI 1.04 to 1.25) and diarrhoea (RR 1.70, 95% CI 1.26 to 2.29).

Somatostatin analogues (6 studies, 138 participants) slightly improved SCr (MD -0.43 mg/dL, 95% CI -0.86 to -0.01) and total kidney volume (MD -0.62 L, 95% CI -1.22 to -0.01) but had no definite effects on GFR (MD 9.50 mL/min, 95% CI -4.45 to 23.44) and caused diarrhoea (RR 3.72, 95% CI 1.43 to 9.68).

Data for calcium channel blockers, eicosapentaenoic acids, statins, vitamin D compounds and antiplatelet agents were sparse and inconclusive.

Random sequence generation was adequate in eight studies, and in almost half of the studies, blinding was not present or not specified. Most studies did not adequately report outcomes, which adversely affected our ability to assess this bias. The overall drop-out rate was over 10% in nine studies, and few were conducted using intention-to-treat analyses.

Authors' conclusions

Although several interventions are available for patients with ADPKD, at present there is little or no evidence that treatment improves patient outcomes in this population and is associated with frequent adverse effects. Additional large randomised studies focused on patient-centred outcomes are needed.

PLAIN LANGUAGE SUMMARY

Which therapies are the most effective to prevent the progression of autosomal dominant polycystic kidney disease?

Current clinical care for people who have autosomal dominant polycystic kidney disease (ADPKD) focuses on controlling future risks for need for dialysis and symptom management, mainly pain and bleeding. Newly discovered molecules that may slow kidney cyst growth has recently switched attention from care and treatment toward preventing disease progression and symptom control.

In this review, we aimed to analyse the benefits and harms of interventions directed at preventing progression of ADPKD. The literature was searched to 6 June 2015. We found 30 studies (involving 2039 participants) that tested 11 different treatments.

Reported outcomes were mostly limited to kidney function and volume. In evidence largely limited to children, it was found that ACEi (angiotensin converting enzyme inhibitor) medicines significantly reduced diastolic blood pressure but had uncertain effects on kidney volumes and how well the kidneys work (tested by measuring the glomerular filtration rate (GFR) and serum creatinine level in patients' blood). In adults, ACEi did not show different effects on GFR and the amount of a protein called albumin in the urine (albuminuria) when compared with beta blockers, or serum creatinine when compared with drugs known as ARBs (angiotensin II receptor blockers). Evidence from a single study was inconclusive concerning the effects of vasopressin receptor 2 antagonists on kidney function and volumes; however, these drugs made patients thirsty and caused dry mouth. Compared with no treatment, the group of medicines known as mTOR inhibitors (mammalian target of rapamycin inhibitors) had uncertain effects on kidney function and volume but caused soft tissue swelling, mouth ulcers, infections and diarrhoea. Drugs known as somatostatin analogues slightly improved serum creatinine and total kidney volume but had no definite effects on GFR and caused diarrhoea. Data for other drugs were sparse and inconclusive.

There is currently insufficient evidence to show that drugs used for people with ADPKD can protect kidney function to delay needing dialysis or a kidney transplant. Further evidence from large, well-designed clinical studies is needed to inform healthcare decision making before these drugs can be chosen routinely to achieve better health outcomes for people with ADPKD.

BACKGROUND

Description of the condition

ADPKD is the most common inherited disorder that affects kidney function and is a major cause of end-stage kidney disease (ESKD). ADPKD is characterised by uncontrolled growth of kidney cysts that alter normal kidney structure and progressively impair kidney function. This means that people with ADPKD often require dialysis or kidney transplantation. Globally, over 12 million people currently live with ADPKD, of whom about 700,000 live in the US (Harris 2009). Annual incidence rates range from 4.0 to 8.7 per million people globally (Torres 2007). Recent data suggest that ADPKD accounts for about 5% of new patients commencing RRT in the US (USRDS 2008) and 3% to 10% in Europe (ERA-EDTA 2011). By 60 years of age, about half of all people with ADPKD develop ESKD (Torres 2009).

ADPKD is a heterogeneous genetic disorder: it can evolve from 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 and are usually associated with a more severe phenotype characterised by an earlier appearance, greater numbers of cysts and faster progression to ESKD. Increases in cyst numbers and size over time lead to hypertension, bleeding, infections, discomfort and pain. Cyst expansion is a major factor for the progressive loss of functional kidney tissue and function, which results from both direct (parenchymal compression) or indirect (fibrosis) mechanisms.

Description of the intervention

Healthcare for people with ADPKD principally focuses on controlling secondary conditions, particularly hypertension, to limit morbidity and mortality after the disease becomes symptomatic. Specific interventions targeting the pathogenesis of ADPKD have yet to be validated in clinical practice. Recent developments arising from better mechanistic understanding of the molecular pathways involved in cyst growth have made targeting disease pathogenesis, rather than disease complications, possible. However, although many interventions have shown promise in experimental models, few have been tested in clinical studies, and available interventions data have not been summarised previously.

How the intervention might work

Cyst growth can be targeted at different levels. Cyclic adenosine monophosphate (cAMP) plays a central role in cystogenesis (Hanaoka 2000). A hormone, arginine-vasopressin (AVP), is the main inductor of cAMP production, working to activate an enzyme, adenylate-cyclase, via vasopressin receptor-2 (VR2) binding. Administration of V2R antagonists has been shown to reduce cyst and kidney volume and prevent kidney function impairment in polycystic kidney disease/vasopressin (PKD/AVP) knock-out rats (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. Experimental findings confirm that chronic high fluid intake is effective in limiting cyst growth (Nagao 2006).

cAMP accumulation can be prevented by stimulating the somatostatin receptors (SRs) 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 mTOR kinase, is another potential target. This was initially investigated following a retrospective analysis that showed both liver and kidney volume decreased among people with ADPKD who received rapamycin therapy following kidney transplantation (Qian 2008) and confirmed by experimental models (Wahl 2006; Wu 2007) where the administration of mTOR inhibitors limited cyst enlargement and slowed progression of chronic kidney disease (CKD).

Other interventions, including dietary supplements of long-chain omega 3 polyunsaturated (eicosapentaenoic) fatty acids (Ogborn 2000), and administration of statins (Gile 1995), have demonstrated efficacy to slow kidney impairment and contract cyst growth in different experimental models of PKD, probably as a result of a specific kidney anti-inflammatory effect. However, it remains unclear whether other interventions broadly used to slow CKD, such as ACEis and ARBs, produce similar beneficial effects on kidney function in people with ADPKD (Schrier 2009). An ongoing clinical study, HALT-PKD (Torres 2012), has been designed to clarify whether the combination of ACEi and ARBs could be more effective than ACEi alone to slow the decline of GFR in people with ADPKD who have stage 3 CKD and prevent CKD onset in earlier stages.

Why it is important to do this review

Kidney cyst growth usually precedes 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 kidney disease and improve patient outcomes. However, no systematic assessments of the existing efficacy and safety evidence are yet available to inform practice or policy.

OBJECTIVES

Our objectives were to evaluate:

- the effects of interventions to prevent progression of ADPKD as measured by kidney function (GFR, SCr), doubling of SCr concentration, proteinuria or urinary albumin excretion) and clinical endpoints (ESKD, need for RRT)
- the effects of those interventions on kidney structure (total kidney volume, parenchymal volume, and kidney cyst volume)
- the effects of those interventions on patient-centred endpoints such as incidence of fatal and nonfatal cardiovascular events, sudden death, all-cause mortality, hospitalisations, blood pressure control, quality of life, and kidney pain
- general and specific adverse effects related to those interventions such as dizziness, diarrhoea, abdominal cramps and nausea (all treatments); hypernatraemia, thirst, dry mouth, and headache (V2R antagonists); angioedema and infections (mTOR inhibitors); alopecia (somatostatin agonists); and hyperkalaemia (ACEi and ARBs).

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 have been included, without duration restrictions. The first period only was considered for randomised cross-over studies. There were no language restrictions.

Types of participants

Inclusion criteria

Studies enrolling patients (adults or children) with 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 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) and/or on haemodialysis and/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

- ACEi alone versus placebo, other therapy or both
- ARB alone versus placebo, other therapy or both
- ACEi versus ARB and standard therapy
- ARB versus ACEi and standard therapy
- ACEi plus ARB versus ACEi or ARB alone
- VR2 antagonists (selective or nonselective) versus placebo and/or standard therapy
- mTOR selective inhibitors alone or in association with other therapies versus placebo other therapy or both
- Somatostatin agonists alone or in association with other therapies versus placebo and/or other therapies
- Antiplatelet agents versus placebo, standard therapy or both
- Eicosapentaenoic acids versus placebo, standard therapy or both
- Statins versus placebo, standard therapy or both
- Vitamin D or vitamin D derivatives versus other therapies
- Increased versus standard fluid intake (as required).

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

- Kidney function: SCr (mg/dL), measured or estimated GFR (eGFR) (mL/min or mL/min/1.73 m^2), creatinine clearance (CrCl), doubling of creatinine, need for RRT or transplantation at the end of treatment.

Secondary outcomes

- Total kidney volume (mL or L), total cyst volume (mL or L), total parenchymal volume (mL or L) assessed by magnetic nuclear imaging scan, echo tomography or computed tomography (CT)
- Urinary protein excretion: 24 hour proteinuria or 24 hour albuminuria (mg/dL) (mg/d) or urine protein-creatinine ratio (mg/g or g/g) or urine albumin-creatinine ratio (mg/g or g/g)
- Blood pressure (BP): systolic BP and diastolic BP (mm Hg), mean BP (mm Hg)
- Fatal and nonfatal cardiovascular events including but not limited to myocardial infarction (MI), cerebrovascular accident (CVA), congestive heart failure (CHF)
- All-cause mortality
- Quality of life (assessed by validated scales or any other instrument as reported by authors, such as SF-36 or KDQOL-SF questionnaires)
- Kidney pain (rate of episodes or subjective perception as assessed by any analogue pain scale)
- Any admission to hospital and duration of hospital stay (if long-term data were available from the studies)
- Adverse events: including but not limited to dizziness, diarrhoea, abdominal cramps and nausea (all treatments), hypernatraemia, thirst, dry mouth, transaminases elevation, and 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 Renal Group's Specialised Register to 6 June 2015 through contact with the Trials' Search Co-ordinator using search terms relevant to this review. The Cochrane Renal Group's Specialised Register contains studies identified from:

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. Searches of the International Clinical Trials Register (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 Renal 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 Renal 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 titles and abstracts of studies relevant to the review. Titles and abstracts were screened independently by two authors (DB, MR) 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 (DB, MR) using a standardised electronic data extraction form. Studies reported in non-English and non-Italian 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 was 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

Risk of bias was independently assessed by two authors using the risk of bias assessment tool (Higgins 2011) (see Appendix 2).

Measures of treatment effect

For dichotomous outcomes (ESKD, need for RRT, all-cause mortality, 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, quality of life, 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 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 2011).

Assessment of heterogeneity

Heterogeneity was analysed 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). I^2 values of 25%, 50% and 75% were considered to correspond to low, medium and high levels of heterogeneity, respectively.

Assessment of reporting biases

Although we had planned to investigate the existence possible small study bias, the overall paucity of available studies meant that it was not possible to conduct such assessment (Higgins 2011).

Data synthesis

Data for treatment effects were pooled using the random-effects model.

Subgroup analysis and investigation of heterogeneity

We attempted to analyse where age (adults or children), stage and severity of disease (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. However, this was not possible due to the small number of included studies.

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 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.

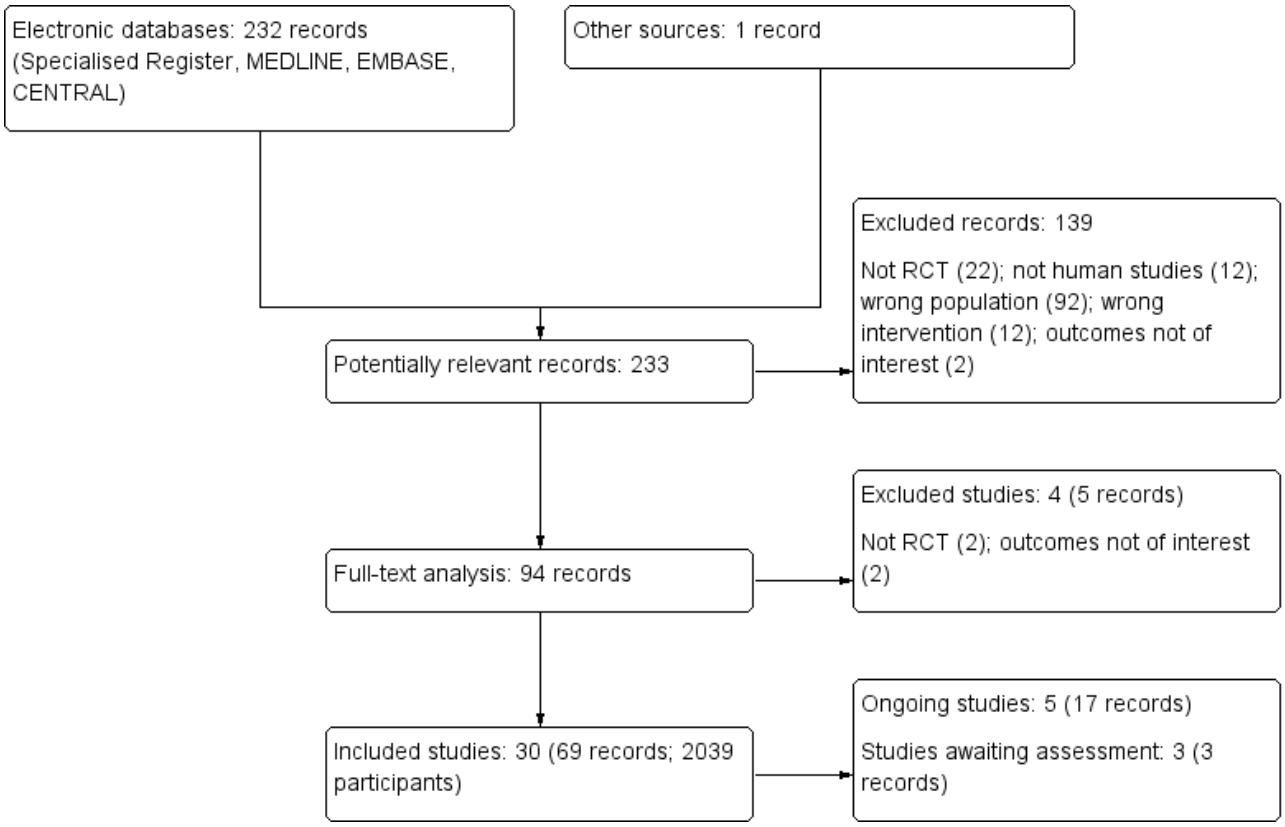
RESULTS

Description of studies

Results of the search

The search identified 232 records; one additional record identified from personal research was added. Full-text assessment of 93 records resulted in the inclusion of 30 eligible studies (69 reports) that enrolled a total of 2039 participants with ADPKD (AIPRI Study 1996; ALADIN Study 2013; ELATE Study 2011; Biao 1997; Cadnapaphornchai 2005; Ecder 1999; Fassett 2010; Higashihara 2008; Hogan 2010; LOCKCYST Study 2009; Melemadathil 2013; Mora 2013; Nakamura 2001d; Nakamura 2012a; Nutahara 2005; RAPYD Study 2012; Ruggenenti 2005; SIRENA Study 2010; Soliman 2009; SUISSE ADPKD Study 2007; Temmerman 2012; TEMPO 248 & 249 2005; TEMPO 250 2011; TEMPO 3-4 Study 2011; Ulusoy 2010; van Dijk 2001; van Dijk 2003; Walz 2010; Watson 1999; Zeltner 2008) and three ongoing studies (three reports) (DIPAK 1 Study 2014; NCT00345137; NCT01932450). Authors of some included studies were contacted for additional information with respect to study methods and/or unreported data; four investigators responded to our queries (LOCKCYST Study 2009; Soliman 2009; Temmerman 2012; Walz 2010). Figure 1 depicts the study inclusion and exclusion process.

Figure 1. Study flow diagram



Prior to publication of this review a final search of the Specialised Register identified three new potential studies and these will be assessed for inclusion in a future update of this review (Braun 2014; NCT01233869; Vienna RAP Study 2015).Two ongoing studies have recently been completed and will be assessed in a future update of this review (Cadnapaphornchai 2011; HALT-PKD Study 2008)

Included studies

Among the included studies, three were cross-over studies (Ruggenenti 2005; SIRENA Study 2010; van Dijk 2001). In five studies (AIPRI Study 1996; ELATE Study 2011; Hogan 2010; LOCKCYST Study 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 Study 2011; LOCKCYST Study 2009). The number of participants was not specified in Watson 1999. With the exception of Cadnapaphornchai 2005 and Mora 2013, all studies were conducted in adults. Study duration ranged from five days to 60 months.

ADPKD assessment at baseline and end of treatment was performed by echo tomography in 12 studies (Biao 1997; Cadnapaphornchai 2005; Ecder 1999; Fassett 2010; Nakamura 2001d; Nakamura 2012a; Nutahara 2005; Ulusoy 2010; van Dijk 2001; van Dijk 2003; Watson 1999; Zeltner 2008); computed tomography in seven studies (ELATE Study 2011; Higashihara 2008; Hogan 2010; LOCKCYST Study 2009; Ruggenenti 2005; SIRENA Study 2010; Temmerman 2012); and magnetic nuclear resonance imaging in nine studies (ALADIN Study 2013; Melemadathil 2013; Mora 2013; RAPYD Study 2012; Soliman 2009; SUISSE ADPKD Study 2007; TEMPO 250 2011; TEMPO 3-4 Study 2011; Walz 2010). Methods of assessment were not specified in two studies (AIPRI Study 1996; TEMPO 248 & 249 2005).

Genetic characterisation of PKD mutations was only made only in RAPYD Study 2012, Melemadathil 2013 (according to both study protocols only participants with the PKD1 mutation were enrolled), and Ruggenenti 2005 (patients with PKD1 and PKD2 mutations were both enrolled).

All studies excluded patients with eGFR < 15 mL/min/1.73 m^2. Mean eGFR ranged from 38.2 to 124 mL/min in adult ADPKD patients and from 102 to 142 mL/min in children.

Total kidney volume was estimated in 16 studies (ALADIN Study 2013; Cadnapaphornchai 2005; ELATE Study 2011; Higashihara 2008; Hogan 2010; LOCKCYST Study 2009; Melemadathil 2013; Mora 2013; RAPYD Study 2012; Ruggenenti 2005; SIRENA Study 2010; Soliman 2009; SUISSE ADPKD Study 2007; Hogan 2010; TEMPO 3-4 Study 2011; Walz 2010) with mean values ranging from 1000 to 2845 mL in adults and from 157 to 315 mL in children.

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

Enalapril, ramipril or benazepril (ACEi) were compared to the following.

- Placebo or standard therapy in three studies (Cadnapaphornchai 2005; van Dijk 2003; AIPRI Study 1996; 147 participants)
- Amlodipine (calcium channel blocker) in one study (Ecder 1999; 24 participants)
- Losartan or telmisartan (ARB) in two studies (Nakamura 2012a; Ulusoy 2010; 42 participants)
- Atenolol or metoprolol (beta blockers) in three studies (van Dijk 2003; Watson 1999; Zeltner 2008; 65 participants).

Other comparisons were as follows.

- Ramipril at a starting dose of 2.5 mg versus ramipril plus rapamycin (mTOR inhibitor) at low or high target doses (RAPYD Study 2012; 55 participants)
- Telmisartan alone versus telmisartan plus sirolimus (mTOR inhibitor) (Soliman 2009; 16 participants)
- Candesartan (ARB) 2 to 8 mg/d versus to amlodipine (Nutahara 2005) (49 participants)
- High doses (60 + 30 mg/d) tolvaptan (selective V2R antagonist) versus low doses (45 + 15 mg/d) (TEMPO 250 2011; 46 participants)
- Tolvaptan versus placebo (TEMPO 250 2011; TEMPO 3-4 Study 2011; 1491 participants)
- Rapamycin, everolimus or sirolimus (mTOR inhibitors) alone versus placebo or standard therapy in five studies (Melemadathil 2013; Mora 2013; SIRENA Study 2010; SUISSE ADPKD Study 2007; Walz 2010; 616 participants).
- Octreotide or lanreotide (long-acting somatostatin analogues) versus placebo in one parallel (ALADIN Study 2013; 79 participants) and four cross-over studies (Ruggenenti 2005 (12 participants); LOCKCYST Study 2009 (32 participants); Hogan 2010; Temmerman 2012 (48 participants))
- Octreotide alone versus octreotide plus everolimus (ELATE Study 2011; 15 participants)
- Dilazep dihydrochloride (antiplatelet agent) versus placebo (Nakamura 2001d; 22 participants)
- Eicosapentaenoic acids (2.4 g/d) versus standard therapy (Higashihara 2008; 41 participants)
- Pravastatin or simvastatin (statins) versus placebo or standard therapy (Fassett 2010; van Dijk 2001; 69 participants)
- Calcitriol (vitamin D) at 0.25 to 1 µg/d versus traditional Chinese medicine (herbs) (Biao 1997; 34 participants).

Excluded studies

After title and abstract review we excluded 139 records Figure 1. Reasons for initial exclusion were: inappropriate population (92); inappropriate intervention (12); not randomised (22); non-clinical studies (12); outcomes not relevant to this review (2). Four studies (five reports) were excluded after full text evaluation; two studies were not RCTs (Kanno 1996; Sharma 2004); and two studies investigated outcomes that were not relevant to this review (Doulton 2006; Nakamura 2005a). One study was excluded as it was halted in 2008 due to lack of funding (ISRCTN57653760).

Risk of bias in included studies

Summaries of risk of bias in the included studies are depicted in Figure 2 and Figure 3. The overall risk of bias was highly variable since in most studies the information provided (particularly on allocation, blinding of investigators and outcome assessors and attrition) was not sufficient to permit judgment. In some cases, authors were contacted for additional information but only four investigators responded to our queries (LOCKCYST Study 2009; Soliman 2009; Temmerman 2012; Walz 2010)

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

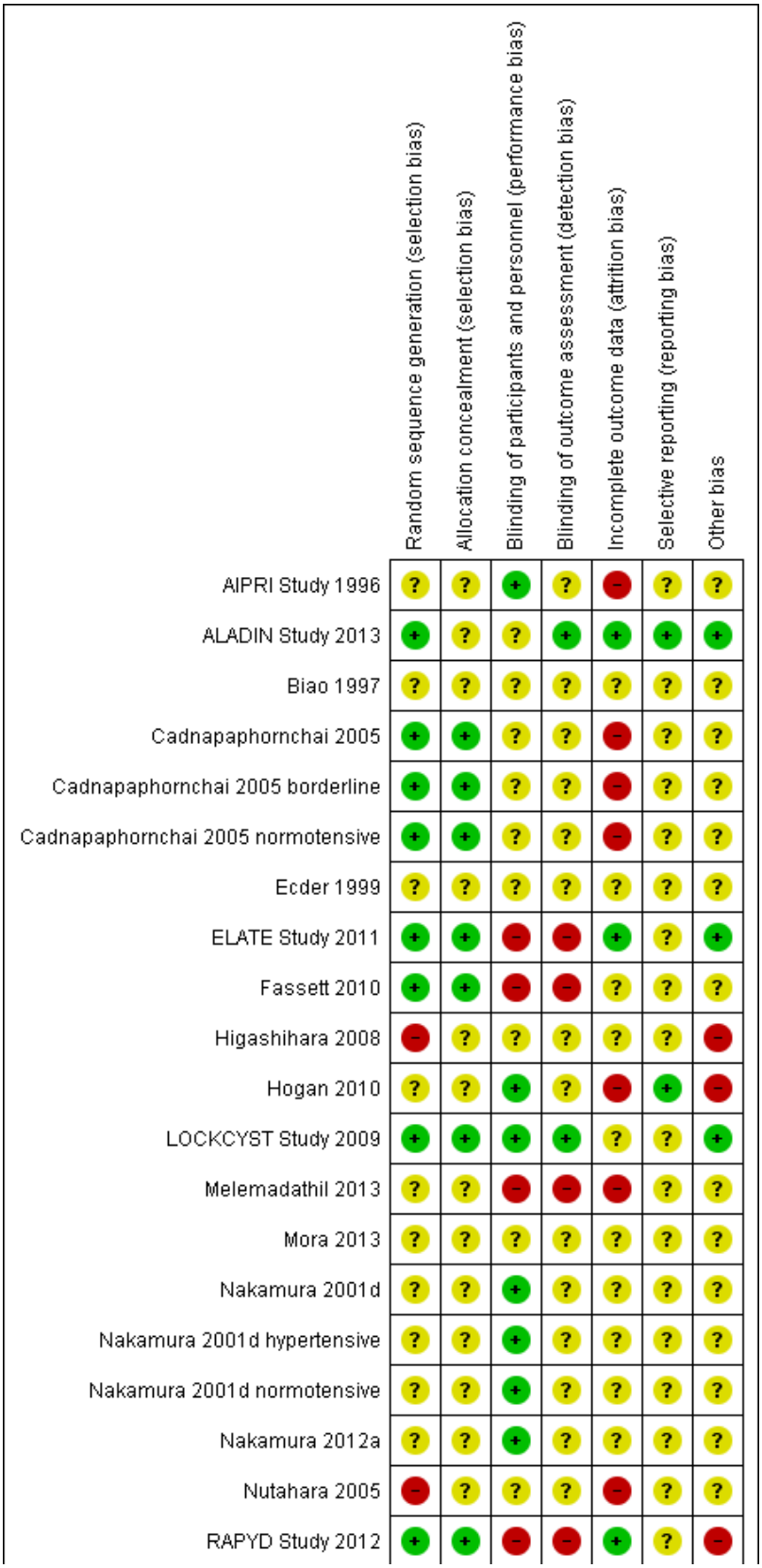


Figure 2. (Continued)

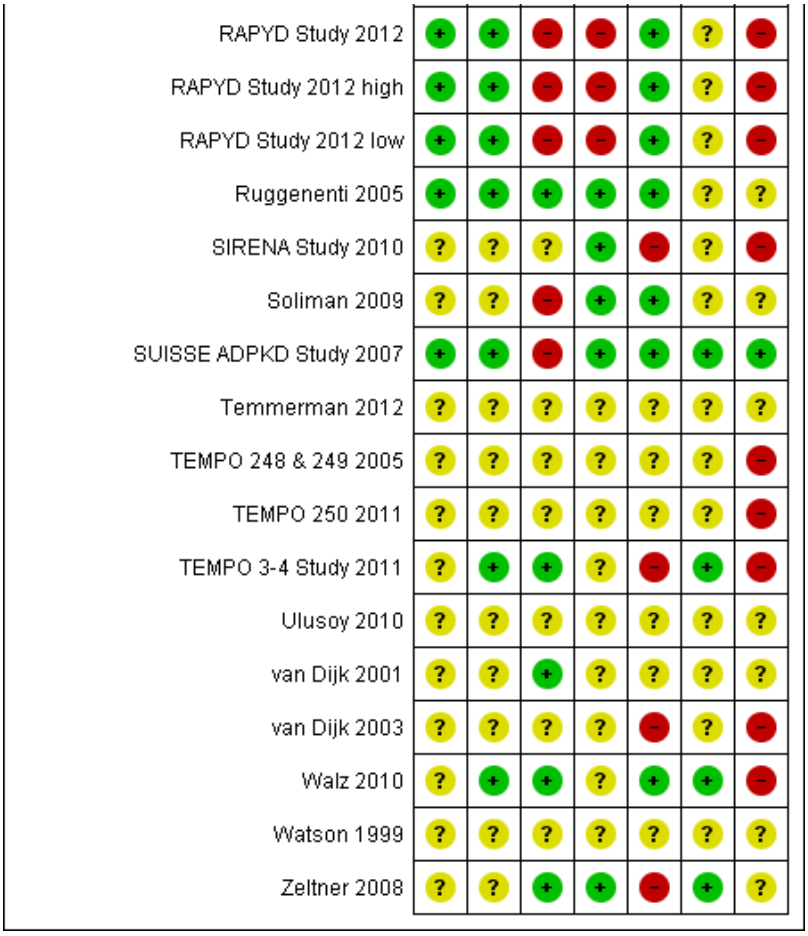
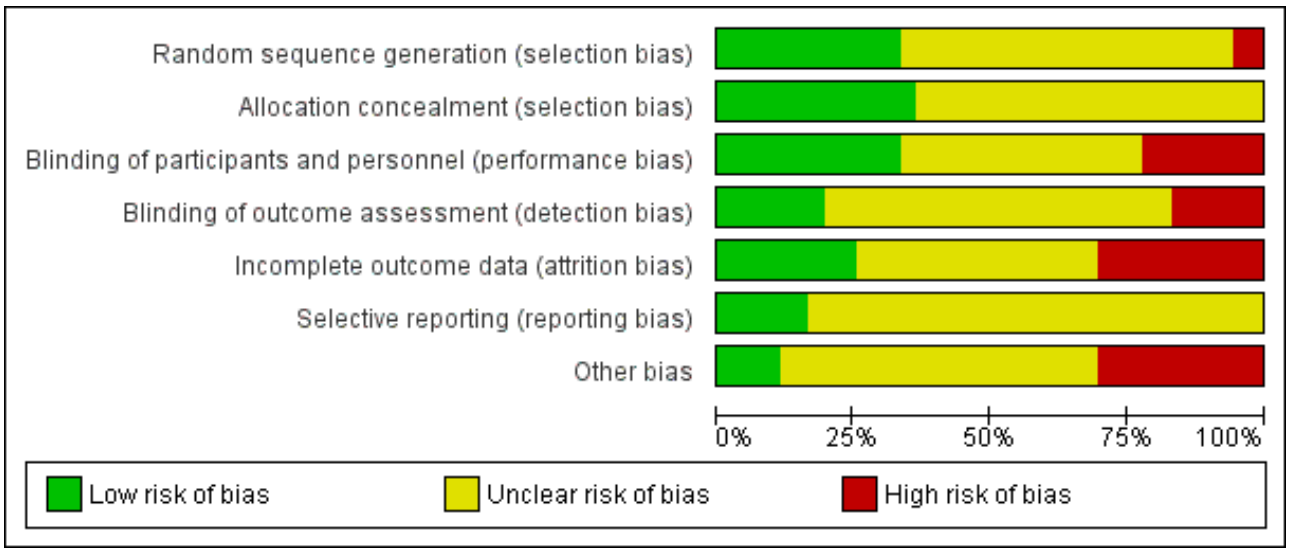


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies



Allocation

Random sequence generation was low risk in eight studies (ALADIN Study 2013; Cadnapaphornchai 2005; ELATE Study 2011; Fassett 2010; LOCKCYST Study 2009; RAPYD Study 2012; Ruggenenti 2005; SUISSE ADPKD Study 2007), high risk in two studies (Higashihara 2008; Nutahara 2005); and there were insufficient data to inform assessment in the remaining 20 studies.

Allocation concealment was low risk in nine studies (Cadnapaphornchai 2005; ELATE Study 2011; Fassett 2010; LOCKCYST Study 2009; RAPYD Study 2012; Ruggenenti 2005; SUISSE ADPKD Study 2007; TEMPO 3-4 Study 2011; Walz 2010) and unclear in 21 studies.

Blinding

The quality of blinding overall was variable. In most cases, blinding of investigators and outcome assessors was not specified. Participants and investigators were blinded in 10 studies (AIPRI Study 1996; Hogan 2010; LOCKCYST Study 2009; Nakamura 2001d; Nakamura 2012a; Ruggenenti 2005; TEMPO 3-4 Study 2011; van Dijk 2001; Walz 2010; Zeltner 2008) and not blinded in six studies (ELATE Study 2011; Fassett 2010; Melemadathil 2013; RAPYD Study 2012; Soliman 2009; SUISSE ADPKD Study 2007).

In ALADIN Study 2013, participants were blinded to the treatment while investigators were aware of the allocated group. Blinding was not specified in the remainder of the studies.

Outcome assessors were blinded in seven studies (ALADIN Study 2013; LOCKCYST Study 2009; Ruggenenti 2005; SIRENA Study 2010; Soliman 2009; SUISSE ADPKD Study 2007; Zeltner 2008) whereas in four studies (ELATE Study 2011; Fassett 2010; Melemadathil 2013; RAPYD Study 2012) assessors were aware of treatment allocation. Outcome assessor blinding was unclear in the remaining 19 studies.

Incomplete outcome data

Attrition bias overall was variable; in most studies, the information provided was insufficient to permit assessment. The overall drop-out rate ranged from 1.6% to 33% with no apparent differences among groups, with the exception of seven studies (Cadnapaphornchai 2005; ELATE Study 2011; Melemadathil 2013; Nutahara 2005; RAPYD Study 2012; TEMPO 3-4 Study 2011; Zeltner 2008). We found that the overall drop-out rate was greater than 10% in nine studies (AIPRI Study 1996; Cadnapaphornchai 2005; ELATE Study 2011; Hogan 2010; Nutahara 2005; SIRENA Study 2010; TEMPO 3-4 Study 2011; van Dijk 2003; Zeltner 2008). Six studies (ALADIN Study 2013; Nutahara 2005; RAPYD Study 2012; SUISSE ADPKD Study 2007; TEMPO 3-4 Study 2011; Walz 2010) were analysed on an intention-to-treat basis. ELATE Study 2011 was analysed on both per-protocol and intention-to-treat bases.

Selective reporting

All predefined outcomes were reported in six studies (ALADIN Study 2013; Hogan 2010; SUISSE ADPKD Study 2007; TEMPO 3-4 Study 2011; Walz 2010; Zeltner 2008). Selective reporting was unclear in the remaining 24 studies.

Other potential sources of bias

We found that 12 studies reported receiving funding from industry (ALADIN Study 2013; ELATE Study 2011; Higashihara 2008; Hogan 2010; LOCKCYST Study 2009; RAPYD Study 2012; SIRENA Study 2010; TEMPO 248 & 249 2005; TEMPO 250 2011; TEMPO 3-4 Study 2011; van Dijk 2003; Walz 2010). In three studies (ALADIN Study 2013; ELATE Study 2011; LOCKCYST Study 2009) the authors specified that the sponsor was not involved in the study design, data collection, data analysis, interpretation of the study results, or writing the manuscript.

Effects of interventions

Overall, outcomes reported were mostly confined to eGFR, SCr and kidney structure (kidney and cyst volumes) while patient-centred outcomes including RRT, mortality, and treatment-related hazards were infrequently reported.

Kidney function

Serum creatinine

Somatostatin analogues significantly reduced SCr compared to placebo (Analysis 11.1 (ALADIN Study 2013; Ruggenenti 2005, 91 participants): MD -0.43 mg/dL, 95% CI -0.86 to -0.01; I^2 = 0%).

There were no significant differences in SCr for the following comparisons.

