# National Institute for Health and Care Excellence

Draft

# Chronic kidney disease

## [H] Evidence reviews for interventions to lower proteinuria

*NICE guideline TBC*

*Evidence reviews underpinning recommendations 1.6.5 to 1.6.11 and research recommendations in the NICE guideline*

*January 2021*

*Draft for Consultation*

*These evidence reviews were developed by Guideline Updates Team*

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# 1 Interventions to lower proteinuria

## 2 1.1 Review question

3 For adults, children and young people with suspected or diagnosed chronic kidney disease
4 (CKD), what is the effect of interventions to lower proteinuria?

### 5 1.1.1 Introduction

6 The NICE guideline on chronic kidney disease in adults: assessment and management
7 (NICE guideline CG182) was reviewed in 2017 as part of NICE's routine surveillance
8 programme to determine whether new evidence was available that could alter current
9 recommendations. The decision was to update the guideline. Therefore, the proposed
10 update went through a scoping process. During scoping, it was decided to add a new review
11 question to investigate the effect of interventions to lower proteinuria in adults, children and
12 young people with suspected or diagnosed CKD and proteinuria or albuminuria.

13 The aim of this review is to assess the effect of interventions to lower proteinuria in adults,
14 children and young people with CKD. This review identified randomised controlled trials
15 (RCTs) that fulfilled the conditions specified in Table 1. For full details of the review protocol,
16 see Appendix A.

### 17 1.1.2 Summary of the protocol

18 **Table 1: PICO table for interventions to lower proteinuria**

| | |
|---|---|
| **Population** | Adults, children and young people with suspected or diagnosed chronic kidney disease stages 1 to 5 and proteinuria or albuminuria.<br>Exclusion:<br>• people receiving renal replacement therapy (RRT)<br>• people with acute kidney injury combined with rapidly progressive glomerulonephritis<br>• people receiving palliative care. |
| **Intervention** | Interventions to lower proteinuria<br>• Blood pressure medication<br>• Diabetes medication<br>• Weight loss/Exercise<br>• Dietary interventions (NaCl, protein)<br>• Endothelin antagonists |
| **Comparator** | • No intervention<br>• Placebo<br>• Other intervention in class to lower proteinuria (for diabetes and blood pressure medication)<br>• Other interclass intervention |
| **Outcome** | Over the follow up of the study:<br>• Reduction in proteinuria<br>• CKD progression: occurrence of end stage kidney disease (ESRD or ESKD as reported by the study)<br>• Mortality (all-cause and cardiovascular)<br>• Specific morbidity:<br>  ○ fractures,<br>  ○ advancement of renal bone disease,<br>  ○ vascular calcification, |

| | |
|---|---|
| | ○ cardiovascular impact,<br>○ anaemia<br>• Health-related quality of life<br>• Adverse outcome:<br>○ AKI,<br>○ drug specific (hypotension/falls, hypoglycaemia, hospitalisation) |

### 1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods in Appendix B.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

The following methods were specific for this review:

1. The evidence was analysed by class of medication because it was assumed that medications within a class would have similar mechanisms of action and similar pharmaceutical effects.
    a. Blood pressure medications (6 classes):
        i. angiotensin-converting-enzyme inhibitors
        ii. aldosterone antagonists
        iii. angiotensin receptor blockers
        iv. calcium channel blockers
        v. direct renin inhibitors
        vi. diuretics
    b. Blood glucose medications (4 classes)
        i. dipeptidyl peptidase-4 inhibitors
        ii. thiazolidinediones
        iii. sodium–glucose cotransporter 2 inhibitors (SGLT2 inhibitors)
        iv. insulin
2. A network meta-analysis was not undertaken for this analysis because of the heterogeneity of the included papers (populations, underlying conditions, length of follow up etc) in 2021. Pairwise meta-analysis was done when studies reported on the same comparison and it was considered feasible to combine.
3. Thresholds were agreed with the committee to identify studies including participants with proteinuria or albuminuria:
    a. Proteinuria
        i. urinary protein:creatinine ratio >15 mg/mmol (>150 mg/g)
        ii. urinary protein 24 h >150 mg/24 h
    b. Albuminuria
        i. urinary albumin:creatinine ratio >3 mg/mmol (30 mg/g)
        ii. urinary albumin 24 h >30 mg/24 h
4. Some studies reported protein:creatinine ratio and albumin:creatinine ratio as mg/g, but the committee highlighted that mg/mmol is the preferred unit of measure in the UK. Therefore, any data on protein:creatinine ratio and albumin:creatinine ratio reported as mg/g were converted to the preferred measure mg/mmol multiplying by 0.113 (KDIGO 2013; some of the conversions were rounded to the closest proteinuria or albuminuria threshold [see bullet point 3 above]). This was done to make outcomes comparable and because mg/mmol is the preferred metric in the UK.