- ACEi versus no treatment (Analysis 1.1 (Cadnapaphornchai 2005, 42 participants): MD -0.02 mg/dL, 95% CI -0.14 to 0.09; I^2 = 23%)
- ACEi versus CCB (Analysis 2.1 (Ecder 1999, 24 participants): MD 0.01 mg/dL, 95% CI -0.10 to 0.12)
- ACEi versus ARB (Analysis 3.1 (Nakamura 2012a; Ulusoy 2010, 52 participants): MD 0.00 mg/dL, 95% CI -0.09 to 0.10; I^2 = 0%)
- ACEi versus beta-blockers (Analysis 4.1 (Zeltner 2008, 37 participants) MD 0.18 mg/dL, 95% CI -0.12 to 0.48)
- ARB versus CCB (Analysis 7.1 (Nutahara 2005, 40 participants) MD -0.45 mg/dL, 95% CI -0.90 to -0.00)
- VR2 antagonists versus placebo (Analysis 8.1 (TEMPO 3-4 Study 2011, 1154 participants): MD -0.01 mg/dL, 95% CI -0.08 to 0.06)
- High versus low dose V2R antagonists (Analysis 9.1 (TEMPO 250 2011, 46 participants): MD -0.12 mg/dL, 95% CI -0.36 to 0.12)
- Antiplatelet agents versus placebo (Analysis 13.1 (Nakamura 2001d, 22 participants): MD -0.13 mg/dL, 95% CI -0.52 to 0.26; I^2 = 69%)
- Eicosapentaenoic acid versus standard therapy (Analysis 14.1 (Higashihara 2008, 41 participants): RR 0.16, 95% CI -0.55 to 0.87)

Glomerular filtration rate

Ecder 1999 reported GFR was significantly lower in the ACEi group compared to the CCB group (Analysis 2.2 (24 participants): (MD -13.00 mL/min/1.73 m^3, 95% CI -17.56 to -8.44).

Biao 1997 reported GFR was significantly higher in the vitamin D group compared to the Chinese herbal medicine group (Analysis 16.2 (34 participants): MD 22.60 mL/min, 95% CI 0.92 to 44.28).

There were no significant differences in GFR for the following comparisons.

- ACEi versus not treatment (Analysis 1.2 (Cadnapaphornchai 2005; van Dijk 2003, 103 participants) MD -3.41 mL/min/1.73 m^3, 95% CI -15.83 to 9.01; I^2 = 46%)
- ACEi versus ARB (Analysis 3.2 (Ulusoy 2010, 32 participants): MD -3.40 mL/min/1.73 m^3, 95% CI -22.69 to 15.89)

- ACEi versus beta-blockers (Analysis 4.2 (van Dijk 2003; Zeltner 2008, 65 participants): MD -8.06 mL/min/1.73 m^3, 95% CI -29.62 to 13.50; I^2 = 95%)
- ARB alone versus ARB + mTOR inhibitor (Analysis 6.1 (1 study, 16 participants): MD -9.60 mL/min/1.73 m^3, 95% CI -28.18 to 8.98)
- ARB versus CCB (Analysis 7.2 (Nutahara 2005, 31 participants): MD 6.30 mL/min/1.73 m^3, 95% CI -8.49 to 21.09)
- mTOR inhibitor versus no treatment (Analysis 10.1 (SIRENA Study 2010; SUISSE ADPKD Study 2007, 115 participants): MD 4.45 mL/min/1.73 m^3, 95% CI -3.20 to 12.11; I^2 = 0%)
- Somatostatin analogues versus placebo (Analysis 11.2 (ALADIN Study 2013; Ruggenenti 2005, 79 participants): MD 9.50 mL/min/1.73 m^3, 95% CI -4.45 to 23.44; I^2 = 0%)
- Antiplatelet agents versus placebo (Analysis 13.2 (Nakamura 2001d, 22 participants): MD 2.24 mL/min/1.73 m^3, 95% CI -8.05 to 12.53; I^2 = 0%)
- Eicosapentaenoic acid versus standard therapy (Analysis 14.2 (Higashihara 2008, 41 participants): MD 6.10 mL/min/1.73 m^3, 95% CI -11.16 to 23.36)

Doubling of creatinine

Fours studies reported doubling of creatinine; none reported any significant differences between the treatments studied.

- ACEi versus no treatment (Analysis 1.3 (AIPRI Study 1996, 64 participants): RR 1.01, 95% CI 0.45 to 2.28)
- ARB alone versus ARB + mTOR inhibitor (Analysis 6.2 (Soliman 2009, 16 participants): RR 3.00, 95% CI 0.39 to 23.07)
- ARB versus CCB (Analysis 7.3 (Nutahara 2005, 49 participants): RR 0.17, 95% CI 0.02 to 1.34)
- V2R antagonists versus placebo (Analysis 8.3 (TEMPO 3-4 Study 2011, 1444 participants): RR 0.96, 95% CI 0.73 to 1.25).

Need for renal replacement therapy or transplantation

Two studies reported need for RRT or transplantation; none reported any significant difference between the treatments studied.

- ACEi versus beta-blockers (Analysis 4.4 (Zeltner 2008, 37 participants): RR 0.39, 95% CI 0.02 to 8.97)
- mTOR inhibitor versus no treatment: RRT (Analysis 10.3 (Walz 2010, 431 participants): RR 3.04, 95% CI 0.12 to 74.26); transplantation (Analysis 10.4 (Walz 2010, 431 participants): RR 1.01, 95% CI 0.06 to 16.11).

Total kidney, cyst and parenchymal volume

Total kidney volume

Soliman 2009 reported a significant increase in total kidney volume with ARB alone compared to ARB + mTOR inhibitor (Analysis 6.3 (16 participants): MD 0.37 L, 95% CI 0.04 to 0.70).

Somatostatin analogues significantly decreased total kidney volume compared to placebo (Analysis 11.3 (ALADIN Study 2013; LOCKCYST Study 2009; Ruggenenti 2005, 114 participants) MD -0.62 L, 95% CI -1.22 to -0.01; I^2 = 11%).

There were no significant differences in total kidney volume for the following comparisons.

- ACEi versus no treatment (Analysis 1.4 (Cadnapaphornchai 2005, 42 participants): MD -42.50 mL, 95% CI -115.68 to 30.67; I^2 = 0%)
- ACEi alone versus ACEi + mTOR inhibitor (Analysis 5.2; (RAPYD Study 2012, 69 participants): MD 285.79 mL, 95% CI -21.92 to 593.50; I^2 = 0%)
- mTOR inhibitor versus no treatment Analysis 10.5; (SIRENA Study 2010; SUISSE ADPKD Study 2007, 115 participants): MD -0.08 L, 95% CI -0.75 to 0.59; I^2 = 0%)
- Eicosapentaenoic acid versus standard therapy Analysis 14.3 (Higashihara 2008, 41 studies): MD -209.00 mL, 95% CI -729.06 to 311.06)

Cyst volume

Four studies reported cyst volume; none reported any significant differences between the treatments studied.

- ACEi alone versus ACEi + mTOR inhibitor (Analysis 5.3 (RAPYD Study 2012, 69 participants): MD 36.32 mL, 95% CI -6.99 to 79.64; I^2 = 0%)
- mTOR inhibitor versus no treatment (Analysis 10.7 (SIRENA Study 2010, 15 participants): MD -55.00 mL, 95% CI -862.98 to 752.98)
- Somatostatin analogues versus placebo (Analysis 11.4 (ALADIN Study 2013; Ruggenenti 2005, 82 participants): MD -0.50 L, 95% CI -1.18 to 0.18; I^2 = 37%).

Total parenchymal volume

Three studies reported total parenchymal volume; none reported any significant differences between the treatments studied.

- mTOR inhibitor versus no treatment (Analysis 10.9 (SIRENA Study 2010, 15 participants): MD 15.00 mL, 95% CI -75.44 to 105.44)
- Somatostatin analogues versus placebo (Analysis 11.5 (ALADIN Study 2013; Ruggenenti 2005, 82 participants): MD -67.67 mL, 95% CI -249.45 to 114.12; I^2 = 78%).

Urinary protein excretion

Ecder 1999 reported a significant decrease in albuminuria with ACEi compared to CCB (Analysis 2.3 (24 participants): MD -134.00 mg/g, 95% CI -176.01 to -91.99).

Nutahara 2005 reported ARB significantly decreased albuminuria (Analysis 7.4 (25 participants): MD -304.00 mg/d, 95% CI -578.54 to -29.46) and proteinuria (Analysis 7.5 (24 participants): MD -238.00 mg/d, 95% CI -394.61 to -81.39) compared to CCB.

There were no significant differences in either proteinuria or albuminuria for the following comparisons.

- ACEi versus no treatment (Analysis 1.5 (Nakamura 2001d; van Dijk 2003, 103 participants): SMD -0.12, 95% CI -0.51 to 0.26; I^2 = 0%)
- ACEi versus beta-blockers (Analysis 4.5 (van Dijk 2003; Zeltner 2008, (65 participants) SMD -0.19, 95% CI -1.77 to 1.39; I^2 = 89%)
- V2R antagonists versus placebo (Analysis 8.5 (TEMPO 3-4 Study 2011, 1157 participants): MD -1.60 mg/mmol, 95% CI -3.95 to 0.75)

- mTOR inhibitor versus no treatment: proteinuria (Analysis 10.11 (SIRENA Study 2010; Walz 2010, 446 participants): (SMD 0.34, 95% CI -0.29 to 0.98; I^2 = 45%); albuminuria (Analysis 10.13 (SIRENA Study 2010; SUISSE ADPKD Study 2007, 115 participants): SMD 0.25, 95% CI -0.27 to 0.78; participants; I^2 = 23%)
- Somatostatin analogues versus placebo: proteinuria (Analysis 11.6 (ALADIN Study 2013, 79 participants): MD -0.05 g/24 h, 95% CI -0.17 to 0.07); albuminuria (Analysis 11.7, (ALADIN Study 2013; Ruggenenti 2005, 91 participants): SMD -0.10, 95% CI -0.51 to 0.31; I^2 = 0%)
- Antiplatelet agent versus placebo (Analysis 13.3 (Nakamura 2001d, 22 participants): MD -60.53 µg/min, 95% CI -129.06 to 8.01; I^2 = 74%).

Blood pressure

Systolic blood pressure

Ecder 1999 reported ACEi significantly decreased systolic BP compared to CCB (Analysis 2.4 (24 participants): MD -5.00 mm Hg, 95% CI -8.62 to -1.38).

TEMPO 250 2011 reported high dose V2R antagonists significantly reduced systolic BP compared to low dose V2R antagonists (Analysis 9.2 (46 participants): MD -9.00 mm Hg, 95% CI -16.98 to -1.02).

There were no significant differences in systolic BP for the following comparisons.

- ACEi versus no treatment (Analysis 1.6 (Cadnapaphornchai 2005, 42 participants): MD -5.44 mm Hg, 95% CI -14.26 to 3.38; I^2 = 96%)
- ACEi versus ARB (Analysis 3.3 (Ulusoy 2010, 32 participants): MD -3.50 mm Hg, 95% CI -9.75 to 2.75)
- ACEi versus beta-blocker (Analysis 4.6 (Zeltner 2008, 37 participants): MD -1.00 mm Hg, 95% CI -2.29 to 0.29)
- mTOR inhibitor versus no treatment (Analysis 10.14 (SIRENA Study 2010; SUISSE ADPKD Study 2007, 112 participants): MD 2.48 mm Hg, 95% CI -2.07 to 7.03; I^2 = 0%)
- Somatostatin analogues versus placebo (Analysis 11.8 (ALADIN Study 2013; Ruggenenti 2005, 91 participants): MD 0.79 mm Hg, 95% CI -3.54 to 5.13; I^2 = 0%)
- Antiplatelet agent versus placebo (Analysis 13.4 (Nakamura 2001d, 22 participants): MD 5.04 mm Hg, 95% CI -7.34 to 17.43; I^2 = 0%)
- Statins versus no treatment (Analysis 15.4 (Fassett 2010, 49 participants): MD 1.70 mm Hg, 95% CI -6.39 to 9.79).

Diastolic blood pressure

Cadnapaphornchai 2005 reported ACEi significantly reduce diastolic BP compared to no treatment (Analysis 1.7 (42 participants): MD -4.96 mm Hg, 95% CI -8.88 to -1.04; I^2 = 90%)

Ecder 1999 reported ACEi significantly decreased diastolic BP compared to CCB (Analysis 2.5 (24 participants): MD -3.00 mm Hg, 95% CI -5.40 to -0.60)

Zeltner 2008 reported beta-blockers significantly decrease diastolic BP compared to ACEi (Analysis 4.7 (37 participants): MD 1.00 mm Hg, 95% CI 0.35 to 1.65)

TEMPO 250 2011 reported high dose V2R antagonists significantly reduced diastolic BP compared to low dose V2R antagonists (Analysis 9.3 (46 participants): MD -6.00 mm Hg, 95% CI -11.21 to -0.79)

There were no significant differences in diastolic BP for the following comparisons.

- ACEi versus ARB (Analysis 3.4 (Ulusoy 2010, 32 participants): MD -1.80 mm Hg, 95% CI -5.23 to 1.63)
- mTOR inhibitor versus no treatment (Analysis 10.15 (SIRENA Study 2010; SUISSE ADPKD Study 2007, 112 participants): MD 0.27 mm Hg, 95% CI -3.30 to 3.85; I^2 = 0%)
- Somatostatin analogues versus placebo (Analysis 11.9 (ALADIN Study 2013; Ruggenenti 2005, 91 participants): MD -0.38 mm Hg, 95% CI -3.68 to 2.92; I^2 = 0%)
- Antiplatelet agent versus placebo (Analysis 13.5 (Nakamura 2001d, 22 participants): MD 6.24 mm Hg, 95% CI -3.27 to 15.74; I^2 = 0%)
- Statins versus no treatment (Analysis 15.5 (Fassett 2010, 49 participants): MD -1.40 mm Hg, 95% CI -5.54 to 2.74).

Mean arterial pressure

van Dijk 2003 reported ACEi significantly decreased MAP compared to no treatment (Analysis 1.8 (61 participants): MD -5.00 mm Hg, 95% CI -6.29 to -3.71).

Ecder 1999 reported ACEi significantly decreased MAP compared to CCB (Analysis 2.6 (24 participants): MD -3.00 mm Hg, 95% CI -5.40 to -0.60).

van Dijk 2003 reported ACEi significantly decreased MAP compared to beta-blockers (Analysis 4.8 (28 participants): MD -3.00 mm Hg, 95% CI -4.92 to -1.08).

There were no significant differences in MAP for the following comparisons.

- ACEi versus ARB (Analysis 3.5 (Ulusoy 2010, 32 participants): MD -2.20 mm Hg, 95% CI -6.41 to 2.01)
- ACEi alone versus ACEi plus mTOR inhibitors (Analysis 5.5 (RAPYD Study 2012, 69 participants): MD 0.64 mm Hg, 95% CI -6.21 to 7.50)
- Somatostatin analogues versus placebo (Analysis 11.10 (ALADIN Study 2013, 79 participants): MD -0.10 mm Hg, 95% CI -3.66 to 3.46).

Cardiovascular events

Cardiovascular events were only reported in Zeltner 2008. There was no significant difference in the number of cardiovascular events between ACEi and beta-blockers (Analysis 4.10 (37 participants): (RR 1.18, 95% CI 0.08 to 17.42).

All-cause mortality

Death was only reported in Walz 2010. There was no significant difference in the number of deaths between mTOR inhibitors and no treatment (Analysis 10.17 (431 participants): RR 2.03, 95% CI 0.19 to 22.20).

Quality of life

Quality of life was not reported in any of the included studies.

Kidney pain

Kidney pain was only reported in TEMPO 3-4 Study 2011. There was no significant difference in the number with kidney between V2R antagonists and placebo (Analysis 8.6 (1444 participants); (RR 0.77, 95% CI 0.66 to 0.90).

Admission to hospital

Admission to hospital was not reported in any of the included studies.

Adverse events

RAPYD Study 2012 reported no significant differences between ACEi alone and ACEi plus mTOR inhibitors in anaemia (Analysis 5.6.1 (53 participants): RR 0.45, 95% CI 0.02 to 8.82), hyperlipidaemia (Analysis 5.6.2 (53 participants): RR 0.10, 95% CI 0.01 to 1.56), infection (Analysis 5.6.3 (53 participants): RR 0.45, 95% CI 0.02 to 8.82), or oral ulcers (Analysis 5.6.4 (53 participants): RR 0.13, 95% CI 0.01 to 2.15).

Soliman 2009 reported no significant difference between ARB alone and ARB plus mTOR inhibitors for infection (Analysis 6.5 (16 participants): RR 0.50, 95% CI 0.13 to 2.00).

Compared to placebo, V2R antagonists significantly increased dry mouth (Analysis 8.7.4 (2 studies, 1455 participants): RR 1.33, 95% CI 1.01 to 1.76; I^2 = 0%) and thirst (Analysis 8.7.6 (1 study, 1444 participants): RR 2.70, 95% CI 2.24 to 3.24). There were no significant differences in headache (Analysis 8.7.1 (2 studies,1455 participants): RR 1.03, 95% CI 0.85 to 1.25; I^2 = 0%), diarrhoea (Analysis 8.7.2 (1 study, 1444 participants): RR 1.21, 95% CI 0.90 to 1.64), dizziness (Analysis 8.7.3 1 study, 1444 participants): RR 1.30, 95% CI 0.93 to 1.83), nausea (Analysis 8.7.5 (1 study, 1444 participants): RR 0.86, 95% CI 0.64 to 1.18), or liver enzyme elevation (Analysis 8.7.7 (1 study, 1444 participants): RR 2.26, 95% CI 0.49 to 10.43).

Compared with no treatment, mTOR inhibitors were associated with significant increases in anaemia (Analysis 10.18.1 (1 study, 431 participants): RR 3.41, 95% CI 1.79 to 6.51), angioedema (Analysis 10.18.2 (3 studies, 560 participants): RR 13.39, 95% CI 2.56 to 70.00; I^2 = 0%), diarrhoea (Analysis 10.18.3 (3 studies 560 participants): RR 1.70, 95% CI 1.26 to 2.29; I^2 = 0%); hyperlipidaemia (Analysis 10.18.4 (1 study, 431 participants): RR 5.68, 95% CI 2.23 to 14.43), infection (Analysis 10.18.5 (3 studies, 560 participants): RR 1.14, 95% CI 1.04 to 1.25; I^2 = 0%), and oral ulcers (Analysis 10.18.7 (3 studies, 560 participants): RR 6.77, 95% CI 4.42 to 10.38; I^2 = 0%), but not nausea (Analysis 10.18.6 (1 study, 431 participants): RR 1.69, 95% CI 0.85 to 3.37).

Somatostatin analogues were associated with significant risk of diarrhoea compared to placebo (Analysis 11.11.3 (2 studies, 91 participants): RR 3.72, 95% CI 1.43 to 9.68; I^2 = 0%) but not alopecia (Analysis 11.11.1 (1 study, 79 participants): RR 4.88, 95% CI 0.24 to 98.47), anaemia (Analysis 11.11.2 (1 study, 79 participants): RR 1.30, 95% CI 0.50 to 3.40), dizziness (Analysis 11.11.4 (1 study, 79 participants): RR 0.97, 95% CI 0.06 to 15.05), or infection (Analysis 11.11.5 (1 study, 79 participants): RR 1.24, 95% CI 0.64 to 2.39).

DISCUSSION

Summary of main results

In this systematic review we could include 30 randomised studies (2039 adults with ADPKD) evaluating 11 interventions (ACEi, ARBs, calcium channel blockers, beta blockers, V2R antagonists, mTOR inhibitors, somatostatin analogues, antiplatelet agents, eicosapentaenoic acids, statins and vitamin D). For most interventions, data were available only from single studies and provided information for surrogate outcomes such as GFR, blood pressure and kidney and cyst volumes, leading to low confidence in estimated treatment effects. Overall, there was little or no evidence that currently available interventions improve patient-related or kidney health outcomes while evidence for adverse events was sparse and showed potential for increased harm.

ACEi significantly reduced diastolic BP but had uncertain effects on mortality, ESKD, kidney volumes, GFR, creatinine levels and albuminuria. ACEi did not produce different effects on kidney function when compared with beta blockers or ARBs.

In meta-analyses of data pooled from two studies, V2R antagonists increased thirst and dry mouth. In addition, data from a single RCT (TEMPO 3-4 Study 2011) showed a greater proportion of patients treated with these drugs had elevations of liver-enzyme levels. V2R antagonists showed apparent benefits on kidney function and volumes but confident interferences about their impact on the progression to ESKD could not be drawn as such benefits were only shown by a single study (TEMPO 3-4 Study 2011). Furthermore, in this study data were analysed on an intention-to-treat basis. A higher percentage of patients in the intervention than in the placebo arm (22.9% versus 13.8%) discontinued the study, mostly due to low compliance to the treatment. This may introduce a significant attrition bias limiting the confidence and the overall applicability of findings.

mTOR inhibitors had uncertain effects on GFR, total kidney volume, BP and other secondary outcomes (albuminuria, proteinuria) but caused oral ulceration, infection, and diarrhoea. Of note the use of these drugs was associated with a remarkable increase in the risk of angioedema (RR 13.39), although the clinical reliability of this point estimate might be questioned due to the very wide confidence interval observed (2.56 to 70.00). Few data were available on mortality and RRT outcomes and treatment effects were accordingly absent.

When compared with placebo, somatostatin analogues reduced SCr and total kidney volume, but had uncertain benefits on GFR and other secondary outcomes, while causing diarrhoea. As shown in a three-year duration study (ALADIN Study 2013), the benefits of these drugs on kidney outcomes (particularly, kidney volumes) seemed to be more evident in the early treatment phase (one year) while they tended to dilute at later stages (three years).

Little or no evidence was found to exist for the impact of calcium channel blockers, eicosapentaenoic acids, statins, vitamin D compounds and antiplatelet agents on disease progression and patient outcomes. These treatments were 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 evidence on available interventions for slowing progression of ADPKD was sparse in both adults and children. Information on ADPKD progression, both in terms of cyst/kidney volumes and deteriorating kidney function was limited, restricted to few interventions and mostly inconclusive because of the availability of single studies only. Most key mortality and cardiovascular outcomes were only marginally addressed. There were few or no data on major patient-centred outcomes, such as CKD progression, mortality, major morbid events, quality of life and disease-related symptoms. Conversely, the vast majority of studies only demonstrated sparse benefits in surrogate endpoints (e.g. change in total kidney or cyst volumes, blood pressure control, proteinuria, albuminuria) without evidence of clear benefits on outcomes of CKD progression (e.g. RRT). Surrogate outcomes are indeed useful as proxies for patient-centred outcomes, particularly in slow-progressing diseases such as ADPKD. However, the main disadvantage of using surrogate outcomes is that favourable effects of interventions do not always translate into clear benefits to harder endpoints. In some cases, surrogate outcomes may even be "hypothesis-generating" at best. Although GFR remains the preferable outcome measure for treatment effectiveness, in the majority of ADPKD patients this parameter remains relatively steady until late in the disease. Total kidney volume has been extensively adopted as surrogate outcome measure in ADPKD studies. However, whether a reduced rate of kidney enlargement effectively translates into slowed kidney function deterioration is still object of debate. Accordingly, recently the FDA did not consider the observed improvement in kidney volumes in the TEMPO studies as enough to justify lifelong therapy with the V2R-antagonist Tolvaptan.

The extreme heterogeneity in study length (ranging from five days to 60 months) also deserves mentioning. Many studies were indeed designed to assess treatment effects in very short time as per their exploratory nature (e.g. pilot or small cross-over studies: Biao 1997; TEMPO 248 & 249 2005; van Dijk 2003). Short-time studies preclude interpretations on hard outcomes (death, dialysis), particularly in slowly progressing chronic diseases. In addition, short-term studies can be powered to investigate the effect of treatments on surrogate endpoints only, showing no proof of significant clinical changes in the long-term. Performing cumulative outcome analyses with such study heterogeneity in follow-up duration is potentially unreliable.

All studies were pilot or cross-over studies conducted on very small populations, with the exception of two multicentre studies (TEMPO 3-4 Study 2011; Walz 2010). Results from small studies are inconclusive in nature and probably more useful to set the stage for larger confirmation studies rather than for providing definite indications for clinical practice.

The applicability of findings is also limited by the large number of drop-out found in most studies. Although the overall drop-out rate varied widely across the studies (1.6% to 33%), this was greater than 10% in nine studies which included all the largest studies conducted on ADPKD patients. Furthermore, in most cases drop-outs were unbalanced among the study groups, being more frequently observed in the active rather than in the control arm (Cadnapaphornchai 2005; ELATE Study 2011; Melemadathil 2013; Nutahara 2005; RAPYD Study 2012; TEMPO 3-4 Study 2011; Zeltner 2008). 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 with high dropout rates. However, such approaches convey a high risk of bias due to selection of patients and may provide clinically dubious information as they may over-estimate the benefit or underestimate the harm of an intervention.

Quality of the evidence

Three of the included studies were cross-over studies (Ruggenenti 2005; SIRENA Study 2010; van Dijk 2001). Most studies focused on small cohorts, were not powered to observe differences in patient-centred outcomes and did not provide adequate study reporting or information on blinding of patients or investigators or both to assess risks of bias properly.

Limitations in study reporting and design markedly reduced confidence in the results. Actual treatment effects may differ significantly from those calculated from existing studies.

Random sequence generation was adequate in only eight studies (ALADIN Study 2013; Cadnapaphornchai 2005; ELATE Study 2011; Fassett 2010; LOCKCYST Study 2009; RAPYD Study 2012; Ruggenenti 2005; SUISSE ADPKD Study 2007), and in almost half the studies, blinding was not present or not specified.

The overall drop-out rate was over 10% in nine studies (AIPRI Study 1996; Cadnapaphornchai 2005; ELATE Study 2011; Hogan 2010; Nutahara 2005; SIRENA Study 2010; TEMPO 3-4 Study 2011; van Dijk 2003; Zeltner 2008) and only six were conducted using intention-to-treat analyses (ALADIN Study 2013; Nutahara 2005; RAPYD Study 2012; SUISSE ADPKD Study 2007; TEMPO 3-4 Study 2011; Walz 2010).

Potential biases in the review process

Despite being the first overall summary of treatment for ADPKD based on a peer-reviewed protocol, a systematic search of electronic databases including the Cochrane Renal 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 data in the available studies represents the key limitation. In most cases, the effect of a given intervention was addressed by single studies, which prevented meta-analyses with sufficient power to draw definitive conclusions on relevant outcomes. Furthermore, data on patient-level outcomes (such as ESKD, mortality and cardiovascular events and adverse effects) were collectively scarce or absent. Study design was heterogeneous with marked differences among studies with respect to follow up duration, baseline kidney function and methods of assessment of ADPKD severity. Finally, in most cases, ADPKD assessment was made by echo tomography, a technique widely recognised to be inaccurate for identifying small changes in kidney volumes and poorly suited for very expanded kidneys.

Agreements and disagreements with other studies or reviews

After decades of symptomatic treatment for ADPKD, we now have several novel interventions targeting ADPKD biology arising from a wealth of experimental and non-randomised studies (Chang 2012). Unfortunately, despite great optimism based on preliminary results, to date there has not been sufficient evidence from the available RCTs to demonstrate clear therapeutic benefits

that outweigh treatment hazards. In addition, large RCTs are needed before these interventions could be considered as effective treatments to improve outcomes in ADPKD.

The Consortium for Radiologic Imaging for the Study of Polycystic Kidney Disease (Rule 2006) demonstrated that in people with ADPKD, baseline kidney volume values predicted the rate of increase in kidney volumes regardless of age, and accordingly, higher rates of kidney enlargement reflected a faster decline in kidney function. Kidney volumes have therefore been proposed and extensively used in studies as surrogate endpoints of disease progression to overcome the difficulty of following kidney function slope for very long periods of time in RCTs. Despite this, the benefits of some interventions (e.g. mTOR inhibitors) on kidney volumes in ADPKD have not corresponded with substantial changes in kidney function decline. This raises the question as to whether these biomarkers are appropriate as outcomes for assessing treatment effectiveness of novel interventions in ADPKD when used in isolation (Grantham 2011) and whether other surrogates of kidney function or damage would be more appropriate in studies of ADPKD patients (Helai 2012). In this regard, negative results of mTOR inhibitors studies were largely disappointing. These drugs have been demonstrated to be powerful inhibitors of cyst growth in experimental models (Wu 2007) and retrospective observations clearly showed a reduced cystic phenotype in the livers of kidney transplant recipients undergoing immunosuppression with mTOR inhibitors (Qian 2008). Future directions have been hypothesised for exploring whether there is room for mTOR inhibitors in the pathogenetic treatment of ADPKD, including higher doses or longer regimens of treatment, lower doses in combination with other therapeutic approaches (to minimise adverse events) or the use of analogues with better side-effects profiles or improved kidney penetration (Wüthrich 2009). We suggest that any future study of higher dose mTOR inhibition requires careful systematic measurement of adverse effects and is based on patient-relevant outcomes.

Although preliminary findings in animal and human studies have suggested that V2R antagonists and somatostatin analogues can be efficacious in slowing cyst growth (Harris 2009), our analyses demonstrated no conclusive effects for V2R and only small effects for somatostatin analogues on kidney function or kidney volumes. On the other hand, concerns might arise concerning the safety profile of these agents because their use is associated with thirst and dry mouth (V2R antagonists) and diarrhoea (somatostatin analogues). Future studies focusing on the effects on kidney function decline rather than kidney volume surrogates are eagerly awaited to confirm and generalise the benefits of these agents in retarding ADPKD progression.

Blood pressure control is currently one of the mainstays of ADPKD management in clinical practice. Hypertensive ADPKD patients have greater and faster annual rates of kidney volumes growth and an increased prevalence of cardiovascular comorbidities and complications with respect to normotensive people (Ecder 2013). Since hypertensive ADPKD patients are at higher risk of kidney disease progression, these people might represent a higher risk population for future studies which would then be powered to capture patient-centred kidney and mortality outcomes.

In our review, the use of ACEi was associated with significant improvement in BP control. Unfortunately, this benefit was mostly confined to children, and meta-analyses were underpowered to detect differences in treatment effects on disease progression. Potentially, results from the ongoing HALT-PKD Study 2008a testing the efficacy of RAAS-blockade on the progression of cystic disease and decline in kidney function, will clarify whether an intensive (≤ 110/75 mm Hg) versus standard (≤ 130/80 mm Hg) BP control might produce different effects on the disease course in ADPKD patients with both early (GFR > 60 mL/min/1.73 m^2) and advanced (GFR 25 to 60 mL/min/1.73 m^2) kidney impairment.

AUTHORS' CONCLUSIONS

Implications for practice

Despite preliminary observations, no hard evidence was found to support the introduction of any of these interventions in clinical practice because treatment effects on patient-centred endpoints are lacking, and although sparse, adverse event data indicate harm. Findings from single studies need to be confirmed by other studies evaluating the long-term impact of these therapies on primary kidney outcomes such as GFR decline and ESKD.

Implications for research

Future studies designed to observe differences in tangible outcomes, such as progression to ESKD, need for transplantation, mortality, hospital admissions, major morbidities and quality of life would be informative. However, clinical studies looking at some of these hard endpoints (e.g. mortality of ESKD) may be problematic in slowly progressing diseases. Alternative strategies should therefore be implemented, mostly focusing on the identification and validation of new endpoints (such as thresholds for clinically meaningful changes in kidney function or the assessment of patient-reported outcomes) and the exact definition of ADPKD patients to be studied in clinical studies as more likely to benefit from early intervention (e.g. in relation to kidney volumes, range of kidney function, tendency to rapid disease progression). Given the high number of interventions tested so far, research efforts should also prioritise a smaller number of drugs and focus on agreed core outcomes to improve generalisability of findings.

More conclusive data on the safety profile of some agents and long-term effects on kidney function as primary outcomes are needed. Studies that include patients at higher risk of clinical outcomes, such as hypertension, might be better placed to indicate treatment effects.

Until then, patient and policy decisions in ADPKD are unsupported by robust study evidence.

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REFERENCES

References to studies included in this review

AIPRI Study 1996 *{published data only}*

Apperloo AJ, Rensma PL. Effect of benazepril in chronic renal insufficiency. *New England Journal of Medicine* 1996;**335**(8):596-7. [MEDLINE: 8684417]

Curren CG. Effect of benazepril in chronic renal insufficiency. *New England Journal of Medicine* 1996;**335**(8):596-7. [MEDLINE: 8684418]

Hogan TJ, Elliott WJ, Seto AH, Bakris GL. Antihypertensive treatment with and without benazepril in patients with chronic renal insufficiency: a US economic evaluation. *Pharmacoeconomics* 2002;**20**(1):37-47. [MEDLINE: 11817991]

Locatelli F, Carbarns IR, Maschio G, Mann JF, Ponticelli C, Ritz E, et al. Long-term progression of chronic renal insufficiency in the AIPRI Extension Study. The Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study Group. *Kidney International - Supplement* 1997;**63**:S63-6. [MEDLINE: 9407424]

Locatelli F, Del Vecchio L, Andrulli S, Marai P, Tentori F. The role of underlying nephropathy in the progression of renal disease. *Kidney International - Supplement* 2000;**75**:S49-55. [MEDLINE: 10828762]

Mann JF, Maschio G, Alberti D, AIPRI investigators. Perspectives of ACE inhibition in progressive renal failure [abstract]. *Nephrology* 1997;**3**(Suppl 1):S39. [CENTRAL: CN-00461248]

Maschio G, Alberti D, Janin G, Locatelli F, Mann J, Motolese M, et al. The use of benazepril in the treatment of progressive renal disease [abstract]. 13th International Congress of Nephrology; 1995 Jul 2-6; Madrid, Spain. 1995:65.