## 1.1.4 Effectiveness evidence

### 1.1.4.1 Included studies

A systematic search was carried out to identify randomised controlled trials (RCTs) and systematic reviews of RCTs, which found 6,046 references (see appendix C for the literature search strategy). Evidence identified from systematic reviews (34 RCTs) was also reviewed. In total, 6,080 references were identified for screening at title and abstract level with 5,904 excluded at this level. Full texts were ordered to be screened for 176 references.

In total 31 RCTs were included based on their relevance to the review protocol (Appendix A). The clinical evidence study selection is presented as a PRISMA diagram in Appendix D.

A second set of searches was conducted at the end of the guideline development process for all updated review questions using the original search strategies, to capture papers published whilst the guideline was being developed. This search returned 316 references for this review question and 2 additional references which were published after the date of the search were identified by a member of the guideline committee which was considered to be relevant for the update, 318 references were screened on title and abstract. Ten references were ordered for full text screening. One RCT was included based on its relevance to the review protocol (Appendix A).

See section 1.1.10.1 Effectiveness for a list of references for included studies.

### 1.1.4.2 Excluded studies

See Appendix L for a list of excluded studies with reasons for exclusion and bibliographic reference.

## 1.1.5 Summary of studies included in the effectiveness evidence

**Table 2: Summary of studies included in the effectiveness evidence**

| Author, year, sample size | Population | Follow-up | Intervention | Comparator | Outcome |
|---|---|---|---|---|---|
| **Adults with type 2 diabetes** | | | | | |
| **Aldosterone antagonist compared to placebo** | | | | | |
| Mehdi, 2009<br>N=81 | **Diabetes**<br>Type 2 around 85%<br>**CKD**<br>diabetic nephropathy<br>**Proteinuria**<br>Urinary albumin/creatinine ratio ≥30 mg/mmol (300 mg/g)[a]<br>**Age**<br>20 to 65 years | 11 months | Spironolactone (aldosterone antagonist) | Placebo | • Reduction in albuminuria<br>• Mortality: cardiovascular<br>• Adverse outcome: hospitalisation |
| van den Meiracker, 2006<br>N=59 | **Diabetes**<br>Type 2<br>**CKD**<br>Diabetic nephropathy<br>**Proteinuria** | 12 months | Spironolactone (aldosterone antagonist) | Placebo | • Reduction in proteinuria<br>• Reduction in albuminuria |