* Maschio G, Alberti D, Janin G, Locatelli F, Mann JF, Motolese F, et al. Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study Group. *New England Journal of Medicine* 1996;**334**(15):939-45. [MEDLINE: 8596594]

Maschio G, Alberti D, Locatelli F, Mann JF, Motolese M, Ponticelli C, et al. Angiotensin-converting enzyme inhibitors and kidney protection: the AIPRI trial. The ACE Inhibition in Progressive Renal Insufficiency (AIPRI) Study Group. *Journal of Cardiovascular Pharmacology* 1999;**33 Suppl 1**:S16-20. [MEDLINE: 10028949]

Maschio, G. Effect of benazepril in chronic renal insufficiency. *New England Journal of Medicine* 1996;**335**(8):596-7.

van Hout BA, Simeon GP, McDonnell J, Mann JF. Economic evaluation of benazepril in chronic renal insufficiency. *Kidney International - Supplement* 1997;**52**(Suppl 63):S159-62. [MEDLINE: 9407447]

ALADIN Study 2013 *{published data only}*

Caroli A, Perico N, Perna A, Antiga L, Brambilla P, Pisani A, et al. Effect of longacting somatostatin analogue on kidney and cyst growth in autosomal dominant polycystic kidney disease (ALADIN): a randomised, placebo-controlled, multicentre trial. *Lancet* 2013;**382**(9903):1485-95. [MEDLINE: 23972263]

Biao 1997 *{published data only}*

Biao S. Clinical observation on adult polycystic kidney disease treated with calcitriol and 'qijudihuang mixt' [abstract no: P1057]. *Nephrology* 1997;**3**(Suppl 1):S338. [CENTRAL: CN-00460393]

Cadnapaphornchai 2005 *{published data only}*

Cadnapaphornchai MA, Fick-Brosnahan GM, Duley I, Johnson AM, Strain JD, DeGroff CG, et al. Design and baseline characteristics of participants in the study of antihypertensive therapy in children and adolescents with autosomal dominant polycystic kidney disease (ADPKD). *Contemporary Clinical Trials* 2005;**26**(2):211-22. [MEDLINE: 15837441]

* Cadnapaphornchai MA, McFann K, Strain JD, Masoumi A, Schrier RW. Prospective change in renal volume and function in children with ADPKD. *Clinical Journal of the American Society of Nephrology: CJASN* 2009;**4**(4):820-9. [MEDLINE: 19346430]

Cadnapaphornchai 2005 borderline *{published data only}*

Cadnapaphornchai MA, Fick-Brosnahan GM, Duley I, Johnson AM, Strain JD, DeGroff CG, et al. Design and baseline characteristics of participants in the study of antihypertensive therapy in children and adolescents with autosomal dominant polycystic kidney disease (ADPKD). *Contemporary Clinical Trials* 2005;**26**(2):211-22. [MEDLINE: 15837441]

* Cadnapaphornchai MA, McFann K, Strain JD, Masoumi A, Schrier RW. Prospective change in renal volume and function in children with ADPKD. *Clinical Journal of the American Society of Nephrology: CJASN* 2009;**4**(4):820-9. [MEDLINE: 19346430]

Cadnapaphornchai 2005 normotensive *{published data only}*

Cadnapaphornchai MA, Fick-Brosnahan GM, Duley I, Johnson AM, Strain JD, DeGroff CG, et al. Design and baseline characteristics of participants in the study of antihypertensive therapy in children and adolescents with autosomal dominant polycystic kidney disease (ADPKD). *Contemporary Clinical Trials* 2005;**26**(2):211-22. [MEDLINE: 15837441]

* Cadnapaphornchai MA, McFann K, Strain JD, Masoumi A, Schrier RW. Prospective change in renal volume and function in children with ADPKD. *Clinical Journal of the American Society of Nephrology: CJASN* 2009;**4**(4):820-9. [MEDLINE: 19346430]

Ecder 1999 *{published data only}*

* Ecder T, Chapman AB, Brosnahan GM, Edelstein CL, Johnson AM, Schrier RW. Effect of antihypertensive therapy on renal function and urinary albumin excretion in hypertensive patients with autosomal dominant polycystic kidney disease. *American Journal of Kidney Diseases* 2000;**35**(3):427-32. [MEDLINE: 10692268]

Ecder T, Edelstein CL, Chapman AB, Johnson AM, Tison L, Gill EA, et al. Reversal of left ventricular hypertrophy with angiotensin converting enzyme inhibition in hypertensive

patients with autosomal dominant polycystic kidney disease. *Nephrology Dialysis Transplantation* 1999;**14**(5):1113-6. [MEDLINE: 10344347]

Ecder T, McFann KK, Johnson AM, Chapman CB, Edelstein CL, Tison M, et al. Reversal of left ventricular hypertrophy in autosomal dominant polycystic kidney disease (ADPKD) patients with rigorous blood pressure (BP) control [abstract]. *Journal of the American Society of Nephrology* 2001;**12**(Program & Abstracts):534A. [CENTRAL: CN-00550560]

Schrier R, McFann K, Johnson A, Chapman A, Edelstein C, Brosnahan G, et al. Cardiac and renal effects of standard versus rigorous blood pressure control in autosomal-dominant polycystic kidney disease: results of a seven-year prospective randomized study. *Journal of the American Society of Nephrology* 2002;**13**(7):1733-9. [MEDLINE: 12089368]

ELATE Study 2011 *{published data only}*

Chrispijn M, Drenth JP. Everolimus and long acting octreotide as a volume reducing treatment of polycystic livers (ELATE): study protocol for a randomized controlled trial. *Trials [Electronic Resource]* 2011;**12**:246. [MEDLINE: 22104015]

Chrispijn M, Gevers TJ, Hol JC, Monshouwer R, Dekker HM, Drenth JP. Everolimus does not further reduce polycystic liver volume when added to long acting octreotide: Results from a randomized controlled trial in polycystic liver disease patients [abstract]. *Journal of Hepatology* 2013;**58**(Suppl 2):S557-8. [EMBASE: 71055656]

* Chrispijn M, Gevers TJ, Hol JC, Monshouwer R, Dekker HM, Drenth JP. Everolimus does not further reduce polycystic liver volume when added to long acting octreotide: results from a randomized controlled trial. *Journal of Hepatology* 2013;**59**(1):153-9. [MEDLINE: 23499726]

Fassett 2010 *{published data only}*

* Fassett RG, Coombes JS, Packham D, Fairley KF, Kincaid-Smith P. Effect of pravastatin on kidney function and urinary protein excretion in autosomal dominant polycystic kidney disease. *Scandinavian Journal of Urology & Nephrology* 2010;**44**(1):56-61. [MEDLINE: 20034362]

Kincaid-Smith P, Vincent J, Fairley K. Randomised controlled trial of HMG CO A reductase inhibitor in polycystic renal disease in man [abstract no: A1733]. *Journal of the American Society of Nephrology* 1997;**8**(Program & Abstracts):375A. [CENTRAL: CN-00446097]

Higashihara 2008 *{published data only}*

Higashihara E, Nutahara K, Horie S, Muto S, Hosoya T, Hanaoka K, et al. The effect of eicosapentaenoic acid on renal function and volume in patients with ADPKD. *Nephrology Dialysis Transplantation* 2008;**23**(9):2847-52. [MEDLINE: 18372389]

Hogan 2010 *{published data only}*

Hogan M, Masyuk TV, Torres V, King BF, Kim BF, LaRusso NF. OctreotideLAR inhibits hepatorenal cystogenesis in the human polycystic liver diseases. *Hepatology* 2009;**50**(Suppl 4):328A. [EMBASE: 70073470]

Hogan MC, Masyuk TV, Page L, Holmes DR 3rd, Li X, Bergstralh EJ, et al. Somatostatin analog therapy for severe polycystic liver disease: Results after 2 years. *Nephrology Dialysis Transplantation* 2012;**27**(9):3532-9. [MEDLINE: 22773240]

* Hogan MC, Masyuk TV, Page LJ, Kubly VJ, Bergstralh EJ, Li X, et al. Randomized clinical trial of long-acting somatostatin for autosomal dominant polycystic kidney and liver disease. *Journal of the American Society of Nephrology* 2010;**21**(6):1052-61. [MEDLINE: 20431041]

LOCKCYST Study 2009 *{published data only}*

Chrispijn M, Keimpema L, Nevens F, Vanslembrouck R, Oijen MG, Hoffmann AD, et al. Growth of liver volume stops after one year of lanreotide in patients with polycystic livers. *Journal of Hepatology* 2010;**52**(Suppl 1):S31. [EMBASE: 70130918]

Chrispijn M, Nevens F, Gevers TJ, Vanslembrouck R, van Oijen MG, Coudyzer W, et al. The long-term outcome of patients with polycystic liver disease treated with lanreotide. *Alimentary Pharmacology & Therapeutics* 2012;**35**(2):266-74. [MEDLINE: 22111942]

van Keimpema L, Nevens F, Vanslembrouck R, van Oijen MG, Hoffmann AL, Dekker HM, et al. Lanreotide reduces the volume of polycystic liver: A randomized, double-blind, placebo-controlled trial [abstract]. *Hepatology* 2009;**50**(Suppl 4):328A.

* van Keimpema L, Nevens F, Vanslembrouck R, van Oijen MG, Hoffmann AL, Dekker HM, et al. Lanreotide reduces the volume of polycystic liver: a randomized, double-blind, placebo-controlled trial. *Gastroenterology* 2009;**137**(5):1661-8. [MEDLINE: 19646443]

Melemadathil 2013 *{published data only}*

Melemadathil S, Kamal M. Efficacy and safety of sirolimus in reducing cyst volume in patients with autosomal dominant polycystic kidney disease [abstract]. *Nephrology Dialysis Transplantation* 2013;**28**:i81-2. [EMBASE: 71075211]

Mora 2013 *{published data only}*

Mora FP, Codianni P, Liern M, Grammatico D, Vallejo G. Use of rapamycin to reduce the pathologic kidney volume growth in autosomal polycystic kidney disease [abstract]. *Pediatric Nephrology* 2013;**28**(8):1492. [EMBASE: 71127367]

Nakamura 2001d *{published data only}*

Nakamura T, Ushiyama C, Takahashi Y, Tanaka A, Shimada N, Ebihara I, et al. Effect of dilazep dihydrochloride on urinary albumin excretion in patients with autosomal dominant polycystic kidney disease. *Nephron* 2001;**88**(1):80-2. [MEDLINE: 11340355]

Nakamura 2001d hypertensive *{published data only}*

Nakamura T, Ushiyama C, Takahashi Y, Tanaka A, Shimada N, Ebihara I, et al. Effect of dilazep dihydrochloride on urinary albumin excretion in patients with autosomal dominant polycystic kidney disease. *Nephron* 2001;**88**(1):80-2. [MEDLINE: 11340355]

Nakamura 2001d normotensive *{published data only}*

Nakamura T, Ushiyama C, Takahashi Y, Tanaka A, Shimada N, Ebihara I, et al. Effect of dilazep dihydrochloride on urinary albumin excretion in patients with autosomal dominant polycystic kidney disease. *Nephron* 2001;**88**(1):80-2. [MEDLINE: 11340355]

Nakamura 2012a *{published data only}*

Nakamura T, Sato E, Fujiwara N, Kawagoe Y, Yamada S, Ueda Y, et al. Changes in urinary albumin excretion, inflammatory and oxidative stress markers in ADPKD patients with hypertension. *American Journal of the Medical Sciences* 2012;**343**(1):46-51. [MEDLINE: 21760473]

Nutahara 2005 *{published data only}*

Nutahara K, Higashihara E, Horie S, Kamura K, Tsuchiya K, Mochizuki T, et al. Calcium channel blocker versus angiotensin II receptor blocker in autosomal dominant polycystic kidney disease. *Nephron* 2005;**99**(1):c18-23. [MEDLINE: 15637459]

RAPYD Study 2012 *{published data only}*

Stallone G, Infante B, Bruno F, Bristogiannis C, Grandaliano G, Macarini L, et al. Rapamycin for treatment of type I autosomal dominant polycystic kidney disease (ADPKD) study: a randomized, controlled study [abstract]. *Nephrology Dialysis Transplantation* 2012;**27**(Suppl 2):ii46-7. [EMBASE: 70765435]

* Stallone G, Infante B, Grandaliano G, Bristogiannis C, Macarini L, Mezzopane D, et al. Rapamycin for treatment of type I autosomal dominant polycystic kidney disease (RAPYD-study): a randomized, controlled study. *Nephrology Dialysis Transplantation* 2012;**27**(9):3560-7. [MEDLINE: 22785114]

RAPYD Study 2012 high *{published data only}*

Stallone G, Infante B, Bruno F, Bristogiannis C, Grandaliano G, Macarini L, et al. Rapamycin for treatment of type I autosomal dominant polycystic kidney disease (ADPKD) study: a randomized, controlled study [abstract]. *Nephrology Dialysis Transplantation* 2012;**27**(Suppl 2):ii46-7. [EMBASE: 70765435]

Stallone G, Infante B, Grandaliano G, Bristogiannis C, Macarini L, Mezzopane D, et al. Rapamycin for treatment of type I autosomal dominant polycystic kidney disease (RAPYD-study): a randomized, controlled study. *Nephrology Dialysis Transplantation* 2012;**27**(9):3560-7. [MEDLINE: 22785114]

RAPYD Study 2012 low *{published data only}*

Stallone G, Infante B, Bruno F, Bristogiannis C, Grandaliano G, Macarini L, et al. Rapamycin for treatment of type I autosomal dominant polycystic kidney disease (ADPKD) study: a randomized, controlled study [abstract]. *Nephrology Dialysis Transplantation* 2012;**27**(Suppl 2):ii46-7. [EMBASE: 70765435]

Stallone G, Infante B, Grandaliano G, Bristogiannis C, Macarini L, Mezzopane D, et al. Rapamycin for treatment of type I autosomal dominant polycystic kidney disease (RAPYD-study): a randomized, controlled study. *Nephrology Dialysis Transplantation* 2012;**27**(9):3560-7. [MEDLINE: 22785114]

Ruggenenti 2005 *{published data only}*

* Caroli A, Antiga L, Cafaro M, Fasolini G, Remuzzi A, Remuzzi G, et al. Reducing polycystic liver volume in ADPKD: effects of somatostatin analogue octreotide. *Clinical Journal of the American Society of Nephrology: CJASN* 2010;**5**(5):783-9. [MEDLINE: 20185596]

Ruggenenti P, Remuzzi A, Ondei P, Fasolini G, Antiga L, Ene-Iordache B, et al. Safety and efficacy of long-acting somatostatin treatment in autosomal-dominant polycystic kidney disease. *Kidney International* 2005;**68**(1):206-16. [MEDLINE: 15954910]

SIRENA Study 2010 *{published data only}*

Perico N, Antiga L, Caroli A, Ruggenenti P, Fasolini G, Cafaro M, et al. Sirolimus therapy to halt the progression of ADPKD. *Journal of the American Society of Nephrology* 2010;**21**(6):1031-40. [MEDLINE: 20466742]

Soliman 2009 *{published data only}*

* Soliman A, Zamil S, Lotfy A, Ismail E. Sirolimus produced S-shaped effect on adult polycystic kidneys after 2-year treatment. *Transplantation Proceedings* 2012;**44**(10):2936–9. [MEDLINE: 23195001]

Soliman AR, Ismail E. Sirolimus therapy for patients with adult polycystic kidney disease - a pilot study [abstract no: TH-PO053]. *Journal of the American Society of Nephrology* 2008;**19**(Abstracts Issue):123A. [CENTRAL: CN-00716073]

Soliman AR, Ismail E, Zamil S, Lotfy A. Sirolimus therapy for patients with adult polycystic kidney disease: a pilot study. *Transplantation Proceedings* 2009;**41**(9):3639–41. [MEDLINE: 19917358]

SUISSE ADPKD Study 2007 *{published data only}*

Braun M, Young J, Reiner CS, Poster D, Krauer F, Kistler AD, et al. Low-dose oral sirolimus and the risk of menstrual-cycle disturbances and ovarian cysts: analysis of the randomized controlled SUISSE ADPKD Trial. *PLoS ONE [Electronic Resource]* 2012;**7**(10):e45868. [MEDLINE: 23071528]

Braun M, Young J, Reiner CS, Poster D, Wuthrich RP, Serra AL. Ovarian toxicity from sirolimus. *New England Journal of Medicine* 2012;**366**(11):1062-4. [MEDLINE: 22417271]

Serra A, Poster D, Kistler AD, Krauer F, Raina F, Voneckardstein A, et al. Safety, tolerability and adherence of sirolimus in autosomal dominant polycystic kidney disease [abstract no: 2.5]. *Swiss Medical Weekly* 2008;**138**(Suppl 167):4S.

Serra AL, Kistler AD, Poster D, Krauer F, Senn O, Raina S, et al. Safety and tolerability of sirolimus treatment in patients with autosomal dominant polycystic kidney disease. *Nephrology Dialysis Transplantation* 2009;**24**(11):3334-42. [MEDLINE: 19525519]

Serra AL, Kistler AD, Poster D, Struker M, Wuthrich RP, Weishaupt D, et al. Clinical proof-of-concept trial to assess the therapeutic effect of sirolimus in patients with autosomal dominant polycystic kidney disease: SUISSE ADPKD study. *BMC Nephrology* 2007;**8**:13. [MEDLINE: 17868472]

* Serra AL, Poster D, Kistler AD, Krauer F, Raina S, Young J, et al. Sirolimus and kidney growth in autosomal dominant

polycystic kidney disease. *New England Journal of Medicine* 2010;**363**(9):820-9. [MEDLINE: 20581391]

Serra AL, Poster D, Kistler AD, Wuthrich RP. Interim analysis of efficacy, safety and tolerability of sirolimus in patients with autosomal dominant polycystic kidney disease (ADPKD) [abstract no: SA064]. World Congress of Nephrology; 2009 May 22-26; Milan, Italy. 2009.

Temmerman 2012 *{published data only}*

Temmerman F, Vanslembrouck R, Coudyzer W, Bammens B, Laleman W, Cassiman D, et al. The reduction in liver volume in polycystic liver disease with lanreotide is dose dependent and is most pronounced in patients with the highest liver volume [abstract]. *Journal of Hepatology* 2012;**56**:S547. [EMBASE: 70749518]

TEMPO 248 & 249 2005 *{published data only}*

* Chapman AB, Torres VE, Grantham JJ, Shoaf SS, Ouyang JJ, Czerwiec FS. A phase IIB pilot study of the safety and efficacy of tolvaptan, a vasopressin V2 receptor antagonist (V2RA), in patients with ADPKD [abstract no: F-FC139]. *Journal of the American Society of Nephrology* 2005;**16**:68A. [CENTRAL: CN-00653783]

Grantham JJ, Chapman AB, Torres VE, Ouyang JJ, Shoaf SE, Czerwiec FS. Acute and chronic osmostasis after vasopressin V2 receptor inhibition with tolvaptan in ADPKD [abstract no: F-PO106]. *Journal of the American Society of Nephrology* 2005;**16**(October):361A. [CENTRAL: CN-00653784]

Torres VE, Wang X, Ward CJ, Grantham JJ, Chapman AB, Ouyang JJ, et al. Urine aquaporin 2 and cyclic AMP responses to tolvaptan administration in autosomal dominant polycystic kidney disease [abstract no: F-PO108]. *Journal of the American Society of Nephrology* 2005;**16**(October):361A. [CENTRAL: CN-00653785]

TEMPO 250 2011 *{published data only}*

Higashihara E, Torres VE, Chapman AB, Grantham JJ, Bae K, Watnick TJ, et al. Tolvaptan in autosomal dominant polycystic kidney disease: three years' experience. *Clinical Journal of The American Society of Nephrology: CJASN* 2011;**6**(10):2499-507. [MEDLINE: 21903984]

* Torres VE, Grantham JJ, Chapman AB, Watnick T, Kedzierski K, Ouyang JJ, et al. Phase 2 open-label study to determine safety, tolerability and efficacy of split-dose tolvaptan in ADPKD [abstract no: SA-PO077]. *Journal of the American Society of Nephrology* 2007;**18**:361A-2A. [CENTRAL: CN-00653786]

TEMPO 3-4 Study 2011 *{published data only}*

Devuyst O, Chapman AB, Gansevoort RT, Grantham JJ, Higashihara E, Perrone RD, et al. Urine osmolality and outcome in ADPKD: Results from the TEMPO 3:4 trial [abstract]. *Nephrology Dialysis Transplantation* 2014;**29**(Suppl 3):iii6. [EMBASE: 71491481]

* Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Grantham JJ, Higashihara E, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *New England Journal of Medicine* 2012;**367**(25):2407-18. [MEDLINE: 23121377]

Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Higashihara E, Perrone RD, et al. Tolvaptan-treatment of ADPKD confers persistent EGFR improvement: Results from the TEMPO 4:4 extension trial [abstract]. *Nephrology Dialysis Transplantation* 2014;**29**(Suppl 3):iii6. [EMBASE: 71491483]

Torres VE, Meijer E, Bae KT, Chapman AB, Devuyst O, Gansevoort RT, et al. Rationale and design of the TEMPO (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and its Outcomes) 3-4 Study. *American Journal of Kidney Diseases* 2011;**57**(5):692-9. [MEDLINE: 21333426]

Ulusoy 2010 *{published data only}*

Ulusoy S, Ozkan G, Orem C, Kaynar K, Kosucu P, Kiris A. A comparison of the effects of ramipril and losartan on blood pressure control and left ventricle hypertrophy in patients with autosomal dominant polycystic kidney disease. *Renal Failure* 2010;**32**(8):913-7. [MEDLINE: 20722556]

van Dijk 2001 *{published data only}*

van Dijk MA, Kamper AM, van Veen S, Souverijn JH, Blauw GJ. Effect of simvastatin on renal function in autosomal dominant polycystic kidney disease. *Nephrology Dialysis Transplantation* 2001;**16**(11):2152-7. [MEDLINE: 11682660]

van Dijk 2003 *{published data only}*

van Dijk MA, Breuning MH, Duiser R, van Es LA, Westendorp RG. No effect of enalapril on progression in autosomal dominant polycystic kidney disease. *Nephrology Dialysis Transplantation* 2003;**18**(11):2314-20. [MEDLINE: 14551359]

Walz 2010 *{published data only}*

Walz G, Budde K, Mannaa M, Nurnberger J, Wanner C, Sommerer C, et al. Everolimus in patients with autosomal dominant polycystic kidney disease. *New England Journal of Medicine* 2010;**363**(9):830-40. [MEDLINE: 20581392]

Watson 1999 *{published data only}*

Watson ML, Macnicol AM, Borg-Costanzi J, Vareesanghip K, Chauveau D, Cohen G, et al. A long-term comparison of the effects of renal function of BP control with either atenolol (A) or enalapril (E) in polycystic kidney disease (PKD) [abstract]. *Journal of the American Society of Nephrology* 1999;**10**(Program & Abstracts):428A.

Zeltner 2008 *{published data only}*

Mueller H, Schmieder RE, Zeltner R, Poliak R, Graf S, Schulze BD. Determinants for the treatment of hypertensive patients with autosomal dominant polycystic kidney disease (ADPKD): choice of drug versus blood pressure (BP) control [abstract]. *Journal of the American Society of Nephrology* 2003;**14**(Nov):109A. [CENTRAL: CN-00653777]

* Zeltner R, Poliak R, Stiasny B, Schmieder RE, Schulze BD. Renal and cardiac effects of antihypertensive treatment with ramipril vs metoprolol in autosomal dominant polycystic kidney disease. *Nephrology Dialysis Transplantation* 2008;**23**(2):573-9. [MEDLINE: 17984104]

References to studies excluded from this review

Doulton 2006 *{published data only}*

Doulton TW, Saggar-Malik AK, He FJ, Carney C, Markandu ND, Sagnella GA, et al. The effect of sodium and angiotensin-converting enzyme inhibition on the classic circulating renin-angiotensin system in autosomal-dominant polycystic kidney disease patients. *Journal of Hypertension* 2006;**24**(5):939-45. [MEDLINE: 16612257]

ISRCTN57653760 *{published data only}*

O'Shaugnessy K. A rotation study through the main therapeutic classes of antihypertensive in patients with polycystic kidney disease and hypertension. controlled-trials.com/ISRCTN57653760 (accessed 1 June 2015).

Kanno 1996 *{published data only}*

Kanno Y, Suzuki H, Okada H, Takenaka T, Saruta T. Calcium channel blockers versus ACE inhibitors as antihypertensives in polycystic kidney disease. *Qjm* 1996;**89**(1):65-70. [MEDLINE: 8730344]

Suzuki H, Kanno Y, Okada H, Konishi K, Nakazato Y, Okamiya Y, et al. Renal protective effects of calcium channel blocker on hypertensive patients with autosomal dominant polycystic kidney disease [abstract]. *Journal of the American Society of Nephrology* 1994;**5**(3):568.

Nakamura 2005a *{published data only}*

Nakamura T, Sugaya T, Kawagoe Y, Ueda Y, Osada S, Koide H. Candesartan reduces urinary fatty acid-binding protein excretion in patients with autosomal dominant polycystic kidney disease. *American Journal of the Medical Sciences* 2005;**330**(4):161-5. [MEDLINE: 16234607]

Sharma 2004 *{published data only}*

Sharma RK, Kohli R, Rathore D, Gupta A, Gupta RK. Magnetic resonance based studies as a marker of disease progression in autosomal-dominant polycystic kidney disease and the effect of simvastatin on disease progression [abstract]. *Indian Journal of Nephrology* 2004;**14**:126.

References to studies awaiting assessment

Braun 2014 *{published data only}*

Braun WE, Schold JD, Stephany BR, Spirko RA, Herts BR. Low-dose rapamycin (sirolimus) effects in autosomal dominant polycystic kidney disease: an open-label randomized controlled pilot study. *Clinical Journal of the American Society of Nephrology: CJASN* 2014;**9**(5):881-8. [MEDLINE: 24721888]

Cadnapaphornchai 2011 *{published data only}*

Cadnapaphornchai MA, George DM, Masoumi A, McFann K, Strain JD, Schrier RW. Effect of statin therapy on disease progression in pediatric ADPKD: design and baseline characteristics of participants. *Contemporary Clinical Trials* 2011;**32**(3):437-45. [MEDLINE: 21266204]

Cadnapaphornchai MA, George DM, McFann K, Wang W, Gitomer B, Strain JD, et al. Effect of pravastatin on total kidney volume, left ventricular mass index, and microalbuminuria in pediatric autosomal dominant polycystic kidney disease. *Clinical Journal of the American Society of Nephrology: CJASN* 2014;**9**(5):889-96. [MEDLINE: 24721893]

HALT-PKD Study 2008 *{published data only}*

Chapman AB. Approaches to testing new treatments in autosomal dominant polycystic kidney disease: insights from the CRISP and HALT-PKD studies. *Clinical Journal of The American Society of Nephrology: CJASN* 2008;**3**(4):1197-204. [MEDLINE: 18579674]

Chapman AB, Torres VE, Perrone RD, Steinman TI, Bae KT, Philip MJ, et al. The HALT polycystic kidney disease trials: design and implementation. *Clinical Journal of The American Society of Nephrology: CJASN* 2010;**5**(1):102-9. [MEDLINE: 20089507]

Miskulin D, Chapman A, Steinman T, Schrier R, Torres V, Perrone R, et al. Impact of autosomal dominant polycystic kidney disease on quality of life: results from the HALT-PKD study [abstract no: TH-PO052]. *Journal of the American Society of Nephrology* 2008;**19**(Abstracts Issue):123A. [CENTRAL: CN-00756923]

Miskulin DC, Abebe KZ, Chapman AB, Perrone RD, Steinman TI, Torres VE, et al. Health-related quality of life in patients with autosomal dominant polycystic kidney disease and CKD stages 1-4: a cross-sectional study. *American Journal of Kidney Diseases* 2014;**63**(2):214-26. [MEDLINE: 24183837]

Perrone RD, Abebe KZ, Schrier RW, Chapman AB, Torres VE, Bost J, et al. Cardiac magnetic resonance assessment of left ventricular mass in autosomal dominant polycystic kidney disease. *Clinical Journal of The American Society of Nephrology: CJASN* 2011;**6**(10):2508-15. [MEDLINE: 21903983]

Rahbari-Oskoui FF, Miskulin DC, Hogan MC, Fielder O, Torres VE, Bost JE, et al. Short-term reproducibility of ambulatory blood pressure monitoring in autosomal dominant polycystic kidney disease. *Blood Pressure Monitoring* 2011;**16**(2):47-54. [MEDLINE: 21415814]

Schrier R, Torres V, Chapman A, Perrone R, Miller JP, Meyers C, et al. Design of the HALT-PKD studies [abstract no: F-PO105]. *Journal of the American Society of Nephrology* 2005;**16**:361A. [CENTRAL: CN-00792560]

Schrier RW, Abebe KZ, Perrone RD, Torres VE, Braun WE, Steinman TI, et al. Blood pressure in early autosomal dominant polycystic kidney disease. *New England Journal of Medicine* 2014;**371**(24):2255-66. [MEDLINE: 25399733]

Steinman TI, Schrier RW, Torres VE, Chapman AB, Perrone RD, Grantham JJ, et al. The HALT-PKD trials: selection of novel endpoints and study update [abstract no: PUB023]. *Journal of the American Society of Nephrology* 2007;**18**(Abstracts Issue):837A. [CENTRAL: CN-00691816]

Torres VE, Abebe KZ, Chapman AB, Schrier RW, Braun WE, Steinman TI, et al. Angiotensin blockade in late autosomal dominant polycystic kidney disease. *New England Journal of Medicine* 2014;**371**(24):2267-76. [MEDLINE: 25399731]

Torres VE, Chapman AB, Perrone RD, Bae KT, Abebe KZ, Bost JE, et al. Analysis of baseline parameters in the HALT polycystic

kidney disease trials. *Kidney International* 2012;**81**(6):577-85. [MEDLINE: 22205355]

Torres VE, Schrier RW, Chapman AB, Perrone RD, Miskulin D, Steinman T, et al. Achievement and maintenance of blood pressure targets in HALT-PKD [abstract no: TH-PO051]. *Journal of the American Society of Nephrology* 2008;**19**(Abstracts Issue):123A. [CENTRAL: CN-00755104]

NCT01233869 *{published data only}*

NCT01233869. A phase 2, multicenter, randomized, double-blind, placebo-controlled study of the safety, clinical activity and pharmacokinetics of bosutinib (PF-05208763) versus placebo in subjects with autosomal dominant polycystic kidney disease (ADPKD). www.clinicaltrials.gov/ct2/show/NCT01233869 2014. [MEDLINE: 9407447]

Vienna RAP Study 2015 *{published data only}*

Riegersperger M, Herkner H, Sunder-Plassmann G. Pulsed oral sirolimus in advanced autosomal-dominant polycystic kidney disease (Vienna RAP Study): study protocol for a randomized controlled trial. *Trials* 2015;**16**(1):182. [MEDLINE: 25899445]

References to ongoing studies

DIPAK 1 Study 2014 *{published data only}*

Meijer E, Drenth JP, d'Agnolo H, Casteleijn NF, de Fijter JW, Gevers TJ, et al. Rationale and design of the DIPAK 1 Study: a randomized controlled clinical trial assessing the efficacy of lanreotide to halt disease progression in autosomal dominant polycystic kidney disease. *American Journal of Kidney Diseases* 2014;**63**(3):446-55. [MEDLINE: 24342522]

NCT00345137 *{published data only}*

NCT00345137. Phase 1 study of systemic effects of Ng-monomethyl-L-arginine on renal hemodynamics in patients with polycystic kidney disease and chronic glomerulonephritis. www.clinicaltrials.gov/ct2/show/NCT00345137 (accessed 1 June 2015).

NCT01932450 *{published data only}*

NCT01932450. A randomized, open-label study investigating the effect of bilateral renal artery sympathetic denervation by catheter-based radiofrequency ablation on blood pressure and disease progression in autosomal dominant polycystic kidney disease. www.clinicaltrials.gov/ct2/show/NCT01932450 2013. [CENTRAL: CN-00874871]

Additional references

Chang 2012

Chang MY, Ong AC. Mechanism-based therapeutics for autosomal dominant polycystic kidney disease: recent progress and future prospects. *Nephron Clinical Practice* 2012;**120**(1):c25-34. [MEDLINE: 22205396]

Ecder 2013

Ecder T. Cardiovascular complications in autosomal dominant polycystic kidney disease. *Current Hypertension Reviews* 2013;**9**(1):2-11. [MEDLINE: 23971638]

ERA-EDTA 2011

ERA-EDTA Registry. ERA-EDTA Registry Annual Report 2011. Academic Medical Center, Department of Medical Informatics, Amsterdam, The Netherlands, 2011. www.era-edta-reg.org/files/annualreports/pdf/AnnRep2011.pdf (accessed 1 June 2015).

Gattone 2003

Gattone VH 2nd, Wang X, Harris PC, Torres VE. Inhibition of renal cystic disease development and progression by a vasopressin V2 receptor antagonist. *Nature Medicine* 2003;**9**(10):1323–6. [MEDLINE: 14502283]

Gile 1995

Gile RD, Cowley BD Jr, Gattone VH 2nd, O'Donnell MP, Swan SK, Grantham JJ. Effect of lovastatin on the development of polycystic kidney disease in the Han:SPRD rat. *American Journal of Kidney Diseases* 1995;**26**(3):501-7. [MEDLINE: 7645559]

Grantham 2006

Grantham JJ, Torres VE, Chapman AB, Guay-Woodford LM, Bae KT, King BF Jr, et al. Volume progression in polycystic kidney disease. *New England Journal of Medicine* 2006;**354**(20):2122–30. [MEDLINE: 16707749]

Grantham 2008

Grantham JJ, Cook LT, Torres VE, Bost JE, Chapman AB, Harris PC, et al. Determinants of renal volume in autosomal-dominant polycystic kidney disease. *Kidney International* 2008;**73**(1):108–16. [MEDLINE: 17960141]

Grantham 2011

Grantham JJ, Bennett WM, Perrone RD. mTOR inhibitors and autosomal dominant polycystic kidney disease. *New England Journal of Medicine* 2011;**364**(3):286-7. [MEDLINE: 21247328]

Hanaoka 2000

Hanaoka K, Guggino W. cAMP regulates cell proliferation and cyst formation in autosomal polycystic kidney disease cells. *Journal of the American Society of Nephrology* 2000;**11**(7):1179-87. [MEDLINE: 10864573]

Harris 2009

Harris PC, Torres VE. Polycystic kidney disease. *Annual Review of Medicine* 2009;**60**:321-37. [MEDLINE: 18947299]

Helai 2012

Helal I, Reed B, Schrier RW. Emergent early markers of renal progression in autosomal-dominant polycystic kidney disease patients: implications for prevention and treatment. *American Journal of Nephrology* 2012;**36**(2):162-7. [MEDLINE: 22846584]

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60. [MEDLINE: 12958120]

Higgins 2011

Higgins JP, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated

March 2011]. The Cochrane Collaboration, 2011. www.cochrane-handbook.org.

Masyuk 2007

Masyuk TV, Masyuk AI, Torres VE, Harris PC, Larusso NF. Octreotide inhibits hepatic cystogenesis in a rodent model of polycystic liver disease by reducing cholangiocyte adenosine 3',5'-cyclic monophosphate. *Gastroenterology* 2007;**132**(3):1104-16. [MEDLINE: 17383431]

Nagao 2006

Nagao S, Nishii K, Katsuyama M, Kurahashi H, Marunouchi T, Takahashi H, et al. Increased water intake decreases progression of polycystic kidney disease in the PCK rat. *Journal of the American Society of Nephrology* 2006;**17**(8):2220-7. [MEDLINE: 16807403]

Ogborn 2000

Ogborn MR, Nitschmann E, Weiler HA, Bankovic-Calic N. Modification of polycystic kidney disease and fatty acid status by soy protein diet. *Kidney International* 2000;**57**(1):159-66. [MEDLINE: 10620197]

Qian 2008

Qian Q, Du H, King BF, Kumar S, Dean PG, Cosio FG, et al. Sirolimus reduces polycystic liver volume in ADPKD patients. *Journal of the American Society of Nephrology* 2008;**19**(3):631-8. [MEDLINE: 18199797]

Rule 2006

Rule AD, Torres VE, Chapman AB, Grantham JJ, Guay-Woodford LM, Bae KT, et al. Comparison of methods for determining renal function decline in early autosomal dominant polycystic kidney disease: the consortium of radiologic imaging studies of polycystic kidney disease cohort. *Journal of the American Society of Nephrology* 2006;**17**(3):854-62. [MEDLINE: 16452494]

Schrier 2009

Schrier RW. Renal volume, renin-angiotensin-aldosterone system, hypertension, and left ventricular hypertrophy in patients with autosomal dominant polycystic kidney disease. *Journal of the American Society of Nephrology* 2009;**20**(9):1888-93. [MEDLINE: 19696226]

Torres 2007

Torres VE, Harris PC, Pirson Y. Autosomal dominant polycystic kidney disease. *Lancet* 2007;**369**(9569):1287-301. [MEDLINE: 17434405]

Torres 2009

Torres VE, Harris PC. Autosomal dominant polycystic kidney disease: the last 3 years. *Kidney International* 2009;**76**(2):149-68. [MEDLINE: 19455193]

Torres 2012

Torres VE, Chapman AB, Perrone RD, Bae KT, Abebe KZ, Bost JE, et al. Analysis of baseline parameters in the HALT polycystic kidney disease trials. *Kidney International* 2012;**81**(6):577-85. [MEDLINE: 22205355]

USRDS 2008

Table A.1.7 Incident counts of reported ESRD: all patients by age, gender, race, ethnicity, & primary diagnosis. IN: US Renal Data Services. Table A.1, Incident counts of reported ESRD: all patients. www.usrds.org/2008/ref/A_incidence_08.pdf (accessed 1 June 2015).

Wahl 2006

Wahl PR, Serra AL, Le Hir M, Molle KD, Hall MN, Wüthrich RP. Inhibition of mTOR with sirolimus slows disease progression in Han:SPRD rats with autosomal dominant polycystic kidney disease (ADPKD). *Nephrology Dialysis Transplantation* 2006;**21**(3):598-604. [MEDLINE: 16221708]

Wu 2007

Wu M, Wahl PR, Le Hir M, Wackerle-Men Y, Wüthrich RP, Serra AL. Everolimus retards cyst growth and preserves kidney function in a rodent model for polycystic kidney disease. *Kidney & Blood Pressure Research* 2007;**30**(4):253-9. [MEDLINE: 17596700]

Wüthrich 2009

Wüthrich RP, Serra AL, Kistler AD. Autosomal dominant polycystic kidney disease: new treatment options and how to test their efficacy. *Kidney & Blood Pressure Research* 2009;**32**(5):380-7. [MEDLINE: 19887826]

References to other published versions of this review

Bolignano 2013

Bolignano D, Ruospo M, Zoccali C, Craig JC, Strippoli GF. Interventions for preventing the progression of autosomal dominant polycystic kidney disease. *Cochrane Database of Systematic Reviews* 2013, Issue 1. [DOI: 10.1002/14651858.CD010294]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

AIPRI Study 1996

Methods	• Study design: parallel, double-blind RCT • Duration of study: January 1989 to December 1990 • Follow-up: 3 years • ADPKD assessment: unclear

AIPRI Study 1996 *(Continued)*

Participants	• Countries: Italy, France, Germany • Setting: international multicentre study (49 centres) • Patients with 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 • Number: treatment group (300); control group (283) (64 diagnosed with ADPKD) • Mean age ± SD (years): treatment group (51± 13); control group (51 ± 12) • Sex (M/F): treatment group (220/80); control group (201/82) • 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
Interventions	Treatment group • Benazepril: 10 mg/d Control group • Placebo Duration of intervention • 3 years
Outcomes	• Doubling SCr concentration • SCr • UPE • DBP
Notes	• Separate data on ADPKD patients were not provided • 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	Low risk	Double blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	"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"

AIPRI Study 1996 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

ALADIN Study 2013

Methods	• Study design**:** RCT, single-blind, placebo controlled RCT • Duration of study: 27 April 2006 to 12 May 2008 • Follow-up: 3 years • ADPKD assessment: magnetic nuclear imaging
Participants	• Country: Italy • Setting: multicentre (5) • Age > 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 • Number: treatment group (40); control group (39) • Mean age ± SD (years): treatment group (36 ± 8); control group (38 ± 8) • Sex (M/F): treatment group (17/23); control group (20/190 • 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 child bearing potential and ineffective contraception (oestrogen therapy in postmenopausal women not stopped)
Interventions	Treatment group • Long-acting somatostatin: 40 mg every 28 days Control group • Placebo: saline solution Duration of intervention • 3 years
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	• 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

ALADIN Study 2013 *(Continued)*

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"

Biao 1997

Methods	• Study design: parallel RCT • Duration of study: not reported • Follow-up: 3 months • ADPKD assessment: Echo
Participants	• Country: China • Setting: not reported • Inclusion criteria: not reported • Number: treatment group (18); control group (16) • Mean age ± SD (years): treatment group (36 ± 8); control group (38 ± 8) • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • Calcitriol: 0.25 to 1.0 µg/d Control group • Qijudihuang mix: 10 mL/d Duration of intervention • 3 months
Outcomes	• Creatinine • GFR
Notes	• Abstract-only publication

Biao 1997 *(Continued)*

- 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

Cadnapaphornchai 2005

Methods	• Study design: parallel RCT • Duration of study: commenced 1998 • Follow-up: 60 months • ADPKD assessment: Echo
Participants	• Country: USA • Setting: single centre, national recruitment • Patients aged 4 to 21 years; normal kidney function • Number: treatment group (45); control group (40) • Mean age ± SD (years): treatment group (11 ± 5); control group (12 ± 5) • Sex (M/F): treatment group (29/16); control group (17/23) • Exclusion criteria: past history of allergy to study medications or inability to comply with the study protocol
Interventions	Treatment group • Enalapril: 0.6 to 40 mg/kg/d Control group • Standard therapy Duration of intervention

Cadnapaphornchai 2005 *(Continued)*

	• 60 months
Outcomes	• BP • Kidney volume • eGFR • LVMI • Albuminuria
Notes	• 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"

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

Methods	• Study design: parallel RCT • Duration of study: commenced 1998 • Follow-up: 60 months • ADPKD assessment: Echo
Participants	• Country: USA • Setting: single centre, national recruitment • Patients aged 4 to 21 years; normal kidney function; borderline hypertension • Number: treatment group (15); control group (12) • Mean age ± SD (years): treatment group (11 ± 5); control group (12 ± 3) • Sex (M/F): treatment group (10/5); control group (5/7)

Cadnapaphornchai 2005 borderline *(Continued)*

	• Exclusion criteria: Past history of allergy to study medications or inability to comply with the study protocol
Interventions	Treatment group • Enalapril: 0.6 to 40 mg/kg/d Control group • Standard therapy Duration of intervention • 60 months
Outcomes	• BP • Kidney volume • eGFR • LVMI • Albuminuria
Notes	• 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"

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 normotensive

Methods	• Study design: parallel RCT • Duration of study: commenced 1998

Cadnapaphornchai 2005 normotensive *(Continued)*

- Follow-up: 60 months
- ADPKD assessment: Echo

Participants	• Country: USA • Setting: single centre, national recruitment • Patients aged 4 to 21 years; normal kidney function; normal BP • Number: treatment group (16); control group (15) • Mean age ± SD (years): treatment group (12 ± 5); control group (12 ± 5) • Sex (M/F): treatment group (9/7); control group (5/10) • Exclusion criteria: past history of allergy to study medications or inability to comply with the study protocol
Interventions	Treatment group • Enalapril: 0.6 to 40 mg/kg/d Control group • Standard therapy Duration of intervention • 60 months
Outcomes	• BP • Kidney volume • eGFR • LVMI • Albuminuria
Notes	• 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"

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

Cadnapaphornchai 2005 normotensive *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Ecder 1999

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

ELATE Study 2011

Methods	• Study design: parallel, open-label RCT • Duration of study: June 2010 to July 2012 • Follow-up: 48 weeks • ADPKD assessment: CT scan
Participants	• Country: Netherlands • Setting: single centre • Patients with symptomatic PLD due to ADPKD or autosomal dominant PLD; aged 18 to 70 years; severe PLD (liver volume > 2500 mL); written informed consent • Number: treatment group (21); control group (23) ○ Patients affected by ADPKD: 15/44 (34%) • Mean age ± SD (years): treatment group (11 ± 5); control group (12 ± 5) • Sex (M/F): treatment group (2/19); control group (3/20) • 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
Interventions	Treatment group • Octreotide: 40 mg (IM) every 4 weeks • Everolimus: 2.5 mg daily Control group • Octreotide: 40 mg (IM) every 4 weeks Duration of intervention • 48 weeks
Outcomes	• Total liver volume • Kidney volume • Quality of life (EuroQoL EQ-5D questionnaire) • Adverse events
Notes	• Separate data on ADPKD patients were available only for kidney volumes • Funding source: Novartis provided the drug everolimus and partially funded the study

ELATE Study 2011 *(Continued)*

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	"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 PP analyses on the primary outcome measure
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Low risk	"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

Methods	• Study design: parallel, open-label RCT • Duration of study: not reported • Follow-up: 24 months • ADPKD assessment: Echo
Participants	• Country: Australia • Setting: multicentre • Patients with Echo diagnosis of ADPKD • Number: treatment group (29); control group (20) • Mean age ± SD (years): treatment group (53 ± 15); control group (49 ± 12) • Sex (M/F): treatment group (12/17); control group (8/12) • Exclusion criteria: participation into other studies
Interventions	Treatment group • Pravastatin: 20 mg/d Control group • Standard therapy Duration of intervention

Fassett 2010 *(Continued)*

	• 24 months
Outcomes	• eGFR • UPE
Notes	• 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	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

Higashihara 2008

Methods	• Study design: parallel, open-label RCT • Duration of study: not reported • Follow-up: 24 months • ADPKD assessment: CT scan
Participants	• Country: Japan • Setting: multicentre • Patients aged 18 to 60 years; clinical and image diagnosis of ADPKD • Number: treatment group (21); control group (20) • Mean age ± SD (years): treatment group (47 ± 11); control group (47 ± 12) • Sex (M/F): treatment group (15/6); control group (14/6) • 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
Interventions	Treatment group • Eicosapentaenoic acid-ethyl ester: 2.4 g/d

Higashihara 2008 *(Continued)*

	Control group • Standard therapy Duration of intervention • 24 months
Outcomes	• Kidney volumes • Fatty acid composition of the total phospholipid fraction of erythrocytes • Plasma cholesterol • Triglycerides • CrCl • UAE
Notes	• 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	"...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	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	High risk	Sponsored by Mochida Pharmaceutical Co. Ltd

Hogan 2010

Methods	• Study design: parallel, double-blind RCT • Duration of study: not reported • Follow-up: 1 year (plus 1 year open-label extension with all patients switched to octreotide) • ADPKD assessment: CT scan or Magnetic nuclear imaging
Participants	• Country: USA • Setting: single centre

Hogan 2010 *(Continued)*

	• 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) • Number: treatment group (28); control group (14) • Mean age ± SD (years): treatment group (50 ± 9); control group (50 ± 7) • Sex (M/F): treatment group (5/23); control group (1/13) • 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
Interventions	Treatment group • Octreotide: 40 mg every 28 ± 5 days Control group • Placebo Duration of intervention • 1 year
Outcomes	• Kidney volume • Kidney function • Quality of life • Safety
Notes	• 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 quality of life and safety • Funding source: "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	"Randomization assignment to octreotide or matching placebo treatment was independently managed by the research pharmacy"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias)	High risk	All patients completed the study but 13 were excluded from kidney outcomes (volume and function) assessment

Hogan 2010 *(Continued)*

All outcomes

Selective reporting (reporting bias)	Low risk	All defined outcomes were reported
Other bias	High risk	Novartis supported the study

LOCKCYST Study 2009

Methods	• Study design: parallel, double-blind RCT • Duration of study: October 2007 to February 2008 • Follow-up: 24 weeks • ADPKD assessment: CT scan
Participants	• Country: Netherlands and Belgium • Setting: international • 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 polycystic liver disease • Number: treatment group (27); control group (27) ○ Affected by ADPKD: 32/54 (59%) • Mean age, range (years): treatment group (50, 34 to 65); control group (50, 33 to 68) • Sex (M/F): treatment group (3/24); control group (4/23) • Exclusion criteria: use of oral contraceptives or oestrogen supplementation; pregnancy or breastfeeding; symptomatic gallstones; HD; history of severe illnesses
Interventions	Treatment group • Lanreotide: 120 mg/d every 28 days Control group • Placebo Duration of intervention • 24 weeks
Outcomes	• Liver volume • Kidney volume • Abdominal symptoms • Health-related quality of life (SF-36) • Type and severity of gastrointestinal symptoms
Notes	• 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
Random sequence generation (selection bias)	Low risk	Computer-generated random number list

LOCKCYST Study 2009 *(Continued)*

Allocation concealment (selection bias)	Low risk	"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
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"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	Unclear risk	Analyses were performed on an ITT basis. Unclear whether all the 32 ADPKD patients completed the established follow-up
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

Methods	• Study design: parallel, open-label RCT • Duration of study: not reported • Follow-up: 1 year • ADPKD assessment: magnetic nuclear imaging
Participants	• Country: India • Setting: not reported • ADPKD type 1 after genetic typing; aged 18 to 60 years; GFR > 40 mL/min/1.73 m^2; proteinuria < 0.5 g/24 h; informed consent • Number: treatment group (40); control group (20) • Mean age ± SD (years): not reported • Sex (M/F): not reported • 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
Interventions	Treatment group • Sirolimus: 2 mg/d Control group • Standard treatment Duration of intervention • 6 months extended to 1 year
Outcomes	• Kidney volume • Cyst volume

Melemadathil 2013 *(Continued)*

	• Parenchymal volume • Proteinuria and other laboratory data • Adverse events
Notes	• 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

Methods	• Study design: parallel RCT • Follow-up: 2 years • ADPKD assessment: magnetic nuclear imaging
Participants	• Country: Argentina • Setting: single centre • Patients with ADPKD diagnosis; eGFR > 60 mL/min/1.73 m^2; negative pregnancy test • Number: treatment group (6); control group (6) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: leukopenia (white cells/mm^3 < 4000); hepatic or systemic disease; coagulation disorders; malignancy
Interventions	Treatment group • Rapamycin: 2 mg/m^2/d Control group

Mora 2013 *(Continued)*

	• Standard therapy Duration of intervention • 24 months
Outcomes	• Kidney volume • eGFR • Proteinuria
Notes	• 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) 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

Methods	• Study design: parallel, double-blind RCT • Duration of study: not reported • Follow-up: 6 months • ADPKD assessment: unclear
Participants	• Country: Japan • Setting: single centre • Normo- or hypertensive ADPKD patients with microalbuminuria • Number: treatment group (11); control group (11) • Mean age ± SD (years): not reported • Sex (M/F): not reported

Nakamura 2001d *(Continued)*

	• Exclusion criteria: creatinine > 1.5 mg/dL and/or eGFR < 70 mL/min
Interventions	Treatment group • Dilazep dihydrochloride: 300 mg/d Control group • Placebo Duration of intervention • 6 months
Outcomes	• UPE • BP • Kidney function
Notes	• 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
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

Methods	• Study design: parallel, double-blind RCT • Duration of study: not reported • Follow-up: 6 months • ADPKD assessment: unclear
Participants	• Country: Japan

Nakamura 2001d hypertensive *(Continued)*

- Setting: single centre
- Hypertensive ADPKD patients with microalbuminuria
- Number: treatment group (5); control group (5)
- Mean age: 52.2 years
- Sex (M/F): 2/8
- Exclusion criteria: creatinine > 1.5 mg/dL and/or eGFR < 70 mL/min

Interventions	Treatment group • Dilazep dihydrochloride: 300 mg/d Control group • Placebo Duration of intervention • 6 months
Outcomes	• UPE • BP • Kidney function
Notes	• 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
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 normotensive

Methods	• Study design: parallel, double-blind RCT

Nakamura 2001d normotensive *(Continued)*

- Duration of study: not reported
- Follow-up: 6 months
- ADPKD assessment: unclear

Participants	• Country: Japan • Setting: single centre • Normotensive ADPKD patients with microalbuminuria • Number: treatment group (6); control group (6) • Mean age: 46.6 years • Sex (M/F): 4/8 • Exclusion criteria: creatinine > 1.5 mg/dL and/or eGFR < 70 mL/min
Interventions	Treatment group • Dilazep dihydrochloride: 300 mg/d Control group • Placebo Duration of intervention • 6 months
Outcomes	• UPE • BP • Kidney function
Notes	• 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
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 2012a

Methods	• Study design: parallel, double-blind RCT • Duration of study: not reported • Follow-up: 12 months • ADPKD assessment: Echo
Participants	• Country: Japan • Setting: single centre • ADPKD; good kidney function; microalbuminuria; hypertension (BP > 140/90 mm Hg) • Number: treatment group (10); control group (10) • Mean age ± SD (years): treatment group (57 ± 6); control group (58 ± 6) • Sex (M/F): treatment group (6/4); control group (5/5) • 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
Interventions	Treatment group • Telmisartan: 80 mg/d Control group • Enalapril: 10 mg/d Duration of intervention • 12 months
Outcomes	• BP • UAE • inflammatory stress markers
Notes	• 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
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

Nakamura 2012a *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Nutahara 2005

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

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"...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

Nutahara 2005 *(Continued)*

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

RAPYD Study 2012

Methods	• Study design: parallel, open-label RCT • Duration of study: November 2007 to November 2008 • Follow-up: 24 months • ADPKD assessment: magnetic nuclear imaging
Participants	• Country: Italy • Setting: multicentre (2) • Clinical, genetic and ultrasonographic diagnosis of type I ADPKD; aged 18 to 65 years; eGFR (MDRD) 40 to 80 mL/min/1.73 m^2 ○ Genetic details: All PKD1 • Number: treatment group 1 (19); treatment group 2 (18); control group 18 • Mean age ± SD (years): treatment group 1 (43 ± 6); treatment group 2 (42 ± 11); control group (45 ± 7) • Sex (M/F): treatment group 1 (6/13); treatment group 2 (6/12); control group (9/9) • 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, with the exception of adequately treated basal and squamous cell carcinomas of the skin; HIV-positive test

Interventions	Treatment 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
	Treatment 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	• Cyst growth • Kidney function

RAPYD Study 2012 *(Continued)*

	• Mean atrial pressure • Proteinuria • Safety
Notes	• 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
Other bias	High risk	Sponsored by Wyeth and Pfizer

RAPYD Study 2012 high

Methods	• Study design: parallel, open-label RCT • Duration of study: November 2007 to November 2008 • Follow-up: 24 months • ADPKD assessment: magnetic nuclear imaging
Participants	• Country: Italy • Setting: multicentre (2) • Clinical, genetic and ultrasonographic diagnosis of type I ADPKD; aged 18 to 65 years; eGFR (MDRD) 40 to 80 mL/min/1.73 m^2 ○ Genetic details: All PKD1 • Number: treatment group 1 (19); treatment group 2 (18); control group 18 • Mean age ± SD (years): treatment group 1 (43 ± 6); treatment group 2 (42 ± 11); control group (45 ± 7) • Sex (M/F): treatment group 1 (6/13); treatment group 2 (6/12); control group (9/9) • 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

RAPYD Study 2012 high *(Continued)*

	the study; clinical evidence of any malignancy within 3 years before enrolment, with the exception of adequately treated basal and squamous cell carcinomas of the skin; HIV-positive test

Interventions	Treatment 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
	Treatment 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	• Cyst growth • Kidney function • Mean atrial pressure • Proteinuria • Safety
Notes	• 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 using random number tables
Allocation concealment (selection bias)	Low risk	Block randomisation and 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 were analysed on ITT basis
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	High risk	Sponsored by Wyeth and Pfizer

RAPYD Study 2012 low

Methods	• Study design: parallel, open-label RCT • Duration of study: November 2007 to November 2008 • Follow-up: 24 months • ADPKD assessment: magnetic nuclear imaging
Participants	• Country: Italy • Setting: multicentre (2) • Clinical, genetic and ultrasonographic diagnosis of type I ADPKD; aged 18 to 65 years; eGFR (MDRD) 40 to 80 mL/min/1.73 m^2 ○ Genetic details: All PKD1 • Number: treatment group 1 (19); treatment group 2 (18); control group 18 • Mean age ± SD (years): treatment group 1 (43 ± 6); treatment group 2 (42 ± 11); control group (45 ± 7) • Sex (M/F): treatment group 1 (6/13); treatment group 2 (6/12); control group (9/9) • 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, with the exception of adequately treated basal and squamous cell carcinomas of the skin; HIV-positive test

Interventions	Treatment 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
	Treatment 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	• Cyst growth • Kidney function • Mean atrial pressure • Proteinuria • Safety
Notes	• 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 using random number tables

RAPYD Study 2012 low *(Continued)*

Allocation concealment (selection bias)	Low risk	Block randomisation and 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
Other bias	High risk	Sponsored by Wyeth and Pfizer

Ruggenenti 2005

Methods	• Study design: double-blind, cross-over RCT • Duration of study: not reported • Follow-up: 6 months • ADPKD assessment: clinical and echographic
Participants	• Country: Italy • Setting: single centre • Patients aged ≥ 18 years; clinical and echographic diagnosis of ADPKD; SCr < 3.0 mg/dL, but > 1.2 mg/dL (males) or > 1.0 mg/dL (females) ○ Genetic details: PKD 1 and 2 • Number: 6 • Mean age (range): 44 years (35 to 58) • Sex (M/F): 9/3 • 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
Interventions	Treatment group • Long-acting octreotide: 40 mg IM every 28 days Control group • Placebo Duration of intervention • 6 months
Outcomes	• Kidney and cyst volume

Ruggenenti 2005 *(Continued)*

	• Kidney function • UAE • BP
Notes	• 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
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

SIRENA Study 2010

Methods	• Study design: cross-over RCT • Duration of study: not reported • Follow-up: 6 months • ADPKD assessment: CT scan
Participants	• Country: Italy • Setting: single centre • Patients aged > 18 years; clinical and ultrasonographic diagnosis of ADPKD; eGFR > 40 mL/min/1.73 m^2 • Number: treatment group (7); control group (8) • Mean age (range): 39.1 years (28 to 46) • Sex (M/F): 12/3 • Exclusion criteria: concomitant systemic renal parenchymal (proteinuria > 1 g/24 h); urinary tract disease; DM; cancer; psychiatric disorders
Interventions	Treatment group • Sirolimus: starting dose 3 mg/d (drug levels to be maintained 5 to 10 ng/mL) Control group

SIRENA Study 2010 *(Continued)*

	• Standard therapy Duration of intervention • 6 months
Outcomes	• Kidney volume • Cyst volume • BP • mGFR • Albuminuria • Proteinuria
Notes	• 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	"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	High risk	Wyeth-Lederle S.p.A. supplied the study drug

Soliman 2009

Methods	• Study design: parallel, single blind RCT • Duration of study: not reported • Follow-up: 24 months • ADPKD assessment: magnetic nuclear imaging
Participants	• Country: Egypt • Setting: single centre • Patients aged 30 to 50 years; SCr < 2 mg/dL or GFR > 30 mL/min/1.73 m^2 (MDRD); UPE < 0.5 g/24 h; clinical and ultrasound diagnosis of ADPKD, documented kidney volume progression

Soliman 2009 *(Continued)*

- Number: treatment group (8); control group (8)
- Mean age, range (years): treatment group (40, 32 to 50); control group (41, 30 to 49)
- Sex (M/F): treatment group (7/1); control group (6/2)
- 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

Interventions	Treatment group • Sirolimus: 1 mg/d • Telmisartan: dosage not reported Control group • Telmisartan; dosage not reported Duration of intervention • 24 months
Outcomes	• Kidney volume • Kidney function • Adverse events • BP
Notes	• 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
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"...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

Soliman 2009 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

SUISSE ADPKD Study 2007

Methods	• Study design: parallel, open-label RCT • Duration of study: March 2006 to March 2010 • Follow-up: 18 months • ADPKD assessment: magnetic nuclear imaging
Participants	• Country: Switzerland • Setting: single centre • Patients aged 18 to 40 years; eGFR (Cockcroft-Gault) > 70 mL/min • Number: treatment group (50); control group (50) • Mean age ± SD (years): treatment group (31 ± 7); control group (32 ± 6) • Sex (M/F): treatment group 29/21; control group 32/18 • 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
Interventions	Treatment group • Sirolimus: target dose 2 mg/d Control group • Standard therapy Duration of intervention • 18 months
Outcomes	• Kidney volumes • Kidney function • Albuminuria • BP • Adverse events
Notes	• 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

SUISSE ADPKD Study 2007 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Each observer was unaware of all clinical data and the findings of the other observer, and the measurements were performed in random order"
Incomplete outcome data (attrition bias) All outcomes	Low risk	4/100 (4%) patients withdrew. These patients were analysed on ITT basis
Selective reporting (reporting bias)	Low risk	All defined outcomes were reported
Other bias	Low risk	"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"

Temmerman 2012

Methods	• Study design: RCT • Duration of study: not reported • Follow-up: 6 months • ADPKD assessment: CT scan
Participants	• Country: Belgium, Netherlands • Setting: international, multicentre • Inclusion criteria: not reported • Number (ADPKD/total): 56/69 • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • Lanreotide: 120 mg every 4 weeks Control group • Placebo Duration of intervention • 6 months
Outcomes	• Kidney function
Notes	• Abstract-only publication • Separate data in ADPKD were not available

Risk of bias

Bias	Authors' judgement	Support for judgement

Temmerman 2012 *(Continued)*

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

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

TEMPO 248 & 249 2005 *(Continued)*

Notes	• 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
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	High risk	Sponsored by Otsuka pharmaceutical

TEMPO 250 2011

Methods	• Study design: RCT • Duration of study: not reported • Follow-up: 36 months • ADPKD assessment: magnetic Nuclear Imaging
Participants	• Country: USA • Setting: multicentre • Patients aged > 18 years; fulfilled ADPKD Ravine's diagnostic criteria; prior participation in a phase 1 tolvaptan ADPKD trial; willingness to adhere to contraceptive precautions • Number: treatment group 1 (22); treatment group 2 (24) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: inability to comply with study procedures; eGFR < 30 mL/min/1.73 m^2; anticipation of RRT within 1 year; active treatment that would affect endpoint measures (e.g. diuretics)
Interventions	Treatment group 1 • Tolvaptan: 45/15 mg split dose per day Treatment group 2 • Tolvaptan: 60/30 mg split dose per day

TEMPO 250 2011 *(Continued)*

	Duration of intervention • 16 months

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

Notes	• 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	High risk	Sponsored by Otsuka pharmaceutical

TEMPO 3-4 Study 2011

Methods	• Study design: parallel, double blind RCT • Duration of study: January 2007 to January 2009 • Follow-up: 36 months • ADPKD assessment:**m**agnetic nuclear imaging
Participants	• Country: International • Setting: multicentre (129) • ADPKD patients aged 18 to 50 years; total kidney volume ≥ 750 mL (magnetic nuclear imaging); eGFR ≥ 60 mL/min (Cockcroft–Gault formula) • Number: treatment group (961); control group (484)

TEMPO 3-4 Study 2011 *(Continued)*

- Mean age ± SD (years): treatment group (39 ± 7); control group (39 ± 7)
- Sex (M/F): treatment group (495/466); control group (251/233)
- 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 interference 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

Interventions	Treatment group • Tolvaptan: 60 to 120 mg/d Control group • Placebo Duration of intervention • 36 months
Outcomes	• Kidney volume • Kidney function • Kidney pain • BP
Notes	• 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
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
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
Other bias	High risk	Supported by Otsuka Pharmaceuticals and Otsuka Pharmaceutical Development and Commercialization

Ulusoy 2010

Methods	• Study design: parallel RCT • Duration of study: not reported • Follow-up: 12 months • ADPKD assessment: Echo
Participants	• Country: Turkey • Setting: single centre • Stage 1–2 hypertensive ADPKD patients (according to the JNC VII classification); eGFR > 30 mL/min/1.73 m^2; aged 18 to 70 years • Number: treatment group (19); control group (13) • Mean age ± SD (years): treatment group (51 ± 10); control group (48 ± 13) • Sex (M/F): treatment group (6/13); control group (7/6) • 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
Interventions	Treatment group • Losartan: 50 to 100 mg/d Control group • Ramipril: 2.5 to 10 mg/d Duration of intervention • 12 months
Outcomes	• BP • LVMI • Kidney function
Notes	• 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

Ulusoy 2010 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

van Dijk 2001

Methods	• Study design: double-blind, cross-over RCT • Duration of study: not reported • Follow-up: 4 weeks • ADPKD assessment: Echo
Participants	• Country: Netherlands • Setting: single centre • Patients with GFR > 50 mL/min; no medications; normal sodium diet • Number: 10 • Mean age ± SD: 35 ± 13 years • Sex (M/F): 6/4 • Exclusion criteria: not reported
Interventions	Treatment group • Simvastatin: 40 mg/d Control group • Placebo Duration of intervention • 4 weeks
Outcomes	• Kidney blood flow • Vascular reactivity • Kidney function • Cholesterol
Notes	• 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

van Dijk 2001 *(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

van Dijk 2003

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
Participants	• Country: Netherlands • Setting: multicentre • ADPKD patients aged 18 to 70 years; SCr < 225 mmol/L • Number: treatment group (45); control group (44) • Mean age ± SD (years): normotensive treatment group (36 ± 2); normotensive control group (37 ± 2); hypertensive treatment group (40 ± 3); hypertensive control group (33 ± 3) • Sex (M/F): treatment group (16/29); control group (19/25) • 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
Interventions	Treatment 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	• BP • Measured kidney function (by inulin clearance)
Notes	• 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

van Dijk 2003 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"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
Incomplete outcome data (attrition bias) All outcomes	High 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	High risk	"Enalapril and placebo were provided by Merck, Sharp and Dohme"

Walz 2010

Methods	• Study design: parallel, double-blind RCT • Duration of study: December 2006 to September 2007 • Follow-up: 24 months • ADPKD assessment: magnetic nuclear imaging
Participants	• Country: Germany • Setting: multicentre (24) • Clinical diagnosis of both ADPKD and CKD stage 2 or 3 or CKD stage 1; estimated single kidney volume > 1000 mL • Number: treatment group (213); control group (216) • Mean age ± SD (years): treatment group (44 ± 10); control group (44 ± 10) • Sex (M/F): treatment group (109/104); control group (100/116) • 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
Interventions	Treatment group • Everolimus: 2.5 mg twice daily Control group • Placebo Duration of intervention • 24 months
Outcomes	• Kidney volume • Cyst volume

Walz 2010 *(Continued)*

	• Parenchymal volume • Kidney function • Urinary protein excretion • BP • Safety • Mortality
Notes	• 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) All outcomes	Low risk	Double-blind
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	High risk	"Data collection and management were the responsibility of the sponsor"

Watson 1999

Methods	• Study design: parallel RCT • Duration of study: not reported • Follow-up: 36 months • ADPKD assessment: Echo
Participants	• Country: UK • Setting: not reported • Inclusion criteria: not reported • Number (overall): 54 • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported

Watson 1999 *(Continued)*

Interventions	Treatment group • Atenolol: dosage not reported Control group • Enalapril: dosage not reported Duration of intervention • 36 months
Outcomes	• BP • Kidney function
Notes	• 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

Methods	• Study design: parallel, double-blind RCT • Duration of study: 1998 to 2000 • Follow-up: 36 months • ADPKD assessment: Echo
Participants	• Country: Germany • Setting: single centre

Zeltner 2008 *(Continued)*

- Confirmed diagnosis of ADPKD; aged 18 to 65 years; hypertension (casual BP ≥ 140/90 mm Hg and/or presence of an antihypertensive medication); SCr ≤ 4.0 mg/dL
- Number: treatment group (17); control group (20)
- Mean age ± SD (years): treatment group (41 ± 22); control group (41 ± 19)
- Sex (M/F): treatment group (10/7); control group (7/13)
- 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

Interventions	Treatment group • Ramipril: 2.5 to 5 mg/d Control group • Metoprolol: 50 to 100 mg/d Duration of intervention • 36 months
Outcomes	• Combined endpoint of doubling SCr, 50% reduction in GFR, or the need for RRT • SCr • UPE • LVMI
Notes	• 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	"This research was supported by Astra-Zeneca who provided the study medication"

ACEi - angiotensin-converting enzyme inhibitor; ADPKD - autosomal dominant polycystic kidney disease; AST - aminotransferase; AVP - arginine vasopressin; BP - blood pressure; CHF - congestive heart failure; CrCl - creatinine clearance; CVA - cerebrovascular accident; DBP - DBP; DM - diabetes mellitus; ESKD - end-stage kidney disease; eGFR - estimated glomerular filtration rate; GFR - glomerular filtration rate; HD - haemodialysis; IHD - Ischaemic heart disease; IM - intramuscular; ITT - intention-to-treat; LVMI - left ventricular mass index; M/F - male/female; MDRD - Modification of Diet in Renal Disease; mGFR - measured glomerular filtration rate; MI - myocardial infarction; magnetic nuclear imaging - magnetic resonance imaging; mTOR - mammalian target of rapamycin; NSAID - nonsteroidal anti-inflammatory drug; NYHA - New York Heart Association; PLD - polycystic liver disease; PP - per protocol; PVD - peripheral vascular disease; RCT - randomised control trial; RRT - renal replacement therapy; SBP - systolic blood pressure; SCr - serum creatinine; SD - standard deviation; UAE - urinary albumin excretion; UPE - urinary protein excretion

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

Study	Reason for exclusion
Doulton 2006	Outcome not relevant
ISRCTN57653760	Halted in 2008 due to lack of funding; no results published
Kanno 1996	Not RCT
Nakamura 2005a	Wrong outcome
Sharma 2004	Not RCT

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

Braun 2014

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Cadnapaphornchai 2011

Methods	• Country: USA • Study design: double-blinded, placebo controlled, phase III RCT • Follow-up: 5 years • ADPKD assessment: magnetic nuclear imaging
Participants	• 107 children and young adults with ADPKD • Inclusion criteria: ADPKD; aged 8 to 22 years; eGFR (Schwartz formula) > 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 study regimen
Interventions	Treatment group • Pravastatin

Cadnapaphornchai 2011 *(Continued)*

	Control group • Placebo Duration of intervention • 3 years Co-interventions • ACEi (lisinopril)
Outcomes	Combined endpoint of 20% or greater change in: • Total kidney volume • LVMI • UAE Overall change in: • Total kidney volume • LVMI • UAE
Notes	