| Author, year, sample size | Population | Follow-up | Intervention | Comparator | Outcome |
|---|---|---|---|---|---|
| | Urinary albumin excretion >300 mg/24 h or urinary albumin/creatinine ratio >20 mg/mmol<br>**Age**<br>20 to 80 years | | | | |
| **ARB compared to placebo** | | | | | |
| Brenner, 2001<br>N=1513 | **Diabetes**<br>Type 2<br>**CKD**<br>Nephropathy<br>**Proteinuria**<br>Urinary protein excretion ≥0.5 g/24 h<br>**Age**<br>31 to 70 years | 3.4 years (range 2.3 to 4.6) | Losartan (ARB) | Placebo | • Reduction in albuminuria<br>• CKD progression: occurrence of end stage kidney disease<br>• Mortality: all cause<br>• Morbidity: non-fatal CV events<br>• Adverse outcome: hospitalisation |
| Lewis, 2001<br>N=1715 | **Diabetes**<br>Type 2<br>**CKD**<br>Diabetic nephropathy<br>**Proteinuria**<br>Urinary protein excretion at least 900 mg/24 h<br>**Age**<br>30 to 70 years | 2 years | Irbesartan (ARB) | Placebo | • Reduction in proteinuria<br>• CKD progression: occurrence of end stage kidney disease<br>• Mortality: all cause |
| Mehdi, 2009<br>N=81 | See above | 11 months | Losartan (ARB) | Placebo | See above |
| **CCB compared to placebo** | | | | | |
| Lewis, 2001<br>N=1715 | See above | 2 years | Amlodipine (CCB) | Placebo | See above |
| **ACE-I compared to ARB** | | | | | |
| Krairittichai, 2009<br>N=80 | **Diabetes**<br>Type 2<br>**CKD**<br>Diabetic nephropathy<br>**Proteinuria**<br>Urinary protein/creatinine ratio >50 mg/mmol (0.5 g/g)[a]<br>**Age** | 6 months | Enalapril (ACE-I) | Telmisartan (ARB) | • Reduction in proteinuria |

| Author, year, sample size | Population | Follow-up | Intervention | Comparator | Outcome |
|---|---|---|---|---|---|
| | Adults | | | | |
| Saglimbene, 2018<br>N=1287 | **Diabetes**<br>Type 2 around 95%<br>**CKD**<br><br>**Proteinuria**<br>moderate albuminuria (urinary albumin/creatinine ratio 3 to 29 mg/mmol (30–299 mg/g)[a] or severe albuminuria (urinary albumin/creatinine ratio ≥30 mg/mmol (300 mg/g)[a]<br>**Age**<br>≥18 years | 2.7 years | ACE inhibitor | ARB | • CKD progression: occurrence of end stage kidney disease<br>• Mortality: all cause<br>• Mortality: cardiovascular<br>• Morbidity: non-fatal CV events<br>• Adverse outcome: hospitalisation ; hypotension |
| **ARB compared to aldosterone antagonist** | | | | | |
| Mehdi, 2009<br>N=81 | See above | 11 months | Losartan (ARB) | Spironolactone (aldosterone antagonist) | See above |
| **ARB compared to CCB** | | | | | |
| Lewis, 2001<br>N=1715 | See above | 2 years | Irbesartan (ARB) | Amlodipine (CCB) | See above |
| **Gliptin compared to placebo** | | | | | |
| Groop, 2017<br>N=360 | **Diabetes**<br>Type 2<br>**CKD**<br>eGFR ≥30 mL/min/1.73 m²<br>**Proteinuria**<br>Urinary albumin/creatinine ratio 3 to 300 mg/mmol (30 to 3000 mg/g)[a]<br>**Age**<br>18 to 80 years | 6 months | Linagliptin (gliptin) | Placebo | • Reduction in albuminuria<br>• Mortality: all cause<br>• Adverse outcome: hypoglycaemia |
| **Thiazolidinedione compared to placebo** | | | | | |
| Kanjanabuch, 2009<br>N=41 | **Diabetes**<br>Type 2<br>**CKD**<br>Biopsy-proven immunoglobulin A nephropathy<br>**Proteinuria** | 4 months | Pioglitazone (thiazolidinedione) | Placebo | • Reduction in proteinuria |