HALT-PKD Study 2008

Methods	• Country: multicentre • Study design: 2 parallel studies (study A and B); double-blinded, placebo controlled RCT • Follow-up: 4 to 8 years • ADPKD assessment: magnetic nuclear imaging

Participants	• 1018 hypertensive ADPKD patients
	• Inclusion criteria: hypertension of normal BP
	  ◦ Study A: aged 15 to 49 years; GFR > 60 ml/min/1.73 m^2 (MDRD)
	  ◦ Study B: aged 18 to 64 years; GFR 25 to 60 mL/min/1.73 m^2 (MDRD)
	• Exclusion criteria: documented kidney vascular disease; ACR 0.5 (study A) or 1.0 (study B); 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

Interventions	Study A • 548 participants • randomised to one of four arms in a 2-by-2 design ◦ ACEi + ARB therapy versus ACEi alone at two levels of BP control Study B • 470 participants • ACEi + ARB therapy versus ACEi alone, with BP control of 120 to 130/70 to 80 mm Hg

HALT-PKD Study 2008 *(Continued)*

	Co-interventions • Other antihypertensive treatments
Outcomes	Study A • Primary outcome: percent change in kidney volume as assessed by magnetic nuclear imaging at baseline 24 and 48 months • Secondary outcomes: rate of change of albuminuria and 24-h urinary excretion of aldosterone; frequency of all-cause hospitalisations, hospitalisations because of cardiovascular events; quality of life; pain; frequency of PKD-related symptoms; adverse effects of study medications; rate of change in GFR; kidney blood flow; left ventricular mass by magnetic nuclear imaging Study B • Primary outcome: composite endpoint of time to either 50% reduction of baseline eGFR, ESKD (initiation of dialysis or pre-emptive transplant), or death • Secondary outcomes: rate of change of albuminuria and 24-h urinary excretion of aldosterone; frequency of all-cause hospitalisations, hospitalisations because of cardiovascular events; quality of life; pain; frequency of PKD-related symptoms; adverse effects of study medications
Notes	

NCT01233869

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Vienna RAP Study 2015

Methods	
Participants	
Interventions	
Outcomes	
Notes	

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

DIPAK 1 Study 2014

Trial name or title	Study of lanreotide to treat polycystic kidney disease (DIPAK1)

DIPAK 1 Study 2014 *(Continued)*

Methods	• Country: multicentre • Study design: open-label phase 3 RCT • Follow-up: 33 months • ADPKD assessment: unclear
Participants	• 300 subjects • Diagnosed with ADPKD (modified Ravine criteria), based on the revised Ravine criteria, with advanced disease and high likelihood of rapid disease progression (eGFR between 30 and 60 mL/min/1.73 m^2 and aged between 18 and 60 years)
Interventions	Treatment group • Lanreotide: 120 mg (SC) every 28 days Control group • Standard care
Outcomes	• Change in rate of kidney function decline • Change in kidney volume growth • Quality of life • Tolerance
Starting date	June 2012
Contact information	Dr Esther Meijer, Dr Ron Gansevoort; University Medical Centre Groningen, Netherlands
Notes	This study is ongoing, but not recruiting participants

NCT00345137

Trial name or title	Effects of systemic NO-inhibition on renal hemodynamics in patients with polycystic kidney disease and chronic glomerulonephritis
Methods	• Country: Denmark • Study design: single blinded, cross-over, phase 1 RCT • Follow-up: not reported • ADPKD assessment: not reported

Participants	• 75 patients with adult polycystic kidney disease and chronic glomerulonephritides. The results were compared with a group of healthy control subjects
	• Inclusion criteria
	  ◦ Healthy controls: aged 20 to 60 years; both men and women; weight < 100 kg; normal clinical examination and laboratory screening; fertile women only if using contraception; informed consent according to the regulations of the local etic committee
	  ◦ 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
	  ◦ Healthy controls: history or clinical evidence of diseases of the heart and blood vessels, kidneys, liver and pancreas, endocrine organs, lungs, neoplastic disease, myocardial infarction or cerebrovascular insult as evaluated by clinical examination and laboratory screening; current medication; drugs or alcohol abuse; pregnancy; previously within one year received more than 0.2 m SV radioactive treatment or diagnostic substances; donation of blood less than 1 month before the experiments

NCT00345137 *(Continued)*

- Adult polycystic kidney disease: apart from APKD and hypertension no 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

Interventions	Treatment group • Ng-monomethyl-L-arginine Control • Placebo
Outcomes	• Kidney haemodynamics • Kidney sodium excretion and lithium clearance • BP and heart rate • plasma levels of vasoactive hormones
Starting date	2006
Contact information	Prof Erling B Pedersen, Dept. of Medicine, Holstebro Hospital, 7500 Holstebro, Denmark
Notes	This study is ongoing, but not recruiting participants

NCT01932450

Trial name or title	
Methods	
Participants	
Interventions	
Outcomes	
Starting date	
Contact information	
Notes	This study is currently recruiting patients

ACEi - angiotensin-converting enzyme inhibitors; ACR - albumin creatinine ratio; ADPKD - autosomal dominant polycystic kidney disease; ARB - angiotensin receptor blocker; BP - blood pressure; eGFR - estimated glomerular filtration rate; LVMI - left ventricular mass index; MI - myocardial infarction; NSAID - nonsteroidal anti-inflammatory drug; RCT - randomised controlled trial; SCR - serum creatinine; UAE - urinary albumin excretion

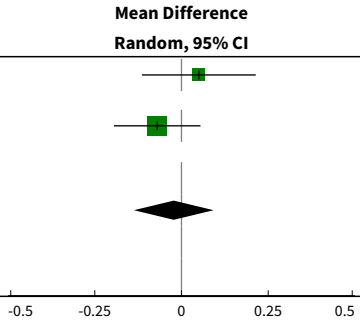
DATA AND ANALYSES

Comparison 1. ACEi versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serum creatinine	2	42	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.14, 0.09]
2 GFR [mL/min/1.73 m^2]	3	103	Mean Difference (IV, Random, 95% CI)	-3.41 [-15.83, 9.01]
3 Doubling of serum creatinine	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Total kidney volume	2	42	Mean Difference (IV, Random, 95% CI)	-42.50 [-115.68, 30.67]
5 Albuminuria	3	103	Std. Mean Difference (IV, Random, 95% CI)	-0.12 [-0.51, 0.26]
6 Systolic blood pressure	2	42	Mean Difference (IV, Random, 95% CI)	-5.44 [-14.26, 3.38]
7 Diastolic blood pressure	2	42	Mean Difference (IV, Random, 95% CI)	-4.96 [-8.88, -1.04]
8 Mean arterial pressure	1	61	Mean Difference (IV, Random, 95% CI)	-5.0 [-6.29, -3.71]

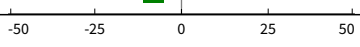
Analysis 1.1. Comparison 1 ACEi versus no treatment, Outcome 1 Serum creatinine.

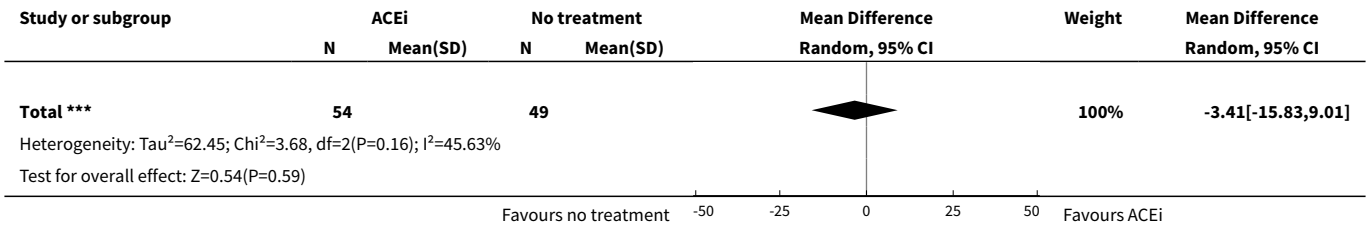
Study or subgroup	ACEi N	ACEi Mean(SD)	No treatment N	No treatment Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Cadnapaphornchai 2005 normotensive	13	0.7 (0.1)	12	0.7 (0.3)		39.74%	0.05[-0.11,0.21]
Cadnapaphornchai 2005 borderline	9	0.7 (0.1)	8	0.8 (0.1)		60.26%	-0.07[-0.19,0.05]
Total ***	**22**		**20**			**100%**	**-0.02[-0.14,0.09]**
Heterogeneity: Tau^2=0; Chi^2=1.3, df=1(P=0.25); I^2=23.22%							
Test for overall effect: Z=0.38(P=0.7)							



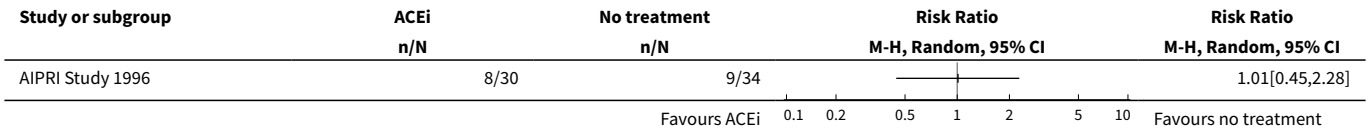
Analysis 1.2. Comparison 1 ACEi versus no treatment, Outcome 2 GFR [mL/min/1.73 m^2].

Study or subgroup	ACEi N	ACEi Mean(SD)	No treatment N	No treatment Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Cadnapaphornchai 2005 normotensive	13	127 (19.6)	12	136 (49)		13.74%	-9[-38.7,20.7]
Cadnapaphornchai 2005 borderline	9	126 (21)	8	114 (21.6)		23.64%	12[-8.3,32.3]
van Dijk 2003	32	97 (5)	29	105 (5)		62.62%	-8[-10.51,-5.49]

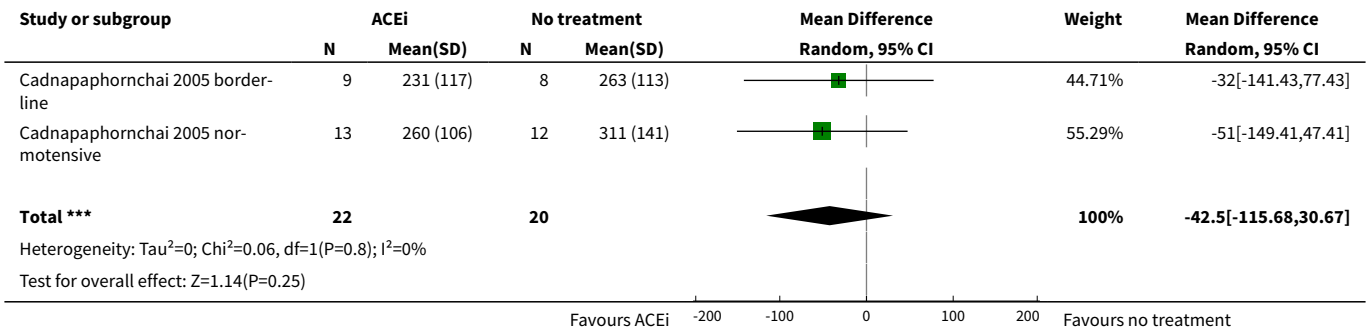




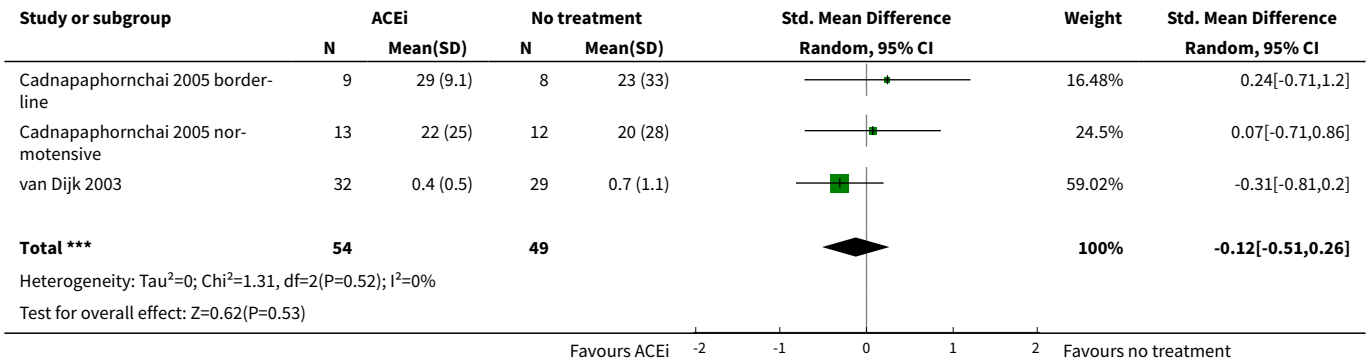
Analysis 1.3. Comparison 1 ACEi versus no treatment, Outcome 3 Doubling of serum creatinine.



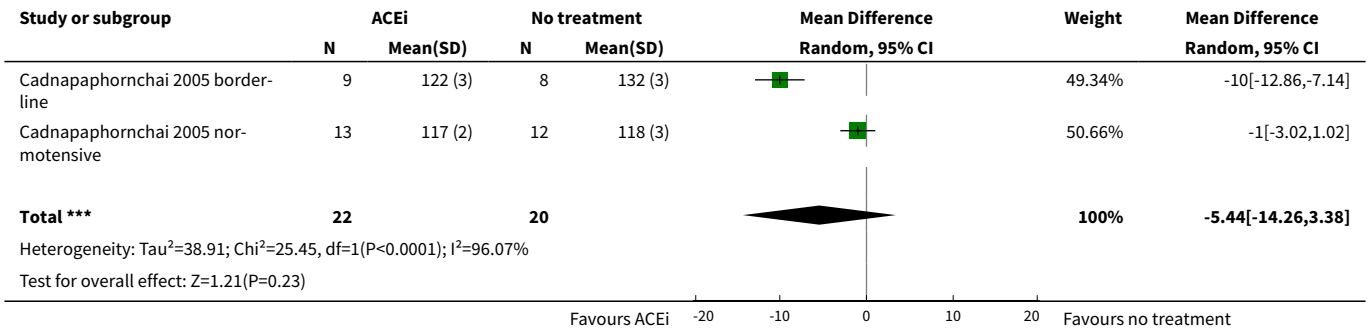
Analysis 1.4. Comparison 1 ACEi versus no treatment, Outcome 4 Total kidney volume.



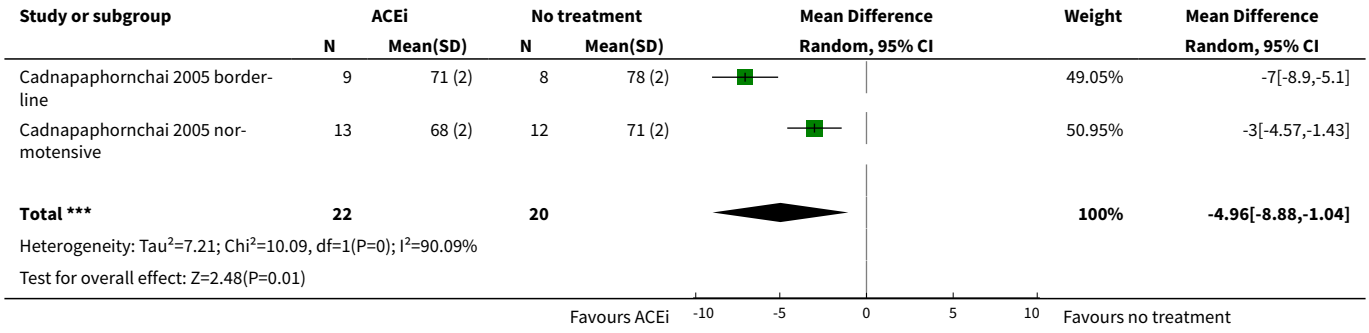
Analysis 1.5. Comparison 1 ACEi versus no treatment, Outcome 5 Albuminuria.



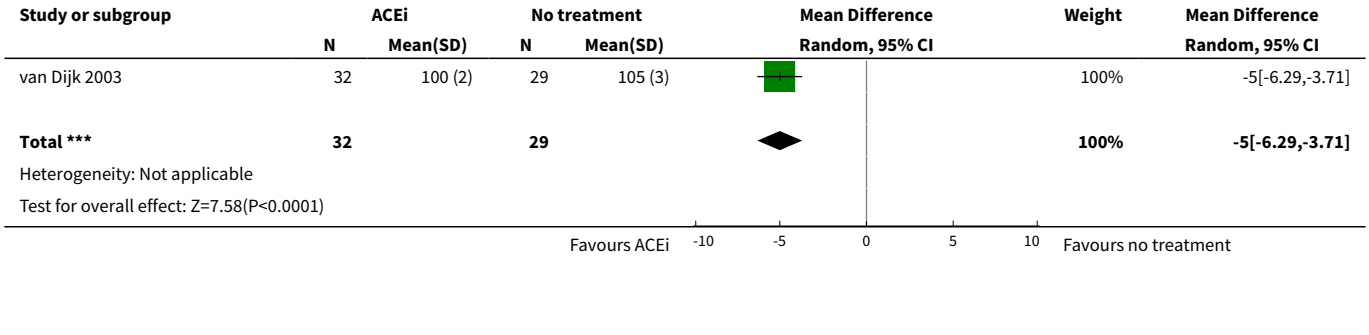
Analysis 1.6. Comparison 1 ACEi versus no treatment, Outcome 6 Systolic blood pressure.



Analysis 1.7. Comparison 1 ACEi versus no treatment, Outcome 7 Diastolic blood pressure.



Analysis 1.8. Comparison 1 ACEi versus no treatment, Outcome 8 Mean arterial pressure.



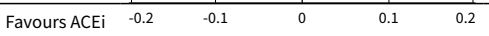
Comparison 2. ACEi versus CCB

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Creatinine	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 GFR [mL/min/1.73 m^2]	1	24	Mean Difference (IV, Random, 95% CI)	-13.00 [-17.56, -8.44]
3 Albuminuria	1	24	Mean Difference (IV, Random, 95% CI)	-134.0 [-176.01, -91.99]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Systolic blood pressure	1	24	Mean Difference (IV, Random, 95% CI)	-5.0 [-8.62, -1.38]
5 Diastolic blood pressure	1	24	Mean Difference (IV, Random, 95% CI)	-3.0 [-5.40, -0.60]
6 Mean arterial pressure	1	24	Mean Difference (IV, Random, 95% CI)	-3.0 [-5.40, -0.60]

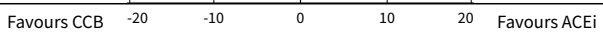
Analysis 2.1. Comparison 2 ACEi versus CCB, Outcome 1 Creatinine.

Study or subgroup	ACEi N	ACEi Mean(SD)	CCB N	CCB Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Ecder 1999	12	1.6 (0.1)	12	1.6 (0.2)		0.01[-0.1,0.12]



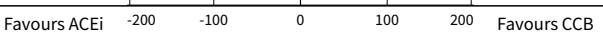
Analysis 2.2. Comparison 2 ACEi versus CCB, Outcome 2 GFR [mL/min/1.73 m^2].

Study or subgroup	ACEi N	ACEi Mean(SD)	CCB N	CCB Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Ecder 1999	12	56 (4)	12	69 (7)		100%	-13[-17.56,-8.44]
Total ***	**12**		**12**			**100%**	**-13[-17.56,-8.44]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%							
Test for overall effect: Z=5.59(P<0.0001)							



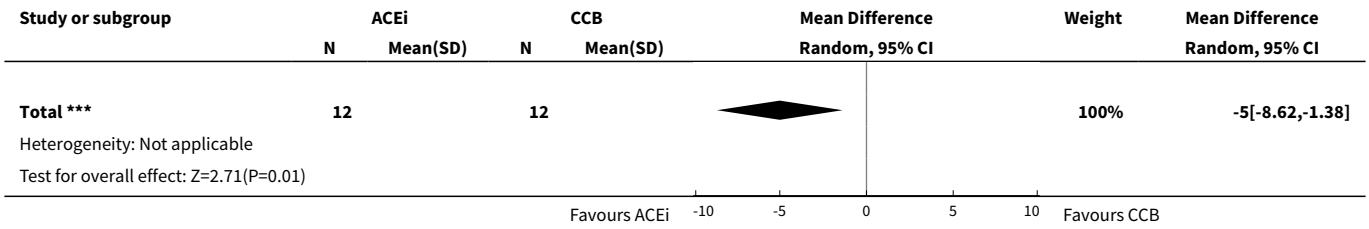
Analysis 2.3. Comparison 2 ACEi versus CCB, Outcome 3 Albuminuria.

Study or subgroup	ACEi N	ACEi Mean(SD)	CCB N	CCB Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Ecder 1999	12	14 (6)	12	148 (74)		100%	-134[-176.01,-91.99]
Total ***	**12**		**12**			**100%**	**-134[-176.01,-91.99]**
Heterogeneity: Not applicable							
Test for overall effect: Z=6.25(P<0.0001)							

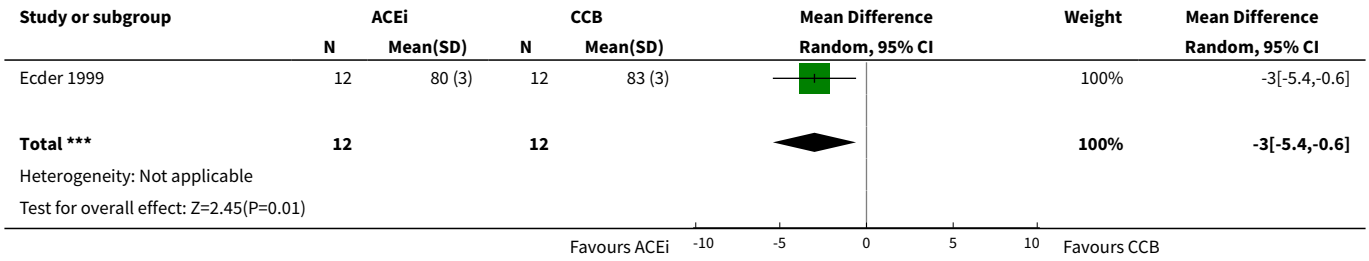


Analysis 2.4. Comparison 2 ACEi versus CCB, Outcome 4 Systolic blood pressure.

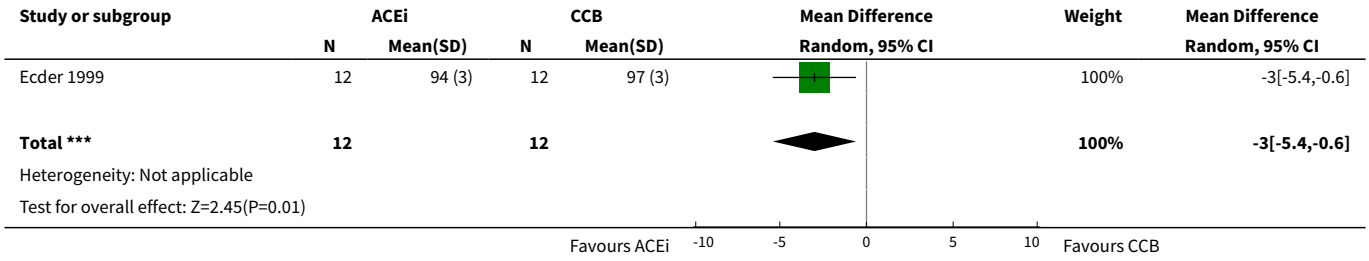
Study or subgroup	ACEi N	ACEi Mean(SD)	CCB N	CCB Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Ecder 1999	12	122 (5)	12	127 (4)		100%	-5[-8.62,-1.38]



Analysis 2.5. Comparison 2 ACEi versus CCB, Outcome 5 Diastolic blood pressure.



Analysis 2.6. Comparison 2 ACEi versus CCB, Outcome 6 Mean arterial pressure.

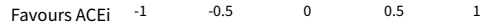


Comparison 3. ACEi versus ARB

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serum creatinine	2	52	Mean Difference (IV, Random, 95% CI)	0.00 [-0.09, 0.10]
2 GFR [mL/min/1.73 m^2]	1	32	Mean Difference (IV, Random, 95% CI)	-3.40 [-22.69, 15.89]
3 Systolic blood pressure	1	32	Mean Difference (IV, Random, 95% CI)	-3.5 [-9.75, 2.75]
4 Diastolic blood pressure	1	32	Mean Difference (IV, Random, 95% CI)	-1.80 [-5.23, 1.63]
5 Mean arterial pressure	1	32	Mean Difference (IV, Random, 95% CI)	-2.20 [-6.41, 2.01]

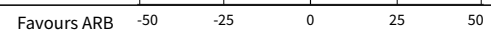
Analysis 3.1. Comparison 3 ACEi versus ARB, Outcome 1 Serum creatinine.

Study or subgroup	ACEi N	ACEi Mean(SD)	ARB N	ARB Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Ulusoy 2010	19	1.3 (0.6)	13	1.5 (0.8)		3.3%	-0.16[-0.67,0.35]
Nakamura 2012a	10	0.8 (0.1)	10	0.8 (0.1)		96.7%	0.01[-0.08,0.1]
Total ***	**29**		**23**			**100%**	**0[-0.09,0.1]**
Heterogeneity: Tau^2=0; Chi^2=0.41, df=1(P=0.52); I^2=0%							
Test for overall effect: Z=0.09(P=0.93)							



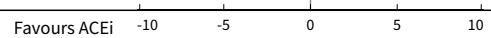
Analysis 3.2. Comparison 3 ACEi versus ARB, Outcome 2 GFR [mL/min/1.73 m^2].

Study or subgroup	ACEi N	ACEi Mean(SD)	ARB N	ARB Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Ulusoy 2010	19	73.8 (27.7)	13	77.2 (27.1)		100%	-3.4[-22.69,15.89]
Total ***	**19**		**13**			**100%**	**-3.4[-22.69,15.89]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.35(P=0.73)							



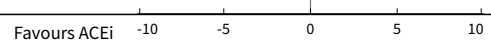
Analysis 3.3. Comparison 3 ACEi versus ARB, Outcome 3 Systolic blood pressure.

Study or subgroup	ACEi N	ACEi Mean(SD)	ARB N	ARB Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Ulusoy 2010	19	116.5 (8.5)	13	120 (9.1)		100%	-3.5[-9.75,2.75]
Total ***	**19**		**13**			**100%**	**-3.5[-9.75,2.75]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.1(P=0.27)							

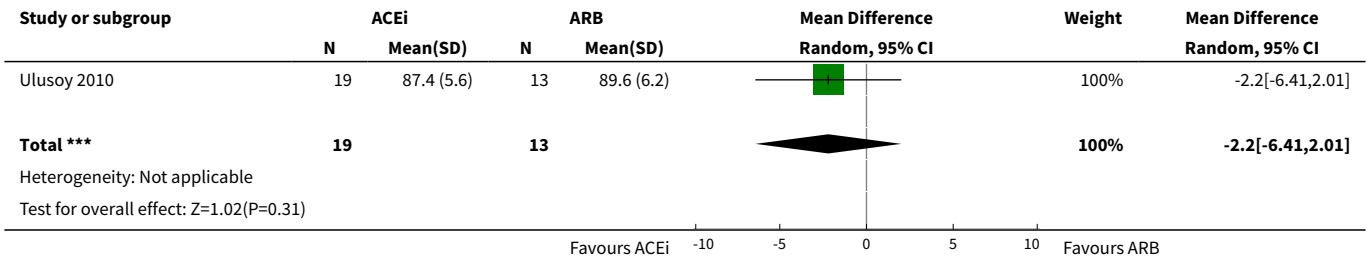


Analysis 3.4. Comparison 3 ACEi versus ARB, Outcome 4 Diastolic blood pressure.

Study or subgroup	ACEi N	ACEi Mean(SD)	ARB N	ARB Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Ulusoy 2010	19	72.8 (4.5)	13	74.6 (5.1)		100%	-1.8[-5.23,1.63]
Total ***	**19**		**13**			**100%**	**-1.8[-5.23,1.63]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%							
Test for overall effect: Z=1.03(P=0.3)							



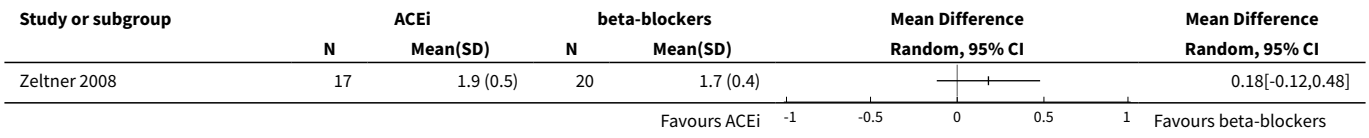
Analysis 3.5. Comparison 3 ACEi versus ARB, Outcome 5 Mean arterial pressure.



Comparison 4. ACEi versus beta-blockers

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Creatinine	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 GFR [mL/min/1.73 m^2]	2	65	Mean Difference (IV, Random, 95% CI)	-8.06 [-29.62, 13.50]
3 GFR descriptive data			Other data	No numeric data
4 Need for renal replacement therapy	1	37	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.02, 8.97]
5 Albuminuria	2	65	Std. Mean Difference (IV, Random, 95% CI)	-0.19 [-1.77, 1.39]
6 Systolic blood pressure	1	37	Mean Difference (IV, Random, 95% CI)	-1.0 [-2.29, 0.29]
7 Diastolic blood pressure	1	37	Mean Difference (IV, Random, 95% CI)	1.0 [0.35, 1.65]
8 Mean arterial pressure	1	28	Mean Difference (IV, Random, 95% CI)	-3.0 [-4.92, -1.08]
9 Blood pressure descriptive data			Other data	No numeric data
10 Cardiovascular events	1	37	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.08, 17.42]

Analysis 4.1. Comparison 4 ACEi versus beta-blockers, Outcome 1 Creatinine.

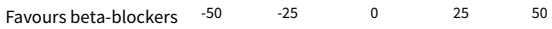


Analysis 4.2. Comparison 4 ACEi versus beta-blockers, Outcome 2 GFR [mL/min/1.73 m^2].

Study or subgroup	ACEi N	ACEi Mean(SD)	beta-blockers N	beta-blockers Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Zeltner 2008	17	81 (11)	20	78 (11)		49.72%	3[-4.11,10.11]
van Dijk 2003	13	64 (9)	15	83 (8)		50.28%	-19[-25.35,-12.65]
Total ***	**30**		**35**			**100%**	**-8.06[-29.62,13.5]**

Heterogeneity: Tau^2=230.17; Chi^2=20.45, df=1(P<0.0001); I^2=95.11%

Test for overall effect: Z=0.73(P=0.46)



Analysis 4.3. Comparison 4 ACEi versus beta-blockers, Outcome 3 GFR descriptive data.

Study	GFR descriptive data
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.

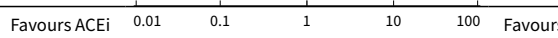
Analysis 4.4. Comparison 4 ACEi versus beta-blockers, Outcome 4 Need for renal replacement therapy.

Study or subgroup	ACEi n/N	beta-blockers n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Zeltner 2008	0/17	1/20		100%	0.39[0.02,8.97]
Total (95% CI)	**17**	**20**		**100%**	**0.39[0.02,8.97]**

Total events: 0 (ACEi), 1 (beta-blockers)

Heterogeneity: Not applicable

Test for overall effect: Z=0.59(P=0.56)

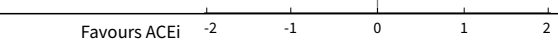


Analysis 4.5. Comparison 4 ACEi versus beta-blockers, Outcome 5 Albuminuria.

Study or subgroup	ACEi N	ACEi Mean(SD)	beta-blockers N	beta-blockers Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
van Dijk 2003	13	1.2 (1.5)	15	0.5 (0.6)		49.46%	0.62[-0.14,1.39]
Zeltner 2008	17	42.6 (12.3)	20	70.3 (35.5)		50.54%	-0.99[-1.68,-0.3]
Total ***	**30**		**35**			**100%**	**-0.19[-1.77,1.39]**

Heterogeneity: Tau^2=1.16; Chi^2=9.42, df=1(P=0); I^2=89.38%

Test for overall effect: Z=0.24(P=0.81)

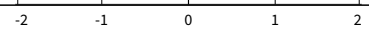


Analysis 4.6. Comparison 4 ACEi versus beta-blockers, Outcome 6 Systolic blood pressure.

Study or subgroup	ACEi N	ACEi Mean(SD)	beta-blockers N	beta-blockers Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Zeltner 2008	17	130 (2)	20	131 (2)		100%	-1[-2.29,0.29]
Total ***	**17**		**20**			**100%**	**-1[-2.29,0.29]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.52(P=0.13)							

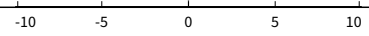
Analysis 4.7. Comparison 4 ACEi versus beta-blockers, Outcome 7 Diastolic blood pressure.

Study or subgroup	ACEi N	ACEi Mean(SD)	beta-blockers N	beta-blockers Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Zeltner 2008	17	83 (1)	20	82 (1)		100%	1[0.35,1.65]
Total ***	**17**		**20**			**100%**	**1[0.35,1.65]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.03(P=0)							



Analysis 4.8. Comparison 4 ACEi versus beta-blockers, Outcome 8 Mean arterial pressure.

Study or subgroup	ACEi N	ACEi Mean(SD)	beta-blockers N	beta-blockers Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
van Dijk 2003	13	102 (3)	15	105 (2)		100%	-3[-4.92,-1.08]
Total ***	**13**		**15**			**100%**	**-3[-4.92,-1.08]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.06(P=0)							

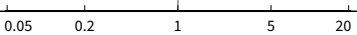


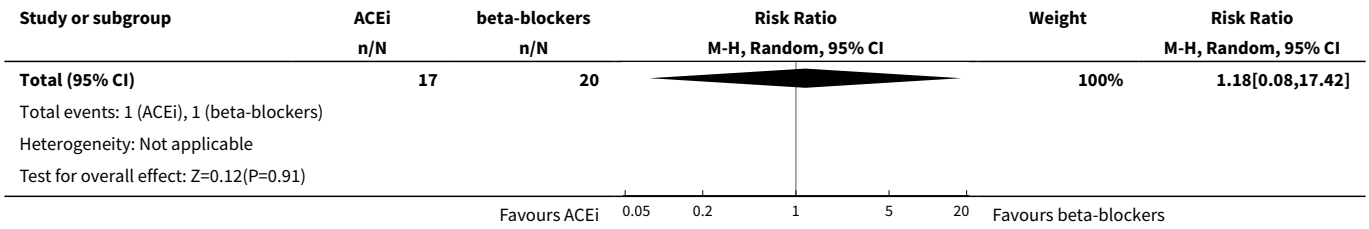
Analysis 4.9. Comparison 4 ACEi versus beta-blockers, Outcome 9 Blood pressure descriptive data.

Study	Blood pressure descriptive data
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 4.10. Comparison 4 ACEi versus beta-blockers, Outcome 10 Cardiovascular events.

Study or subgroup	ACEi n/N	beta-blockers n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Zeltner 2008	1/17	1/20		100%	1.18[0.08,17.42]

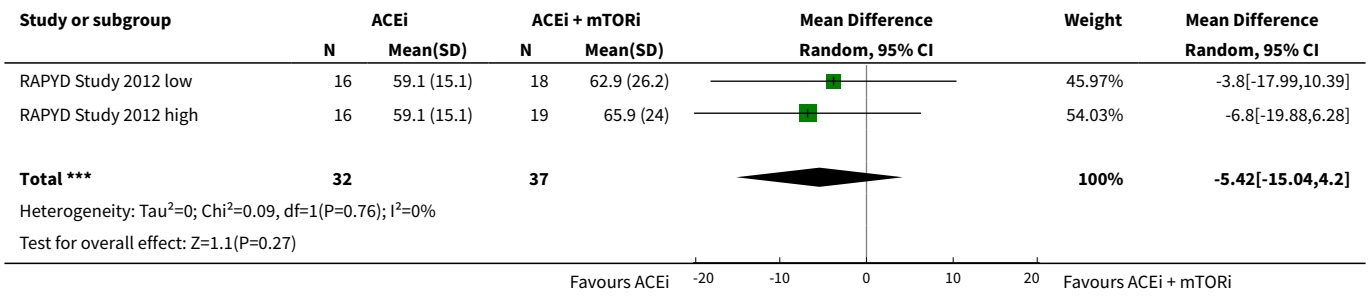




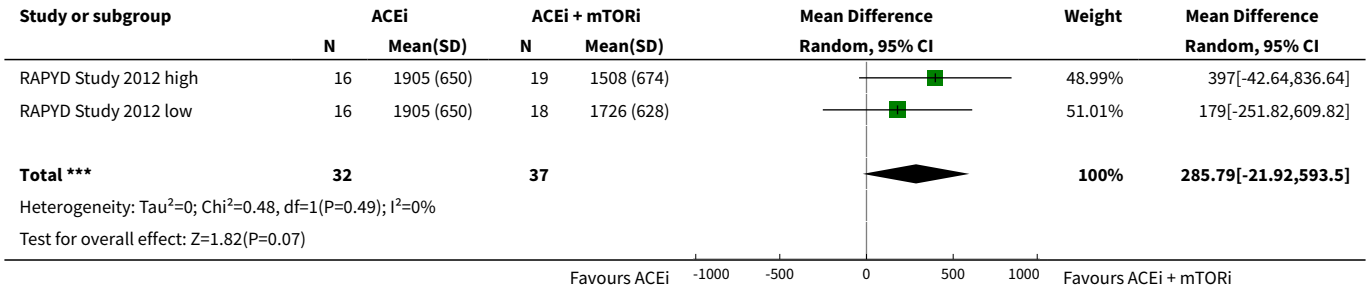
Comparison 5. ACEi alone versus ACEi + mTOR inhibitors

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 GFR [mL/min/1.73 m^2]	2	69	Mean Difference (IV, Random, 95% CI)	-5.42 [-15.04, 4.20]
2 Total kidney volume	2	69	Mean Difference (IV, Random, 95% CI)	285.79 [-21.92, 593.50]
3 Cyst volume	2	69	Mean Difference (IV, Random, 95% CI)	36.32 [-6.99, 79.64]
4 Proteinuria	2	69	Mean Difference (IV, Random, 95% CI)	-0.26 [-0.65, 0.12]
5 Mean arterial pressure	2	69	Mean Difference (IV, Random, 95% CI)	0.64 [-6.21, 7.50]
6 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Anaemia	1	53	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.02, 8.82]
6.2 Hyperlipidaemia	1	53	Risk Ratio (M-H, Random, 95% CI)	0.10 [0.01, 1.56]
6.3 Infection	1	53	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.02, 8.82]
6.4 Oral ulcers	1	53	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.01, 2.15]

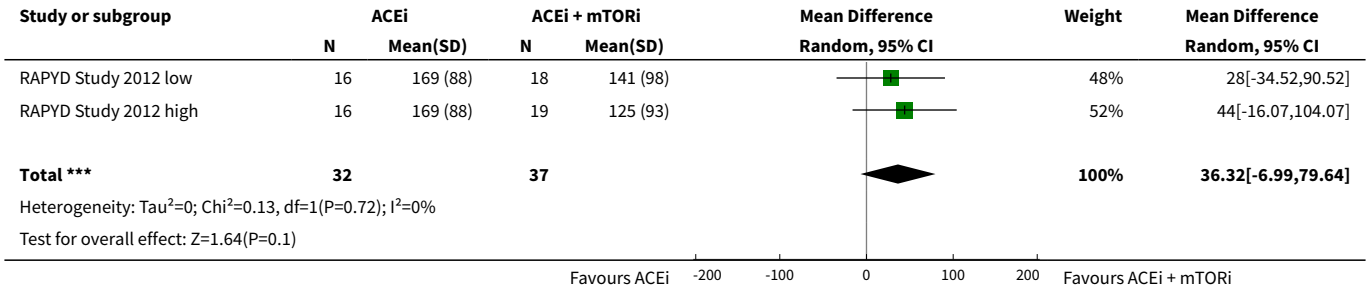
Analysis 5.1. Comparison 5 ACEi alone versus ACEi + mTOR inhibitors, Outcome 1 GFR [mL/min/1.73 m^2].



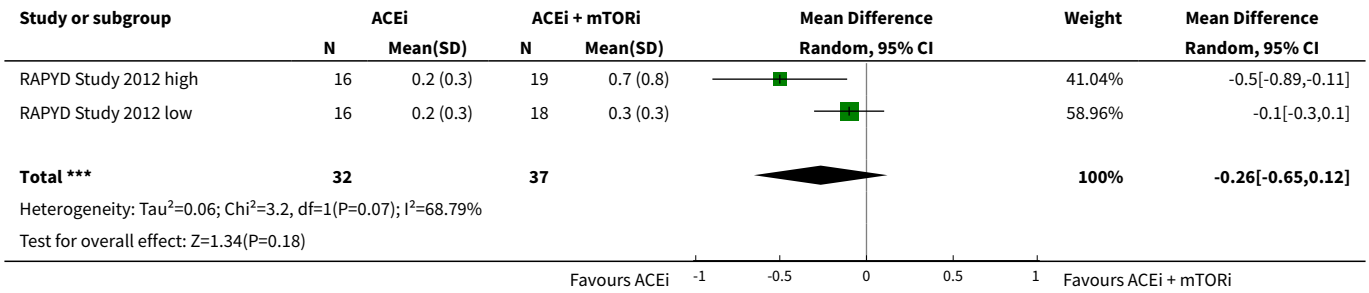
Analysis 5.2. Comparison 5 ACEi alone versus ACEi + mTOR inhibitors, Outcome 2 Total kidney volume.



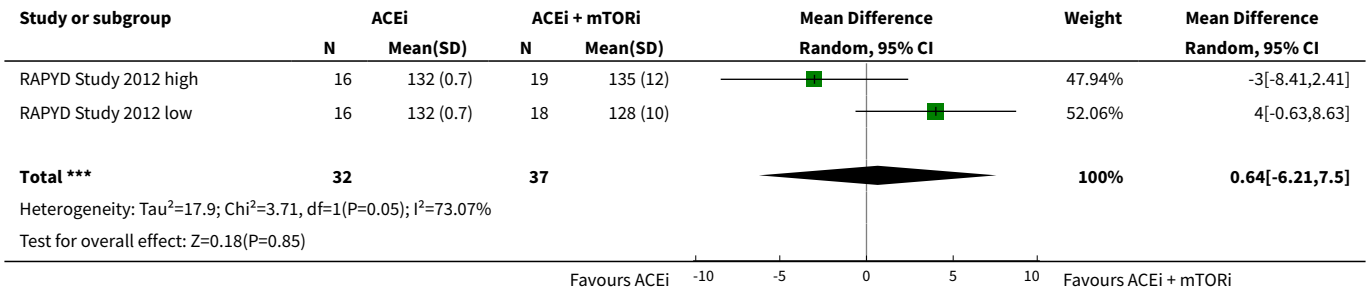
Analysis 5.3. Comparison 5 ACEi alone versus ACEi + mTOR inhibitors, Outcome 3 Cyst volume.



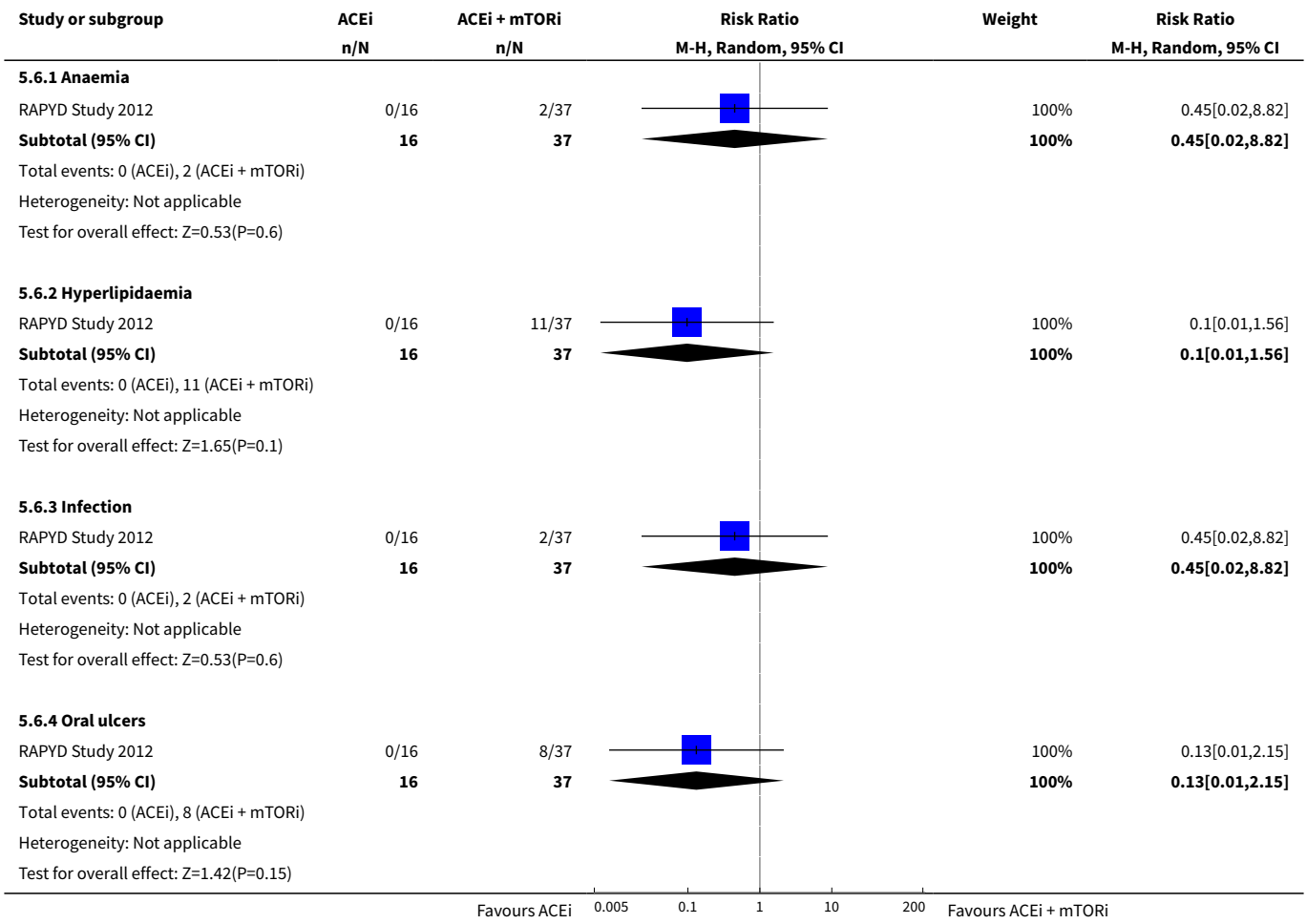
Analysis 5.4. Comparison 5 ACEi alone versus ACEi + mTOR inhibitors, Outcome 4 Proteinuria.



Analysis 5.5. Comparison 5 ACEi alone versus ACEi + mTOR inhibitors, Outcome 5 Mean arterial pressure.



Analysis 5.6. Comparison 5 ACEi alone versus ACEi + mTOR inhibitors, Outcome 6 Adverse events.

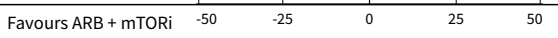


Comparison 6. ARB alone versus ARB + mTOR inhibitors

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 GFR [mL/min/1.73 m^2]	1	16	Mean Difference (IV, Random, 95% CI)	-9.60 [-28.18, 8.98]
2 Doubling of serum creatinine	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Total kidney volume	1	16	Mean Difference (IV, Random, 95% CI)	0.37 [0.04, 0.70]
4 Blood pressure descriptive data			Other data	No numeric data
5 Infection	1	16	Risk Ratio (M-H, Random, 95% CI)	0.5 [0.13, 2.00]

Analysis 6.1. Comparison 6 ARB alone versus ARB + mTOR inhibitors, Outcome 1 GFR [mL/min/1.73 m^2].

Study or subgroup	ARB N	ARB Mean(SD)	ARB + mTORi N	ARB + mTORi Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Soliman 2009	8	35.2 (18.5)	8	44.8 (19.4)		100%	-9.6[-28.18,8.98]
Total ***	**8**		**8**			**100%**	**-9.6[-28.18,8.98]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.01(P=0.31)							



Analysis 6.2. Comparison 6 ARB alone versus ARB + mTOR inhibitors, Outcome 2 Doubling of serum creatinine.

Study or subgroup	ARB n/N	ARBs + mTORi n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Soliman 2009	3/8	1/8		3[0.39,23.07]

Analysis 6.3. Comparison 6 ARB alone versus ARB + mTOR inhibitors, Outcome 3 Total kidney volume.

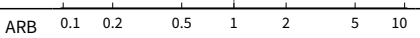
Study or subgroup	ARB N	ARB Mean(SD)	ARBs + mTORi N	ARBs + mTORi Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Soliman 2009	8	3.6 (0.4)	8	3.2 (0.3)		100%	0.37[0.04,0.7]
Total ***	**8**		**8**			**100%**	**0.37[0.04,0.7]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.21(P=0.03)							

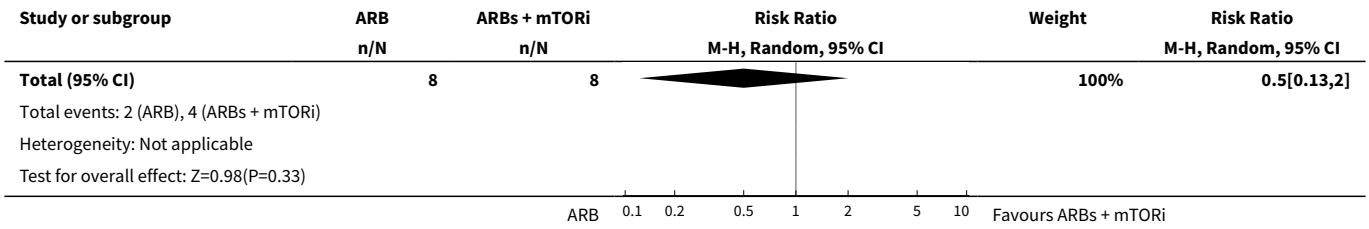
Analysis 6.4. Comparison 6 ARB alone versus ARB + mTOR inhibitors, Outcome 4 Blood pressure descriptive data.

Study	Blood pressure descriptive data
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 6.5. Comparison 6 ARB alone versus ARB + mTOR inhibitors, Outcome 5 Infection.

Study or subgroup	ARB n/N	ARBs + mTORi n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Soliman 2009	2/8	4/8		100%	0.5[0.13,2]

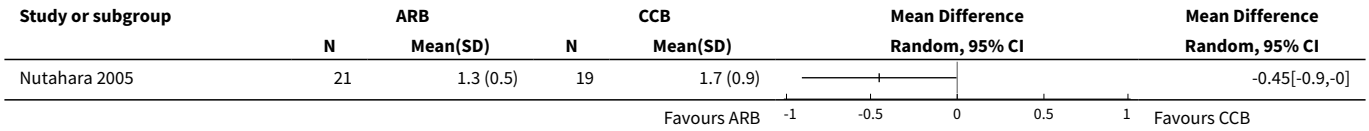




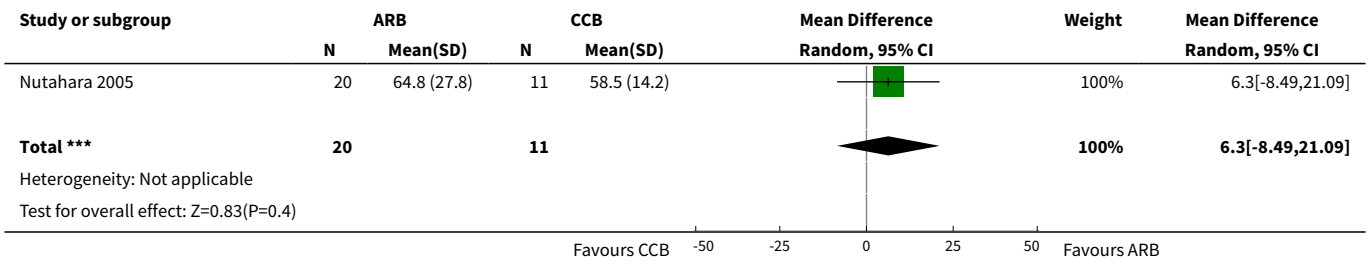
Comparison 7. ARB versus CCB

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Creatinine	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 GFR [mL/min/1.73 m^2]	1	31	Mean Difference (IV, Random, 95% CI)	6.30 [-8.49, 21.09]
3 Doubling of serum creatinine	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Proteinuria	1	25	Mean Difference (IV, Random, 95% CI)	-304.0 [-578.54, -29.46]
5 Albuminuria	1	24	Mean Difference (IV, Random, 95% CI)	-238.0 [-394.61, -81.39]

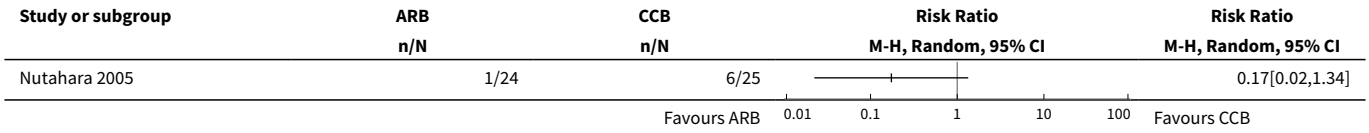
Analysis 7.1. Comparison 7 ARB versus CCB, Outcome 1 Creatinine.



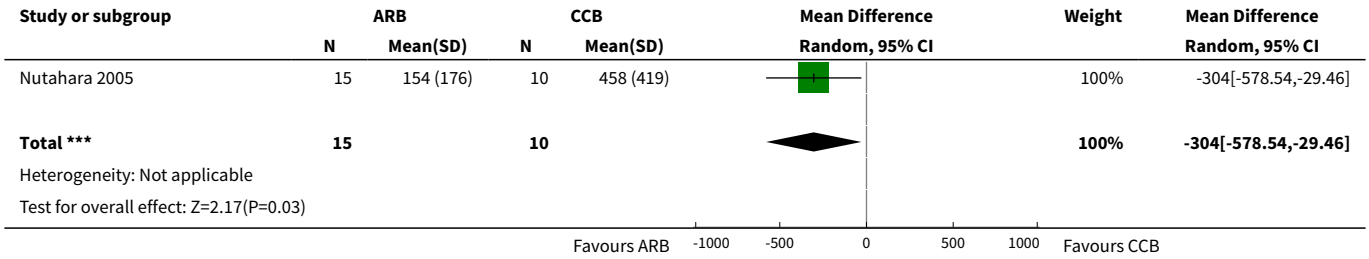
Analysis 7.2. Comparison 7 ARB versus CCB, Outcome 2 GFR [mL/min/1.73 m^2].



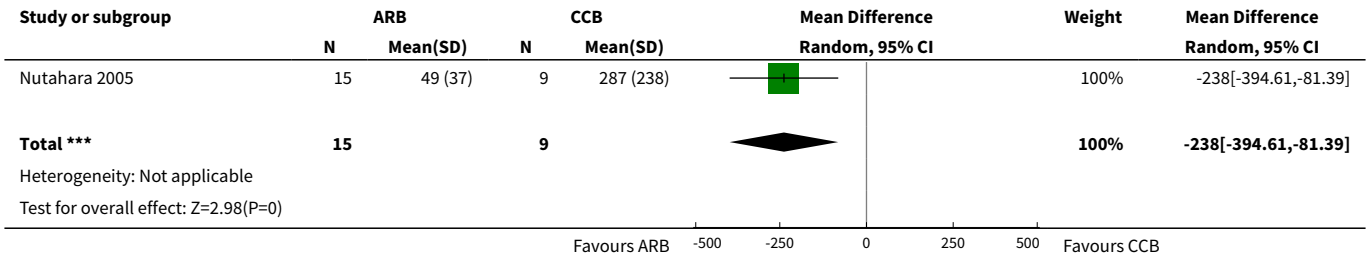
Analysis 7.3. Comparison 7 ARB versus CCB, Outcome 3 Doubling of serum creatinine.



Analysis 7.4. Comparison 7 ARB versus CCB, Outcome 4 Proteinuria.



Analysis 7.5. Comparison 7 ARB versus CCB, Outcome 5 Albuminuria.



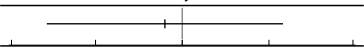
Comparison 8. V2R antagonists versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Creatinine	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 GFR descriptive data			Other data	No numeric data
3 Doubling of serum creatinine	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Total kidney volume descriptive data			Other data	No numeric data
5 Albuminuria	1	1157	Mean Difference (IV, Random, 95% CI)	-1.60 [-3.95, 0.75]
6 Kidney pain	1	1444	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.66, 0.90]
7 Adverse events	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Headache	2	1455	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.85, 1.25]
7.2 Diarrhoea	1	1444	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.90, 1.64]
7.3 Dizziness	1	1444	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.93, 1.83]
7.4 Dry mouth	2	1455	Risk Ratio (M-H, Random, 95% CI)	1.33 [1.01, 1.76]
7.5 Nausea	1	1444	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.64, 1.18]
7.6 Thirst	1	1444	Risk Ratio (M-H, Random, 95% CI)	2.70 [2.24, 3.24]
7.7 Transaminase elevation	1	1444	Risk Ratio (M-H, Random, 95% CI)	2.26 [0.49, 10.43]

Analysis 8.1. Comparison 8 V2R antagonists versus placebo, Outcome 1 Creatinine.

Study or subgroup	V2R antagonists N	V2R antagonists Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
TEMPO 3-4 Study 2011	740	1.3 (0.5)	414	1.3 (0.6)		-0.01[-0.08,0.06]

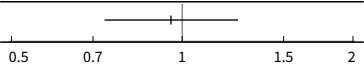


Analysis 8.2. Comparison 8 V2R antagonists versus placebo, Outcome 2 GFR descriptive data.

Study	GFR descriptive data
TEMPO 3-4 Study 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)−1 per year, as compared with −3.81 (mg/mL)−1 per year with placebo; the treatment effect was an increase of 1.20 (mg/mL)−1 per year (95% CI 0.62 to 1.78; P < 0.001)

Analysis 8.3. Comparison 8 V2R antagonists versus placebo, Outcome 3 Doubling of serum creatinine.

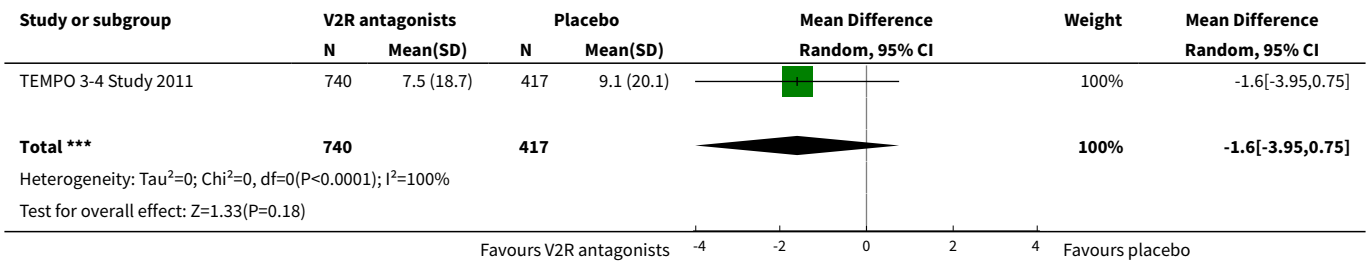
Study or subgroup	V2R antagonists n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
TEMPO 3-4 Study 2011	135/961	71/483		0.96[0.73,1.25]



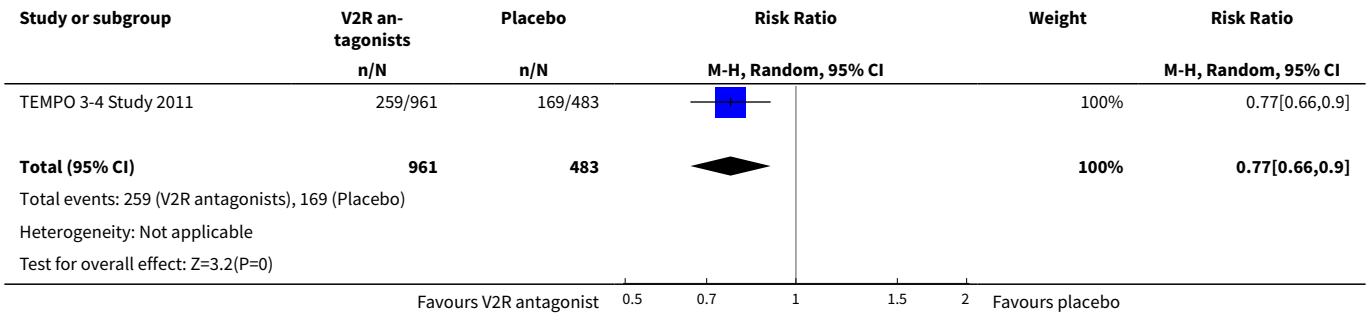
Analysis 8.4. Comparison 8 V2R antagonists versus placebo, Outcome 4 Total kidney volume descriptive data.

Study	Total kidney volume descriptive data
TEMPO 3-4 Study 2011	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"

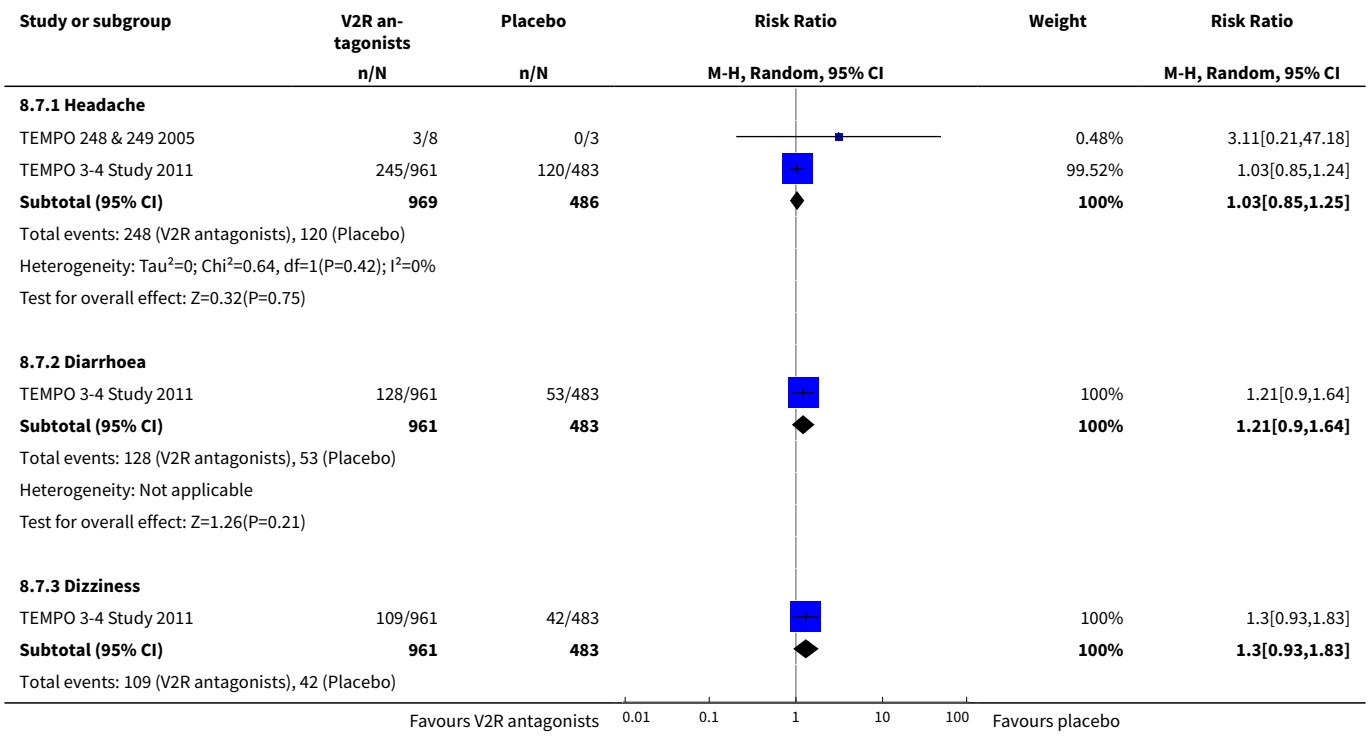
Analysis 8.5. Comparison 8 V2R antagonists versus placebo, Outcome 5 Albuminuria.

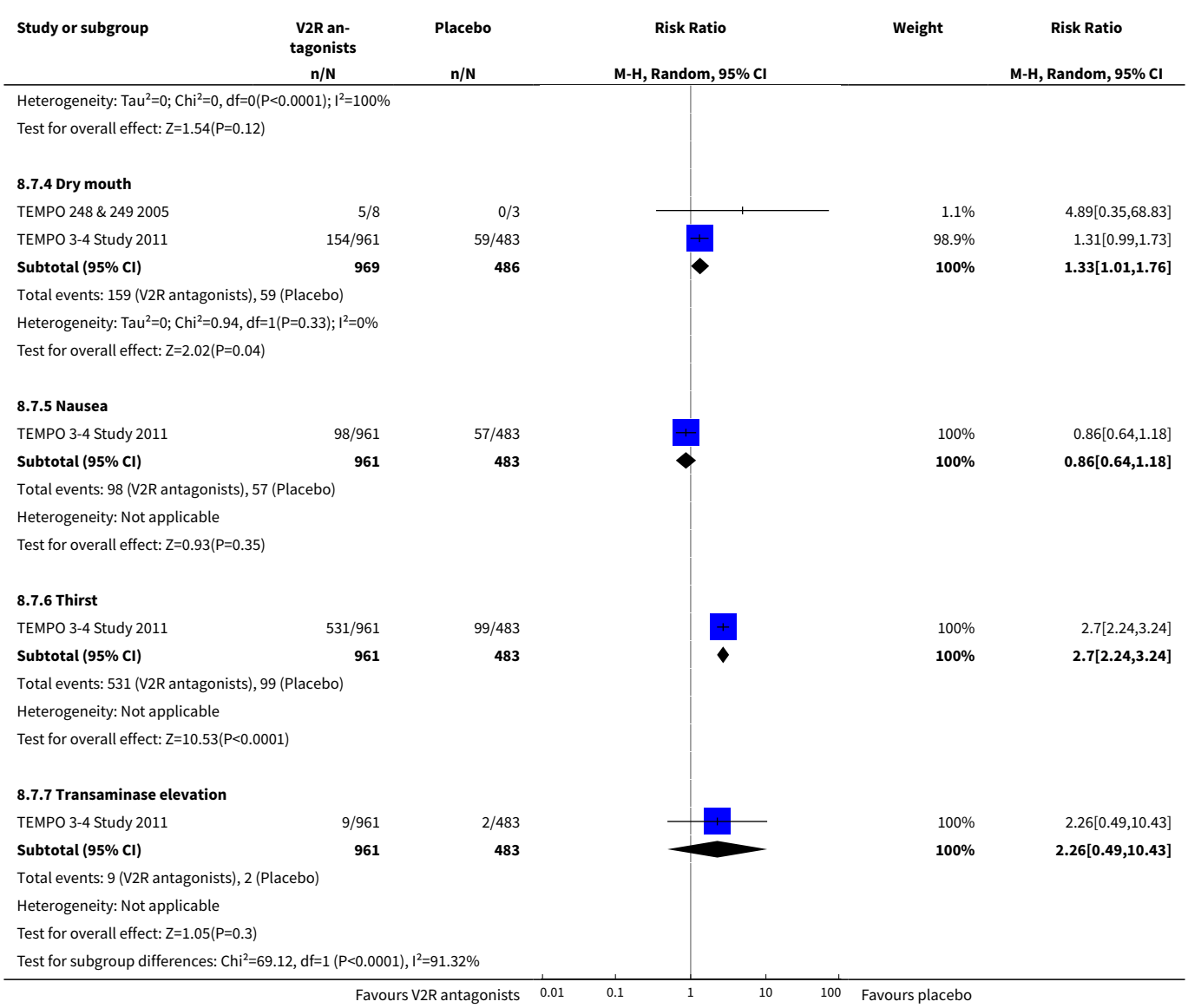


Analysis 8.6. Comparison 8 V2R antagonists versus placebo, Outcome 6 Kidney pain.



Analysis 8.7. Comparison 8 V2R antagonists versus placebo, Outcome 7 Adverse events.