| Author, year, sample size | Population | Follow-up | Intervention | Comparator | Outcome |
|---|---|---|---|---|---|
| | Urinary protein excretion ≥0.5 g/24 h<br>**Age**<br>Adults | | | | |
| **SGLT2 inhibitor compared to placebo** | | | | | |
| Heerspink, 2020<br>N=4,304 | **Diabetes**<br>With and without type 2<br>**CKD**<br>eGFR 25 to 75 mL/min/1.73 m²<br>**Proteinuria**<br>Urinary albumin/creatinine ratio 20 to 50 mg/mmol<br>**Age**<br>Adults | 2.4 years | Dapagliflozin (SGLT2 inhibitor) | Placebo | • CKD progression: occurrence of end stage kidney disease<br>• Mortality: all cause<br>• Mortality: cardiovascular<br>• Morbidity: fracture<br>• Adverse outcome: major hypoglycaemia |
| Neuen, 2019<br>N=3026 | **Diabetes**<br>Type 2<br>**CKD**<br>Microalbuminuria, macroalbuminuria<br>**Proteinuria**<br>microalbuminuria (urinary albumin/creatinine ratio 3 to 30 mg/mmol (30 to <300 mg/g)[a], macroalbuminuria (urinary albumin/creatinine ratio ≥30 mg/mmol (300 mg/g)[a]<br>**Age**<br>≥30 years | 6 years | Canagliflozin (SGLT2 inhibitor) | Placebo | • Mortality: all cause |
| Perkovic, 2019<br>N=4401 | **Diabetes**<br>Type 2<br>**CKD**<br>eGFR 30 to <90 ml per minute per 1.73 m²<br>**Proteinuria**<br>Urinary albumin/creatinine ratio >30 to 500 | 6 months | Canagliflozin (SGLT2 inhibitor) | Placebo | • CKD progression: occurrence of end stage kidney disease<br>• Mortality: all cause<br>• Mortality: cardiovascular |

| Author, year, sample size | Population | Follow-up | Intervention | Comparator | Outcome |
|---|---|---|---|---|---|
| | mg/mmol (300 to 5000 mg/g)[a]<br>**Age**<br>≥30 years | | | | • Adverse outcome: hospitalisation ; acute kidney injury |
| Pollock, 2019<br>N=461 | **Diabetes**<br>Type 2<br>**CKD**<br>eGFR 20 to 80 mL/min/1.73 m²<br>**Proteinuria**<br>Urinary albumin/creatinine ratio 3 to 350 mg/mmol (30 to 3500 mg/g)[a]<br>**Age**<br>≥18 years | 6 months | Dapagliflozin (SGLT2 inhibitor) | Placebo | • Reduction in albuminuria<br>• Mortality: all cause<br>• Adverse outcome: hypoglycaemia |
| **SGLT2 inhibitor + gliptin compared to SGLT2 inhibitor** | | | | | |
| Pollock, 2019<br>N=461 | See above | 6 months | Dapagliflozin (SGLT2 inhibitor) plus Saxagliptin (gliptin) | Dapagliflozin (SGLT2 inhibitor) | See above |
| **Exercise compared to no intervention** | | | | | |
| Leehey, 2009<br>N=13 | **Diabetes**<br>Type 2<br>**CKD**<br>stage 2-4 CKD (eGFR 15-90 mL/min/1.73 m²)<br>**Proteinuria**<br>Urinary protein/creatinine ratio >20 mg/mmol (200 mg/g)[a]<br>**Age**<br>Adults | 6 months | Exercise | No intervention (patients did not participate in any exercise training) | • Reduction in proteinuria<br>• Reduction in albuminuria |
| **Exercise compared to diet** | | | | | |
| Leehey, 2016<br>N=36 | **Diabetes**<br>Type 2<br>**CKD**<br>CKD stages 2–4 (eGFR 15 to 90 ml/min/ 1.73 m²)<br>**Proteinuria**<br>Urinary protein/creatinine ratio >20 mg/mmol (200 mg/g)[a]<br>**Age**<br>Adults | 12 months | Exercise plus Diet | Diet-Alone | • Health-related quality of life |
| **ACE-I + ARB compared to ARB** | | | | | |