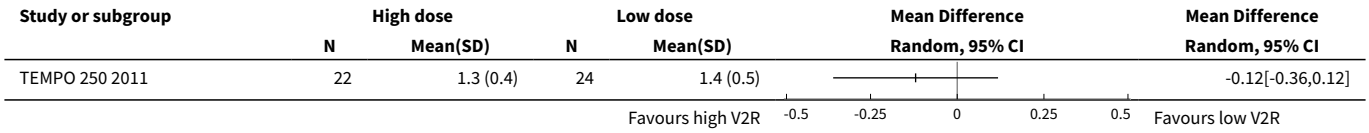




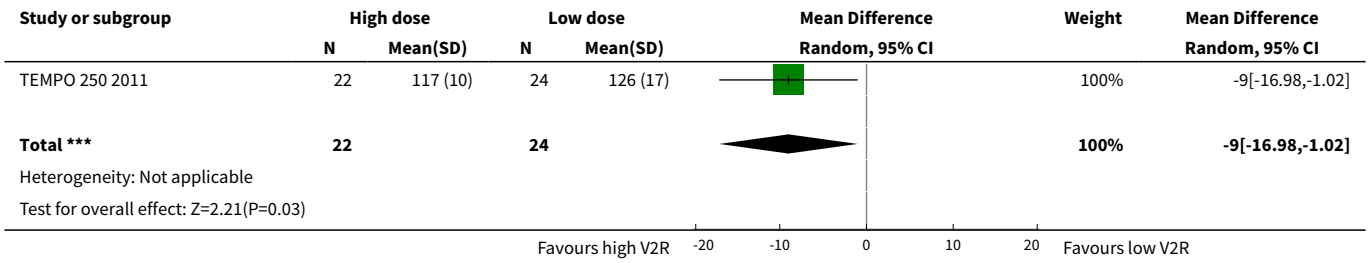
Comparison 9. High versus low dose V2R antagonists

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Creatinine	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Systolic blood pressure	1	46	Mean Difference (IV, Random, 95% CI)	-9.0 [-16.98, -1.02]
3 Diastolic blood pressure	1	46	Mean Difference (IV, Random, 95% CI)	-6.0 [-11.21, -0.79]

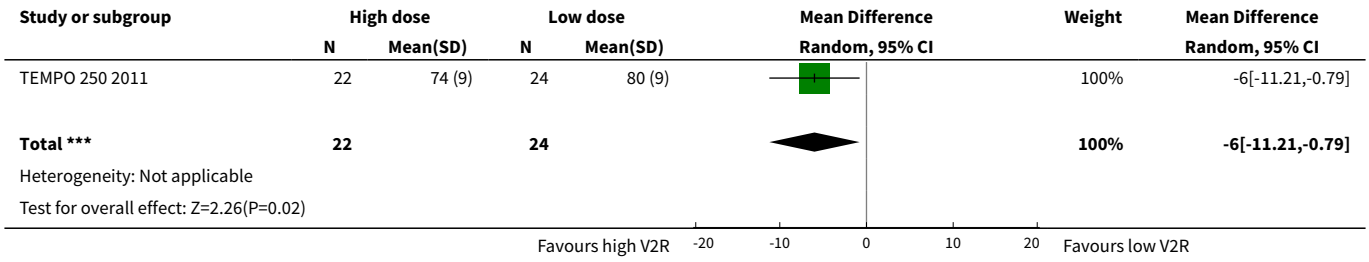
Analysis 9.1. Comparison 9 High versus low dose V2R antagonists, Outcome 1 Creatinine.



Analysis 9.2. Comparison 9 High versus low dose V2R antagonists, Outcome 2 Systolic blood pressure.



Analysis 9.3. Comparison 9 High versus low dose V2R antagonists, Outcome 3 Diastolic blood pressure.

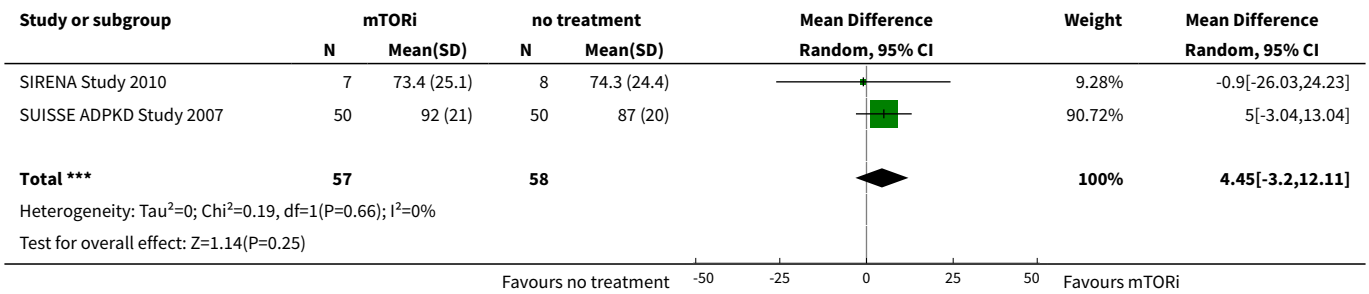


Comparison 10. mTOR inhibitors versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 GFR [mL/min/1.73 m^2]	2	115	Mean Difference (IV, Random, 95% CI)	4.45 [-3.20, 12.11]
2 GFR descriptive data			Other data	No numeric data
3 Need for renal replacement therapy	1	431	Risk Ratio (M-H, Random, 95% CI)	3.04 [0.12, 74.26]
4 Need for transplantation	1	431	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.06, 16.11]
5 Total kidney volume	2	115	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.75, 0.59]
6 Total kidney volume descriptive data			Other data	No numeric data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Cyst volume	1	15	Mean Difference (IV, Random, 95% CI)	-55.0 [-862.98, 752.98]
8 Cyst volume descriptive data			Other data	No numeric data
9 Parenchymal volume	1	15	Mean Difference (IV, Random, 95% CI)	15.0 [-75.44, 105.44]
10 Parenchymal volume descriptive data			Other data	No numeric data
11 Proteinuria	2	446	Std. Mean Difference (IV, Random, 95% CI)	0.34 [-0.29, 0.98]
12 Proteinuria descriptive data			Other data	No numeric data
13 Albuminuria	2	115	Std. Mean Difference (IV, Random, 95% CI)	0.25 [-0.27, 0.78]
14 Systolic blood pressure	2	112	Mean Difference (IV, Random, 95% CI)	2.48 [-2.07, 7.03]
15 Diastolic blood pressure	2	112	Mean Difference (IV, Random, 95% CI)	0.27 [-3.30, 3.85]
16 Blood pressure descriptive data			Other data	No numeric data
17 All-cause mortality	1	431	Risk Ratio (M-H, Random, 95% CI)	2.03 [0.19, 22.20]
18 Adverse effects	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
18.1 Anaemia	1	431	Risk Ratio (M-H, Random, 95% CI)	3.41 [1.79, 6.51]
18.2 Angioedema	3	560	Risk Ratio (M-H, Random, 95% CI)	13.39 [2.56, 70.00]
18.3 Diarrhoea	3	560	Risk Ratio (M-H, Random, 95% CI)	1.70 [1.26, 2.29]
18.4 Hyperlipidaemia	1	431	Risk Ratio (M-H, Random, 95% CI)	5.68 [2.23, 14.43]
18.5 Infection	3	560	Risk Ratio (M-H, Random, 95% CI)	1.14 [1.04, 1.25]
18.6 Nausea	1	431	Risk Ratio (M-H, Random, 95% CI)	1.69 [0.85, 3.37]
18.7 Oral ulcers	3	560	Risk Ratio (M-H, Random, 95% CI)	6.77 [4.42, 10.38]

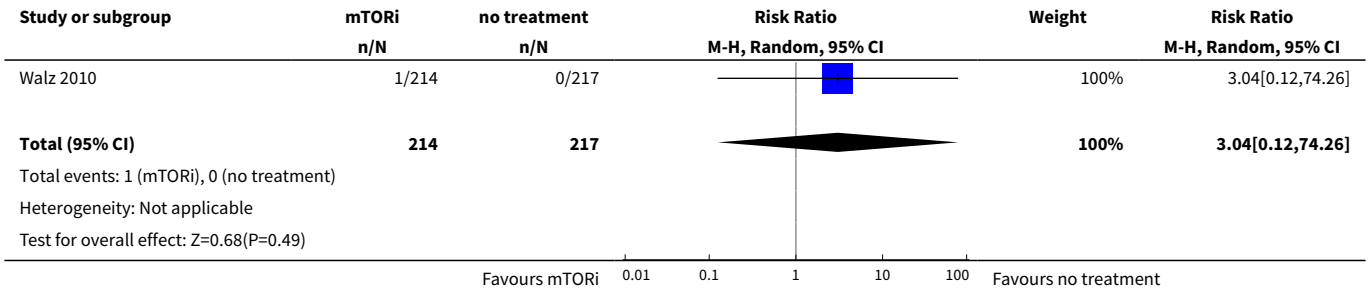
Analysis 10.1. Comparison 10 mTOR inhibitors versus no treatment, Outcome 1 GFR [mL/min/1.73 m^2].



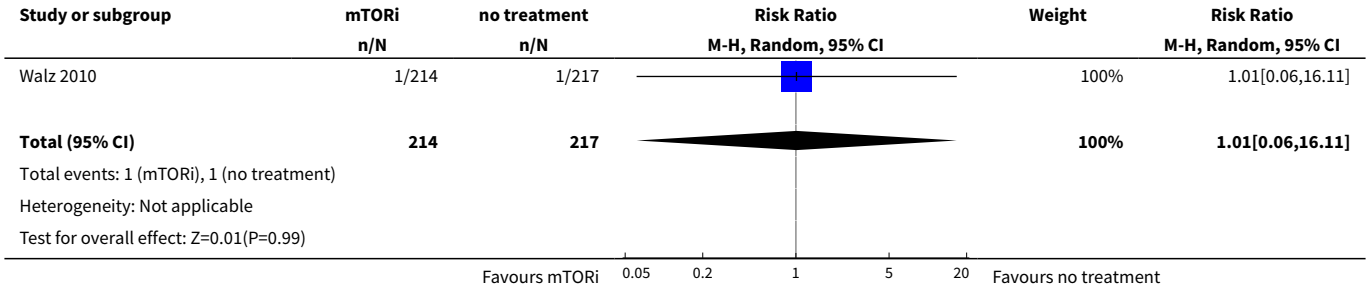
Analysis 10.2. Comparison 10 mTOR inhibitors versus no treatment, Outcome 2 GFR descriptive data.

Study	GFR descriptive data
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 10.3. Comparison 10 mTOR inhibitors versus no treatment, Outcome 3 Need for renal replacement therapy.



Analysis 10.4. Comparison 10 mTOR inhibitors versus no treatment, Outcome 4 Need for transplantation.



Analysis 10.5. Comparison 10 mTOR inhibitors versus no treatment, Outcome 5 Total kidney volume.

Study or subgroup	mTORi N	mTORi Mean(SD)	no treatment N	no treatment Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
SIRENA Study 2010	7	2 (1.1)	8	2 (1.1)		36.25%	-0.02[-1.14,1.1]
SUISSE ADPKD Study 2007	50	1 (2.1)	50	1.1 (2.2)		63.75%	-0.12[-0.96,0.73]
Total ***	**57**		**58**			**100%**	**-0.08[-0.75,0.59]**
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.89); I^2=0%							
Test for overall effect: Z=0.23(P=0.82)							

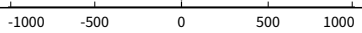
Favours mTORi — Favours no treatment

Analysis 10.6. Comparison 10 mTOR inhibitors versus no treatment, Outcome 6 Total kidney volume descriptive data.

Study	Total kidney volume descriptive data
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 10.7. Comparison 10 mTOR inhibitors versus no treatment, Outcome 7 Cyst volume.

Study or subgroup	mTORi N	mTORi Mean(SD)	no treatment N	no treatment Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
SIRENA Study 2010	7	1112 (780)	8	1167 (815)		100%	-55[-862.98,752.98]
Total ***	**7**		**8**			**100%**	**-55[-862.98,752.98]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.13(P=0.89)							



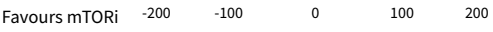
Favours mTORi — Favours no treatment

Analysis 10.8. Comparison 10 mTOR inhibitors versus no treatment, Outcome 8 Cyst volume descriptive data.

Study	Cyst volume descriptive data
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 10.9. Comparison 10 mTOR inhibitors versus no treatment, Outcome 9 Parenchymal volume.

Study or subgroup	mTORi N	mTORi Mean(SD)	no treatment N	no treatment Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
SIRENA Study 2010	7	327 (91)	8	312 (87)		100%	15[-75.44,105.44]
Total ***	**7**		**8**			**100%**	**15[-75.44,105.44]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.33(P=0.75)							

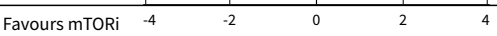


Analysis 10.10. Comparison 10 mTOR inhibitors versus no treatment, Outcome 10 Parenchymal volume descriptive data.

Study	Parenchymal volume descriptive data
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 10.11. Comparison 10 mTOR inhibitors versus no treatment, Outcome 11 Proteinuria.

Study or subgroup	mTORi N	mTORi Mean(SD)	no treatment N	no treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
SIRENA Study 2010	7	0.2 (0.1)	8	0.1 (0)		24.15%	0.92[-0.17,2]
Walz 2010	214	564 (1177)	217	393 (936)		75.85%	0.16[-0.03,0.35]
Total ***	**221**		**225**			**100%**	**0.34[-0.29,0.98]**
Heterogeneity: Tau^2=0.13; Chi^2=1.82, df=1(P=0.18); I^2=45.06%							
Test for overall effect: Z=1.06(P=0.29)							

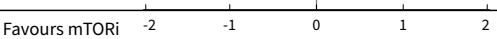


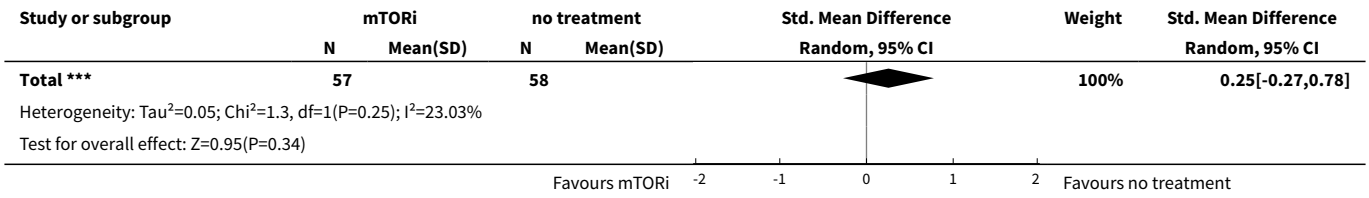
Analysis 10.12. Comparison 10 mTOR inhibitors versus no treatment, Outcome 12 Proteinuria descriptive data.

Study	Proteinuria descriptive data
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"

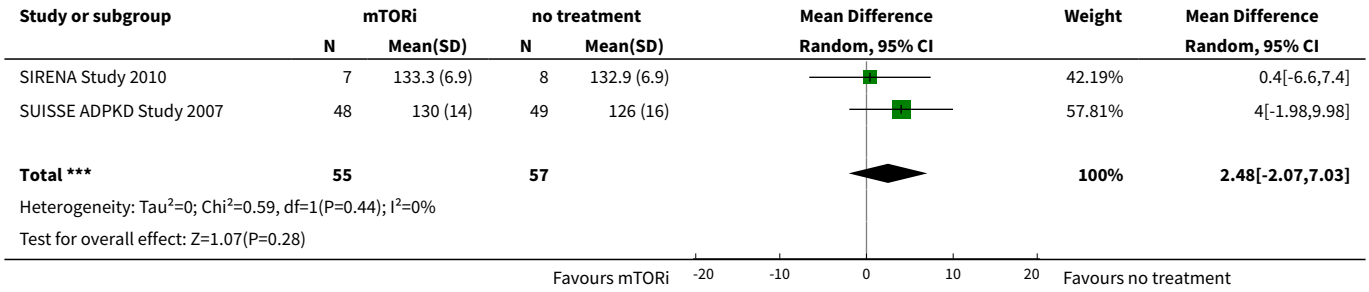
Analysis 10.13. Comparison 10 mTOR inhibitors versus no treatment, Outcome 13 Albuminuria.

Study or subgroup	mTORi N	mTORi Mean(SD)	no treatment N	no treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
SIRENA Study 2010	7	76.3 (57.3)	8	39 (31.3)		20.72%	0.78[-0.29,1.84]
SUISSE ADPKD Study 2007	50	3.4 (12.9)	50	2 (10.8)		79.28%	0.12[-0.28,0.51]

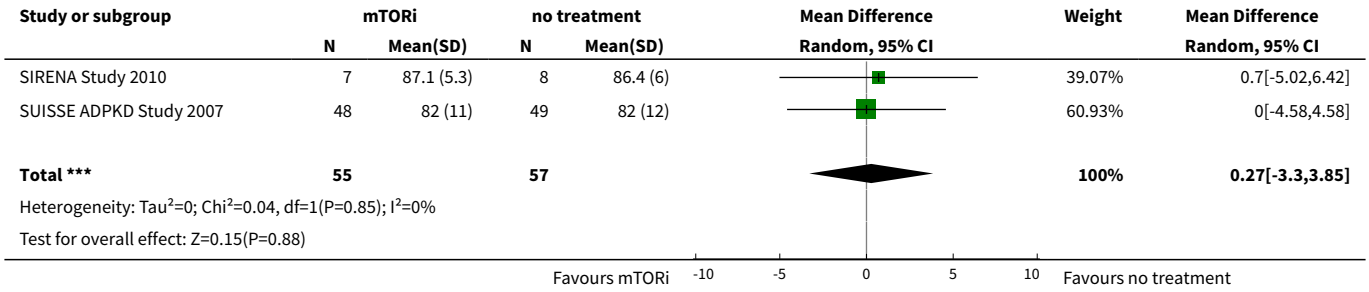




Analysis 10.14. Comparison 10 mTOR inhibitors versus no treatment, Outcome 14 Systolic blood pressure.



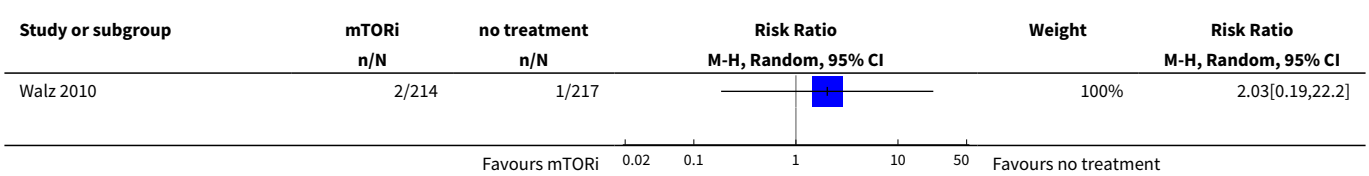
Analysis 10.15. Comparison 10 mTOR inhibitors versus no treatment, Outcome 15 Diastolic blood pressure.

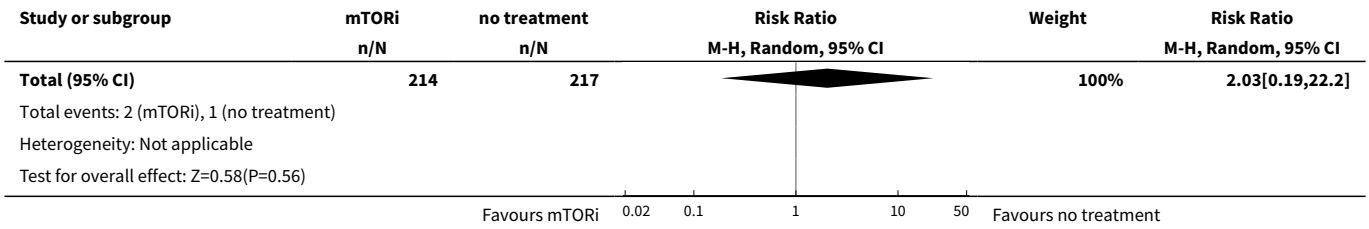


Analysis 10.16. Comparison 10 mTOR inhibitors versus no treatment, Outcome 16 Blood pressure descriptive data.

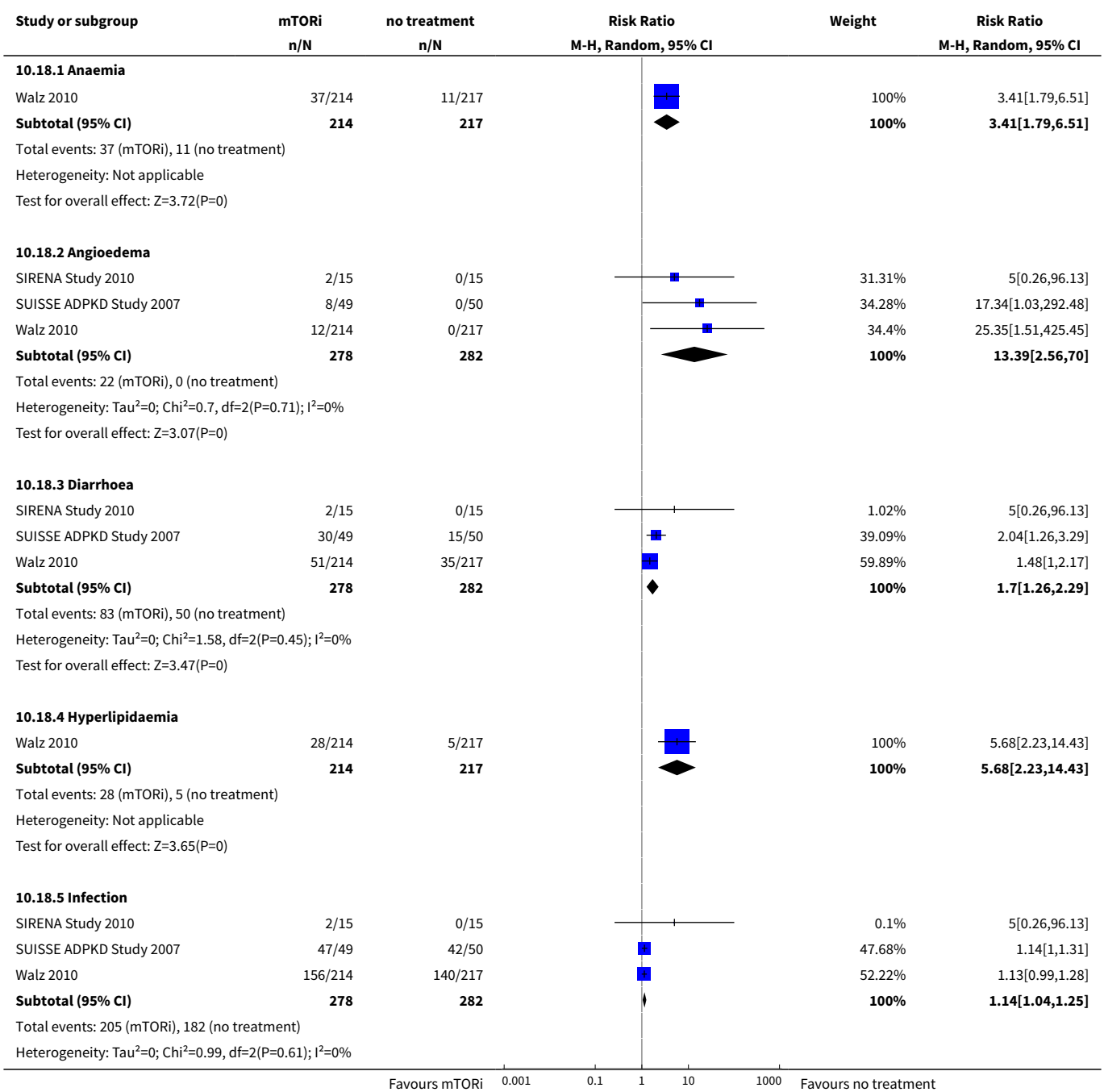
Study	Blood pressure descriptive data
Walz 2010	quote: "The change from baseline in the systolic blood pressure at 24 months was −2.0 mm Hg in the mTOR-inhibitors group and −1.5 mm Hg in the placebo group (P = 0.76); the corresponding changes in diastolic blood pressure were −2.7 mm Hg and −2.6 mm Hg (P = 0.89)"

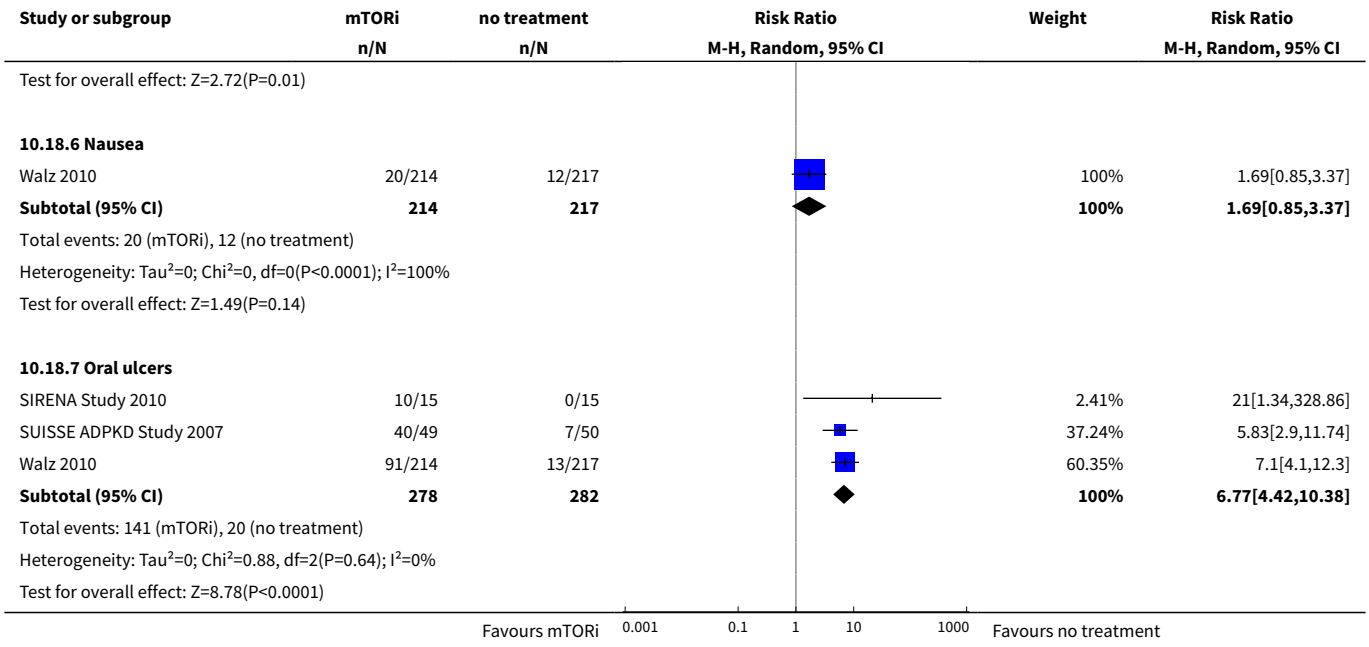
Analysis 10.17. Comparison 10 mTOR inhibitors versus no treatment, Outcome 17 All-cause mortality.





Analysis 10.18. Comparison 10 mTOR inhibitors versus no treatment, Outcome 18 Adverse effects.



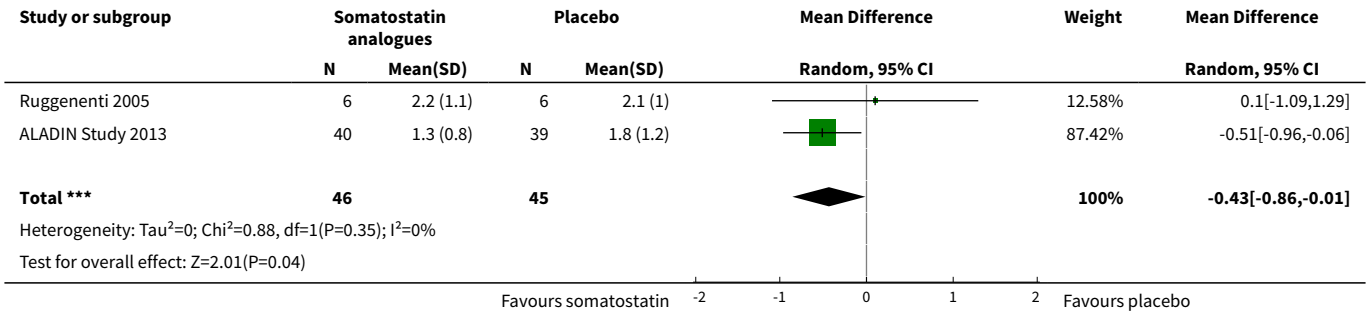


Comparison 11. Somatostatin analogues versus placebo

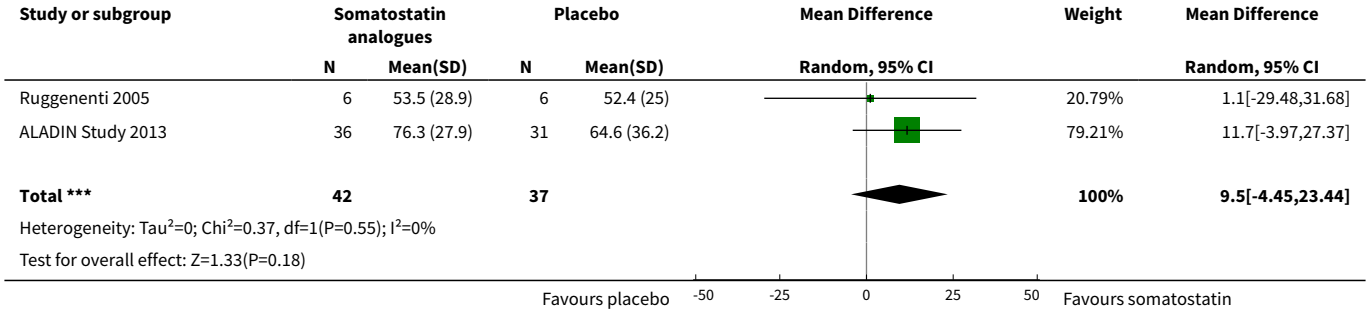
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Creatinine	2	91	Mean Difference (IV, Random, 95% CI)	-0.43 [-0.86, -0.01]
2 GFR [mL/min/1.73 m²]	2	79	Mean Difference (IV, Random, 95% CI)	9.50 [-4.45, 23.44]
3 Total kidney volume	3	114	Mean Difference (IV, Random, 95% CI)	-0.62 [-1.22, -0.01]
4 Cyst volume	2	82	Mean Difference (IV, Random, 95% CI)	-0.50 [-1.18, 0.18]
5 Parenchymal volume	2	82	Mean Difference (IV, Random, 95% CI)	-67.67 [-249.45, 114.12]
6 Proteinuria	1	79	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.17, 0.07]
7 Albuminuria	2	91	Std. Mean Difference (IV, Random, 95% CI)	-0.10 [-0.51, 0.31]
8 Systolic blood pressure	2	91	Mean Difference (IV, Random, 95% CI)	0.79 [-3.54, 5.13]
9 Diastolic blood pressure	2	91	Mean Difference (IV, Random, 95% CI)	-0.38 [-3.68, 2.92]
10 Mean arterial pressure	1	79	Mean Difference (IV, Random, 95% CI)	-0.10 [-3.66, 3.46]
11 Adverse events	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
11.1 Alopecia	1	79	Risk Ratio (M-H, Random, 95% CI)	4.88 [0.24, 98.47]
11.2 Anaemia	1	79	Risk Ratio (M-H, Random, 95% CI)	1.3 [0.50, 3.40]
11.3 Diarrhoea	2	91	Risk Ratio (M-H, Random, 95% CI)	3.72 [1.43, 9.68]
11.4 Dizziness	1	79	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.06, 15.05]
11.5 Infection	1	79	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.64, 2.39]

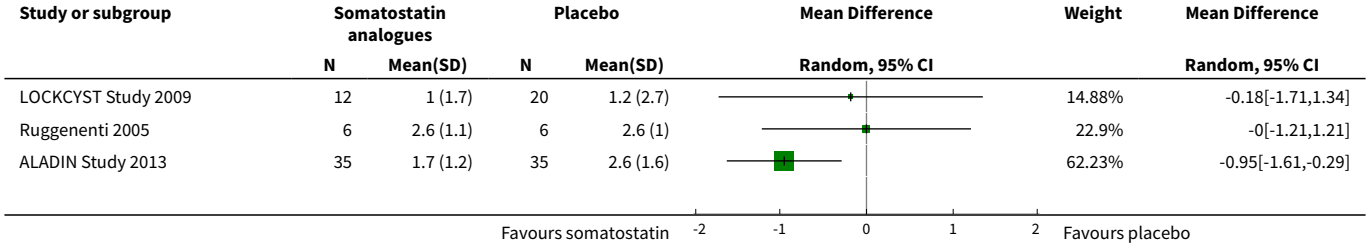
Analysis 11.1. Comparison 11 Somatostatin analogues versus placebo, Outcome 1 Creatinine.

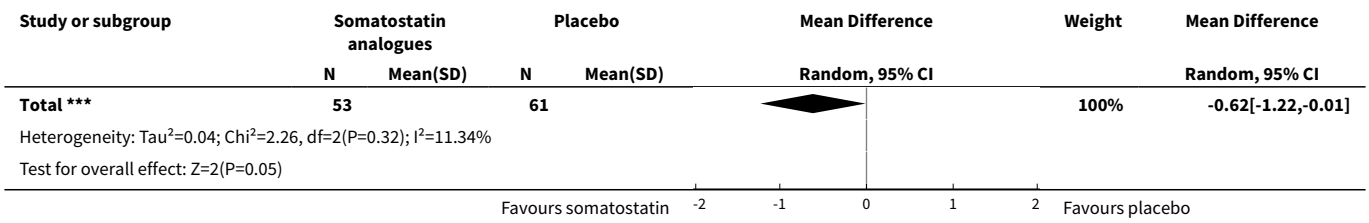


Analysis 11.2. Comparison 11 Somatostatin analogues versus placebo, Outcome 2 GFR [mL/min/1.73 m²].

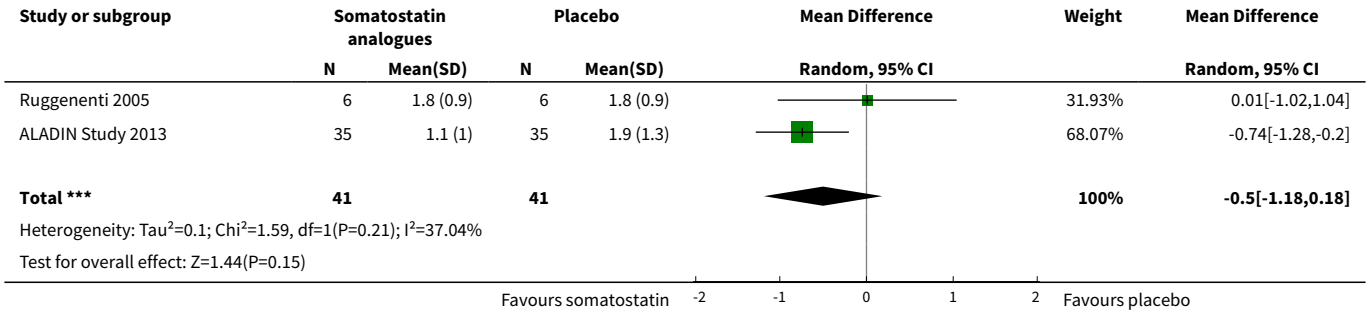


Analysis 11.3. Comparison 11 Somatostatin analogues versus placebo, Outcome 3 Total kidney volume.

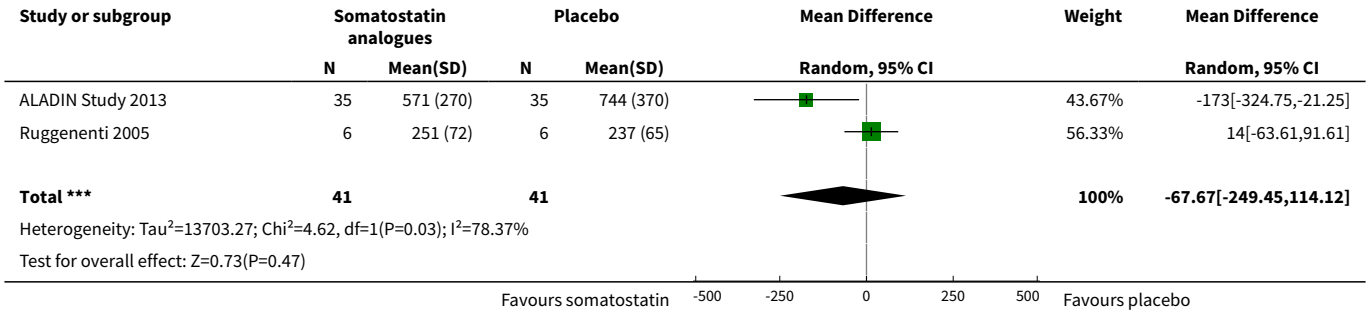




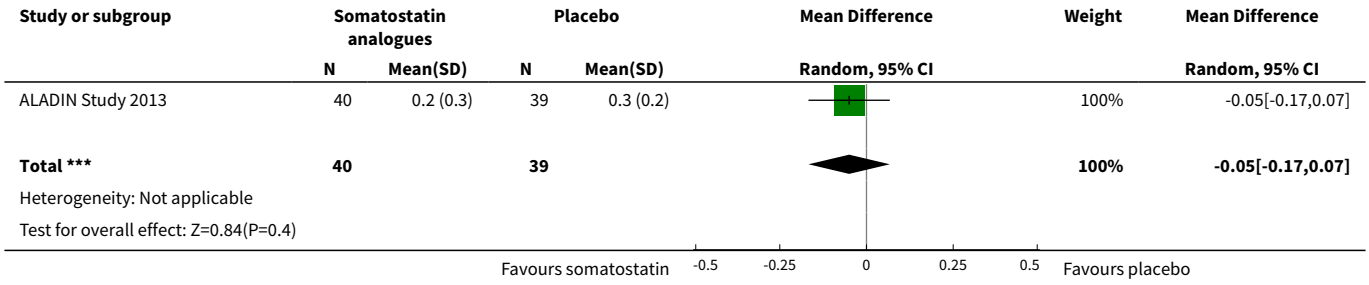
Analysis 11.4. Comparison 11 Somatostatin analogues versus placebo, Outcome 4 Cyst volume.



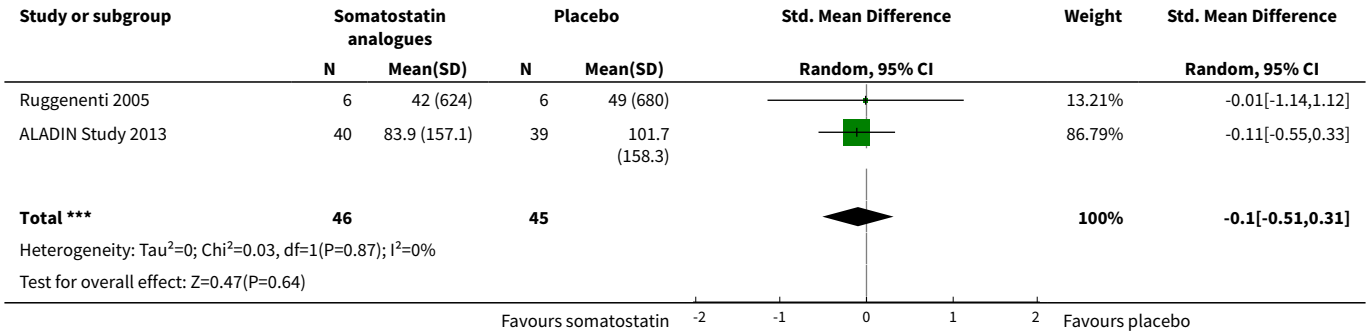
Analysis 11.5. Comparison 11 Somatostatin analogues versus placebo, Outcome 5 Parenchymal volume.



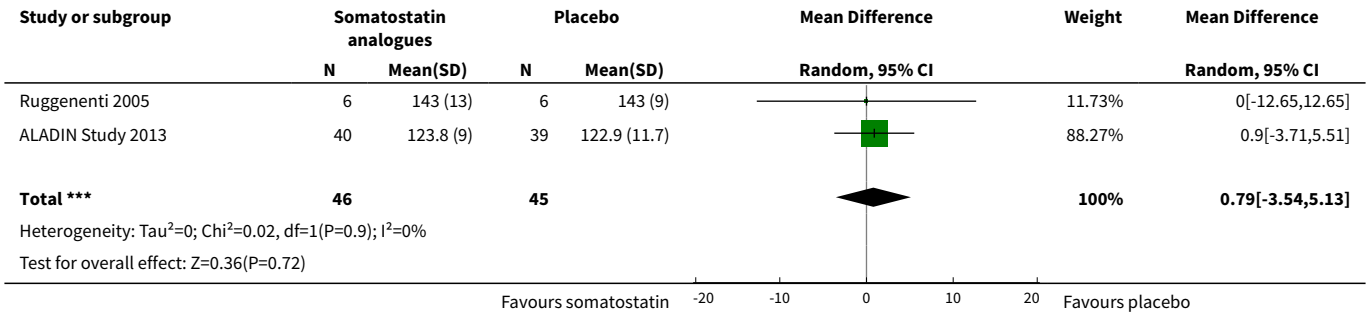
Analysis 11.6. Comparison 11 Somatostatin analogues versus placebo, Outcome 6 Proteinuria.



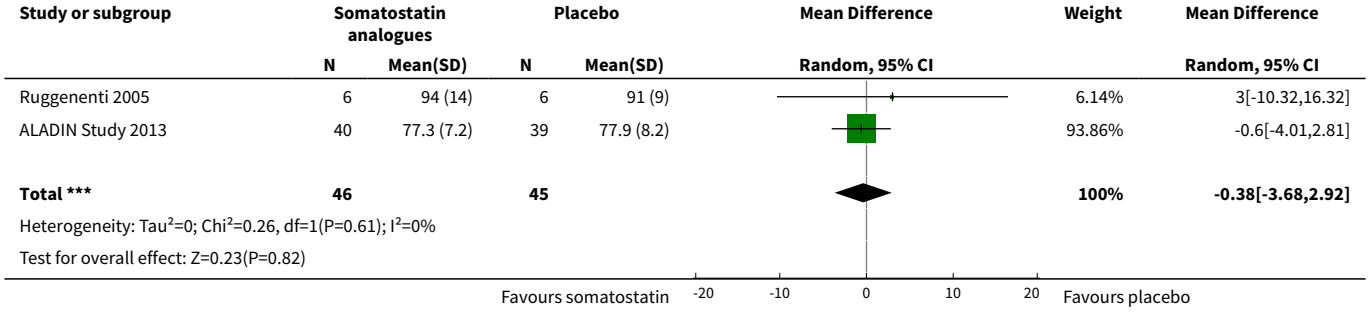
Analysis 11.7. Comparison 11 Somatostatin analogues versus placebo, Outcome 7 Albuminuria.



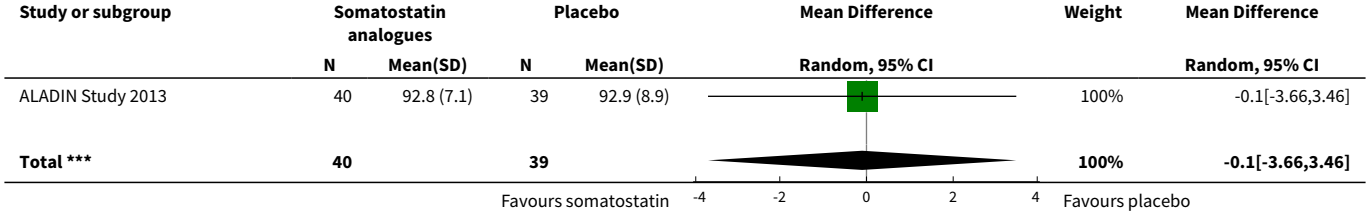
Analysis 11.8. Comparison 11 Somatostatin analogues versus placebo, Outcome 8 Systolic blood pressure.

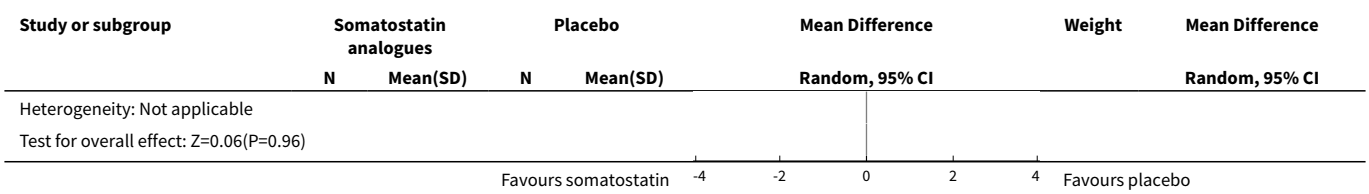


Analysis 11.9. Comparison 11 Somatostatin analogues versus placebo, Outcome 9 Diastolic blood pressure.

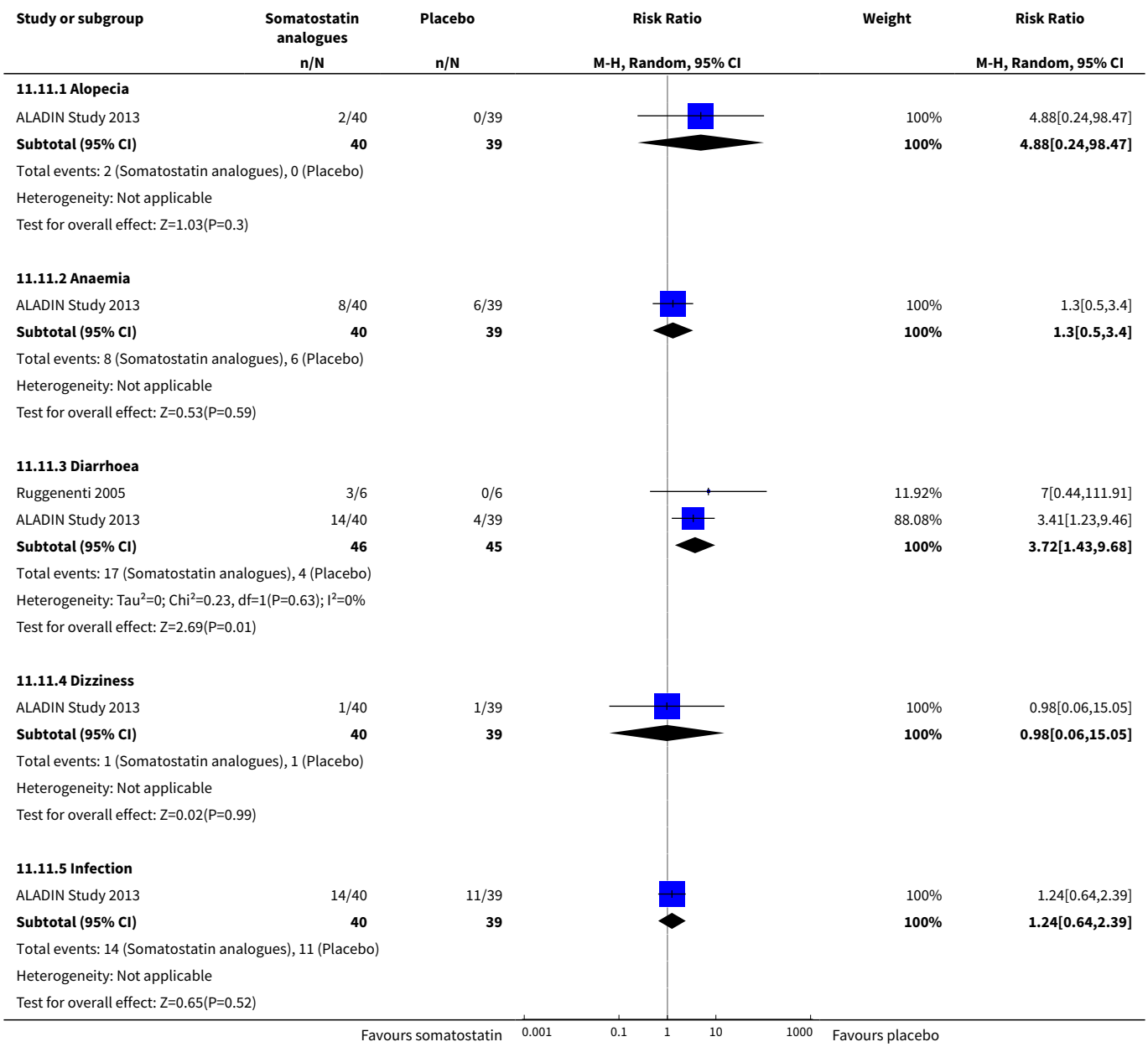


Analysis 11.10. Comparison 11 Somatostatin analogues versus placebo, Outcome 10 Mean arterial pressure.





Analysis 11.11. Comparison 11 Somatostatin analogues versus placebo, Outcome 11 Adverse events.



Comparison 12. Somatostatin analogues + mTOR inhibitors versus somatostatin analogues alone

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

Analysis 12.1. Comparison 12 Somatostatin analogues + mTOR inhibitors versus somatostatin analogues alone, Outcome 1 Total kidney volume descriptive data.

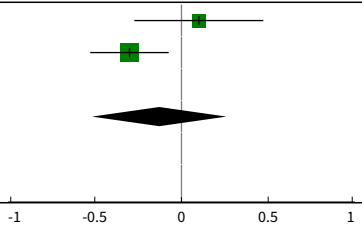
Study	Total kidney volume descriptive data
ELATE Study 2011	quote: "The median kidney volume was not affected by octreotide and did not change significantly in the 6 patients through the course of the trial (from 798 mL (IQR 675–1960 mL) at baseline to 811 mL (IQR 653–1960 mL) after 48 weeks, p=0.75). 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 13. Antiplatelet agents versus placebo

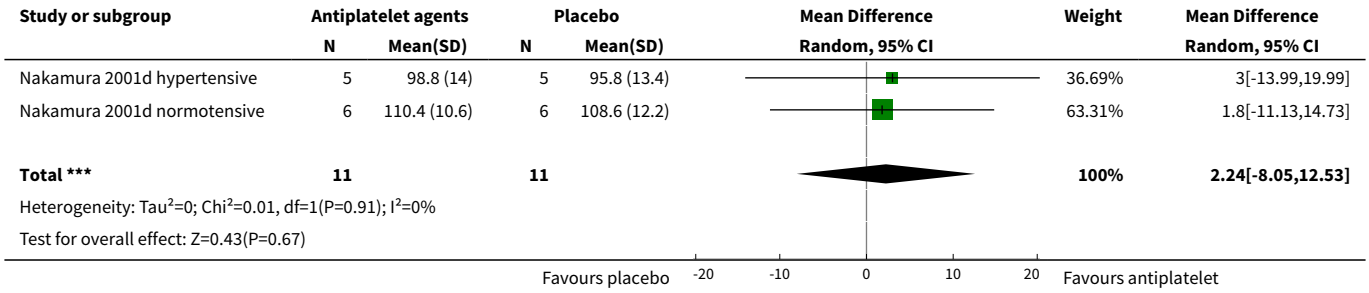
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Creatinine	2	22	Mean Difference (IV, Random, 95% CI)	-0.13 [-0.52, 0.26]
2 GFR [mL/min/1.73 m^2]	2	22	Mean Difference (IV, Random, 95% CI)	2.24 [-8.05, 12.53]
3 Albuminuria	2	22	Mean Difference (IV, Random, 95% CI)	-60.53 [-129.06, 8.01]
4 Systolic blood pressure	2	22	Mean Difference (IV, Random, 95% CI)	5.04 [-7.34, 17.43]
5 Diastolic blood pressure	2	22	Mean Difference (IV, Random, 95% CI)	6.24 [-3.27, 15.74]

Analysis 13.1. Comparison 13 Antiplatelet agents versus placebo, Outcome 1 Creatinine.

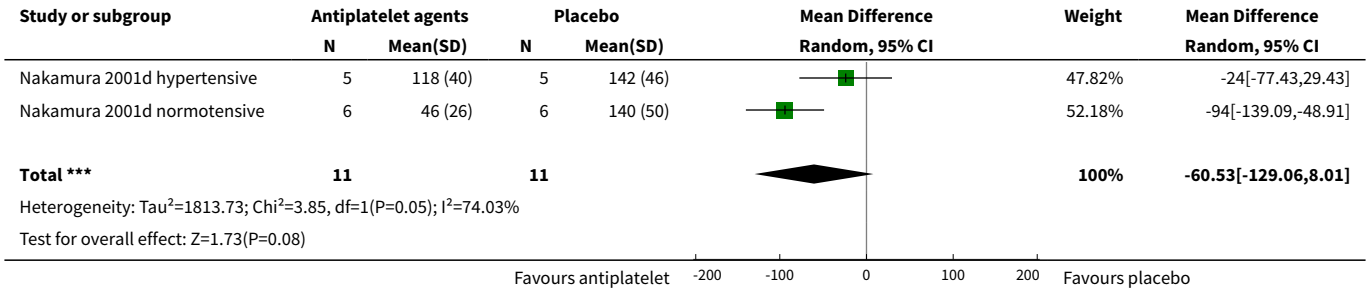
Study or subgroup	Antiplatelet agents N	Antiplatelet agents Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Nakamura 2001d hypertensive	5	1 (0.3)	5	0.9 (0.3)		42.92%	0.1[-0.27,0.47]
Nakamura 2001d normotensive	6	0.7 (0.2)	6	1 (0.2)		57.08%	-0.3[-0.53,-0.07]
Total ***	**11**		**11**			**100%**	**-0.13[-0.52,0.26]**
Heterogeneity: Tau^2=0.06; Chi^2=3.24, df=1(P=0.07); I^2=69.17%							
Test for overall effect: Z=0.65(P=0.52)							



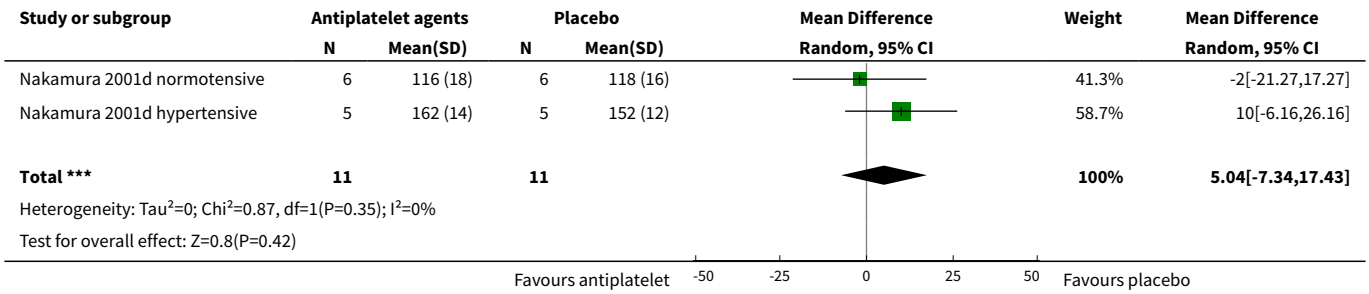
Analysis 13.2. Comparison 13 Antiplatelet agents versus placebo, Outcome 2 GFR [mL/min/1.73 m^2].



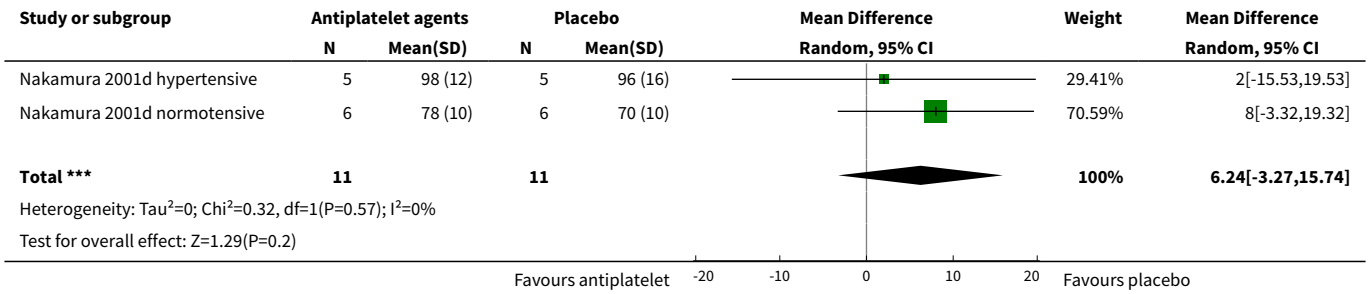
Analysis 13.3. Comparison 13 Antiplatelet agents versus placebo, Outcome 3 Albuminuria.



Analysis 13.4. Comparison 13 Antiplatelet agents versus placebo, Outcome 4 Systolic blood pressure.



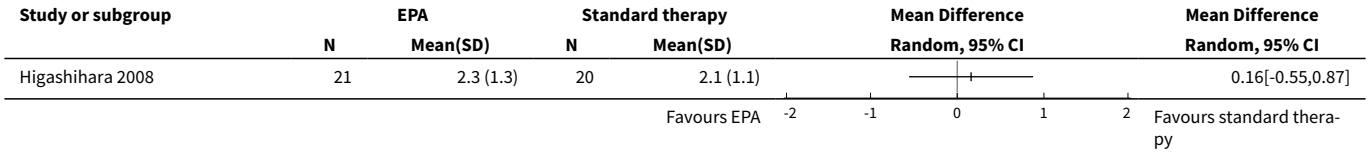
Analysis 13.5. Comparison 13 Antiplatelet agents versus placebo, Outcome 5 Diastolic blood pressure.



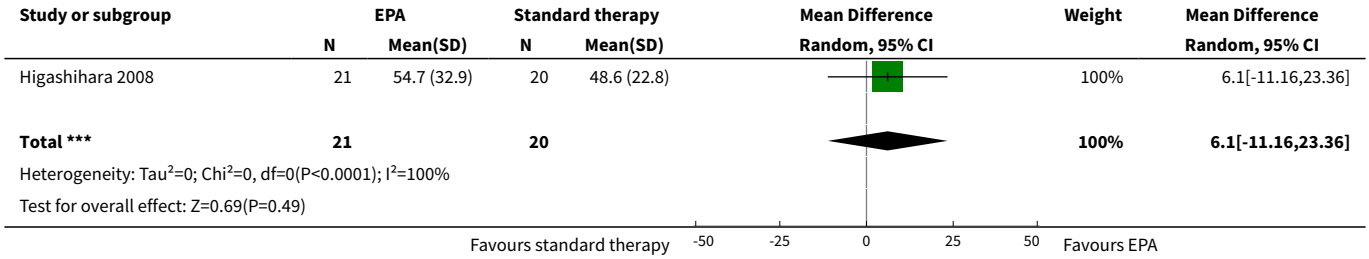
Comparison 14. Eicosapentaenoic acids versus standard therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Creatinine	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 GFR [mL/min/1.73 m^2]	1	41	Mean Difference (IV, Random, 95% CI)	6.10 [-11.16, 23.36]
3 Total kidney volume	1	41	Mean Difference (IV, Random, 95% CI)	-209.0 [-729.06, 311.06]
4 Albuminuria	1	41	Mean Difference (IV, Random, 95% CI)	82.40 [-162.09, 326.89]

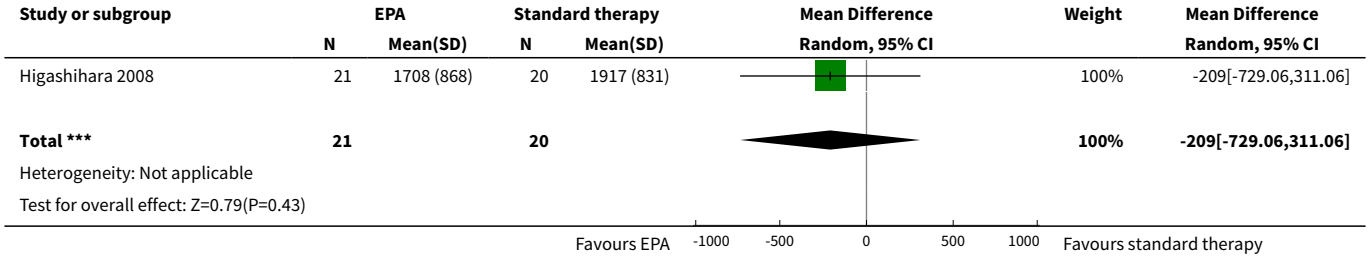
Analysis 14.1. Comparison 14 Eicosapentaenoic acids versus standard therapy, Outcome 1 Creatinine.



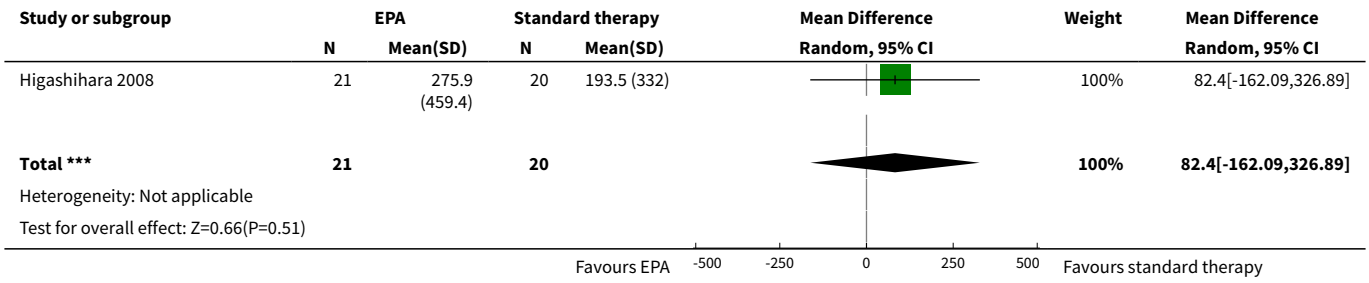
Analysis 14.2. Comparison 14 Eicosapentaenoic acids versus standard therapy, Outcome 2 GFR [mL/min/1.73 m^2].



Analysis 14.3. Comparison 14 Eicosapentaenoic acids versus standard therapy, Outcome 3 Total kidney volume.



Analysis 14.4. Comparison 14 Eicosapentaenoic acids versus standard therapy, Outcome 4 Albuminuria.



Comparison 15. Statins versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 GFR descriptive data			Other data	No numeric data
2 GFR descriptive data from cross-over studies			Other data	No numeric data
3 Proteinuria descriptive data			Other data	No numeric data
4 Systolic blood pressure	1	49	Mean Difference (IV, Random, 95% CI)	1.70 [-6.39, 9.79]
5 Diastolic blood pressure	1	49	Mean Difference (IV, Random, 95% CI)	-1.40 [-5.54, 2.74]

Analysis 15.1. Comparison 15 Statins versus no treatment, Outcome 1 GFR descriptive data.

GFR descriptive data

Study	
Fassett 2010	There was a 23% reduction in the rate of GFR change in statins-treated patients compared with controls, although not statistically significant

Analysis 15.2. Comparison 15 Statins versus no treatment, Outcome 2 GFR descriptive data from cross-over studies.

GFR descriptive data from cross-over studies

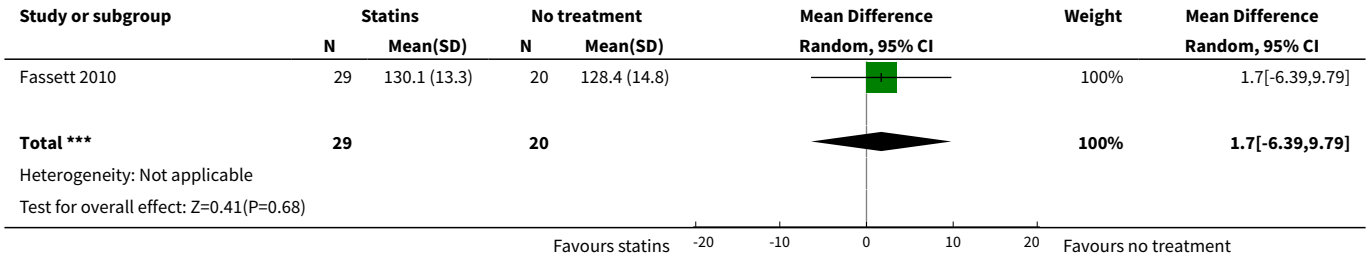
Study	
van Dijk 2001	Compared to placebo, treatment with statins significantly increased GFR from 124 ± 4 mL/min to 132 ± 6 mL/min ($p < 0.05$)

Analysis 15.3. Comparison 15 Statins versus no treatment, Outcome 3 Proteinuria descriptive data.

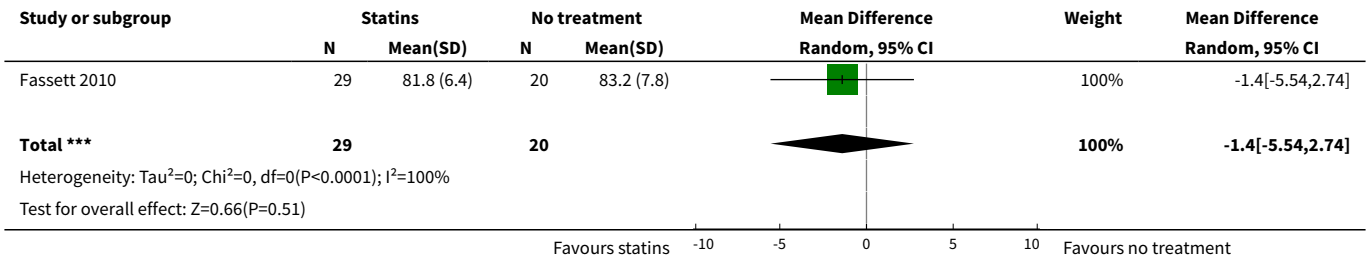
Proteinuria descriptive data

Study	
Fassett 2010	Urinary protein excretion decreased by 2.8% in statins-treated patients and increased by 21.2% in controls

Analysis 15.4. Comparison 15 Statins versus no treatment, Outcome 4 Systolic blood pressure.



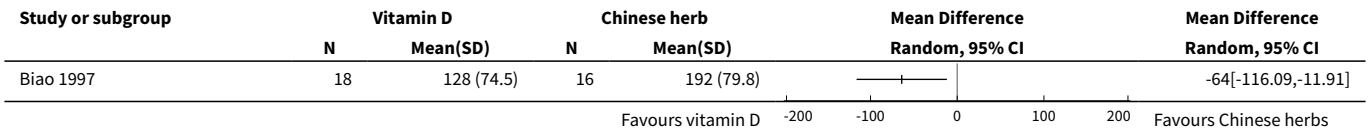
Analysis 15.5. Comparison 15 Statins versus no treatment, Outcome 5 Diastolic blood pressure.



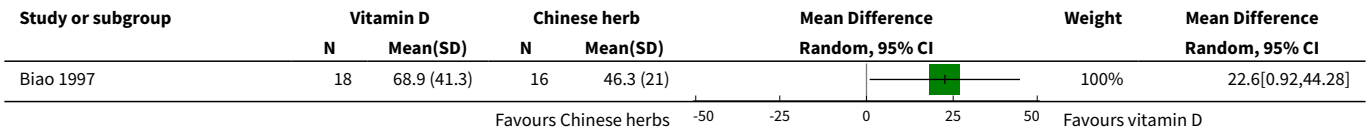
Comparison 16. Vitamin D versus traditional Chinese herbal medicine

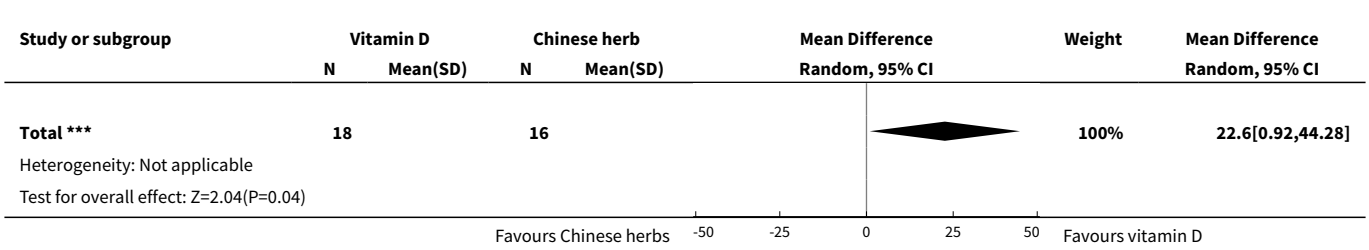
Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Creatinine	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 GFR	1	34	Mean Difference (IV, Random, 95% CI)	22.60 [0.92, 44.28]

Analysis 16.1. Comparison 16 Vitamin D versus traditional Chinese herbal medicine, Outcome 1 Creatinine.



Analysis 16.2. Comparison 16 Vitamin D versus traditional Chinese herbal medicine, Outcome 2 GFR.





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.

(Continued)

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.
	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).

(Continued)

	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
3 September 2015	Amended	Two ongoing studies moved to studies awaiting assessment; one ongoing study move to excluded studies
3 September 2015	Feedback has been incorporated	Ongoing studies now completed

HISTORY

Protocol first published: Issue 1, 2013
Review first published: Issue 7, 2015

Date	Event	Description
31 August 2015	Amended	Correction of search dates

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: DB, JC, GS
2. Study selection: DB, MR
3. Extract data from studies: DB, MR
4. Enter data into RevMan: DB, MR
5. Carry out the analysis: DB, MR, SP, GS
6. Interpret the analysis: DB, SP, GS
7. Draft the final review: DB, CZ, JC, SP, GS
8. Disagreement resolution: SP
9. Update the review: DB, MR, SP, GS

DECLARATIONS OF INTEREST

- Davide Bolignano: none known
- Suetonia C Palmer: none known
- Marinella Ruospo: none known
- Carmine Zoccali: none known
- Jonathan C Craig: none known
- Giovanni FM Strippoli: none known.

INDEX TERMS

Medical Subject Headings (MeSH)

*Disease Progression; Angiotensin-Converting Enzyme Inhibitors [therapeutic use]; Antidiuretic Hormone Receptor Antagonists [therapeutic use]; Eicosapentaenoic Acid [therapeutic use]; Platelet Aggregation Inhibitors [therapeutic use]; Polycystic Kidney, Autosomal Dominant [*prevention & control]; Randomized Controlled Trials as Topic; TOR Serine-Threonine Kinases [antagonists & inhibitors]

MeSH check words

Adult; Child; Humans