| Author, year, sample size | Population | Follow-up | Intervention | Comparator | Outcome |
|---|---|---|---|---|---|
| Fried, 2013<br>N=1448 | **Diabetes**<br>Type 2<br>**CKD**<br>eGFR 30.0 to 89.9 ml/min/1.73 m²<br>**Proteinuria**<br>Urinary albumin/creatinine ratio ≥30 mg/mmol (300 mg/g)[a]<br>**Age**<br>Adults | 2.2 years | Losartan (ARB) plus Lisinopril (ACE-I) | Losartan (ARB) plus Placebo | • Reduction in albuminuria<br>• CKD progression: occurrence of end stage kidney disease<br>• Mortality: all cause<br>• Morbidity: non-fatal CV events<br>• Adverse outcome: acute kidney injury |
| Saglimbene, 2018<br>N=1287 | See above | 2.7 years | ACE inhibitor plus ARB | ARB | See above |
| **ACE-I + ARB compared to ACE-I** | | | | | |
| Saglimbene, 2018<br>N=1287 | See above | 2.7 years | ACE inhibitor plus ARB | ACE inhibitor | See above |
| **Adults without type 2 diabetes** | | | | | |
| **ACE-I compared to placebo** | | | | | |
| GISEN group, 1997<br>N=166 | **CKD**<br>creatinine clearance 20-70 mL/min per 1.73m²<br>**Proteinuria**<br>Urinary protein excretion >1 g/24 h<br>**Age**<br>18 to 70 years | 3 years | Ramipril (ACE-I) | Placebo | • Reduction in proteinuria<br>• CKD progression: occurrence of end stage kidney disease<br>• Mortality: all cause<br>• Mortality: cardiovascular<br>• Morbidity: non-fatal CV events |
| Lewis, 1993<br>N=409 | **Diabetes**<br>Type 1<br>**CKD**<br>Diabetic nephropathy<br>**Proteinuria**<br>Urinary protein excretion ≥500 mg/24 h<br>**Age**<br>18 to 49 years | 3 years | Captopril (ACE-I) | Placebo | • CKD progression: occurrence of end stage kidney disease<br>• Mortality: all cause |

| Author, year, sample size | Population | Follow-up | Intervention | Comparator | Outcome |
|---|---|---|---|---|---|
| Ruggenenti, 1999<br>N=186 | **CKD**<br>chronic nephropathy<br>**Proteinuria**<br>Urinary protein excretion ≥1 g/24 h<br>**Age**<br>18 to 70 years | 6 years | Ramipril (ACE-I) | Placebo | • CKD progression: occurrence of end stage kidney disease<br>• Mortality: cardiovascular |
| **Aldosterone antagonist compared to placebo** | | | | | |
| Ando, 2014b<br>N=336 | **CKD**<br>eGFR ≥50 mL/min per 1.73 m²<br>**Proteinuria**<br>Urinary albumin/creatinine ratio 3 to 59 mg/mmol (30–599 mg/g)[a]<br>**Age**<br>20 to 79 years | 12 months | Eplerenone (aldosterone antagonist) | Placebo | • Reduction in albuminuria<br>• Mortality: all cause<br>• Morbidity: non-fatal CV events |
| **ARB compared to placebo** | | | | | |
| Li, 2006<br>N=109 | **CKD**<br>Biopsy-confirmed immunoglobulin A nephropathy<br>**Proteinuria**<br>Urinary protein excretion ≥1 g/24 h<br>**Age**<br>≥18 years | 2 years | Valsartan (ARB) | Placebo | • Reduction in proteinuria<br>• Morbidity: non-fatal CV events |
| **ARB compared to control** | | | | | |
| Lee, 2011<br>N=32 | **CKD**<br>Chronic non-diabetic CKD<br>**Proteinuria**<br>Urinary protein/creatinine ratio 40 to 200 mg/mmol (0.4 to 2.0 g/g)[a]<br>**Age**<br>20 to 65 years | 24 months | Losartan (ARB) | Control (usual antihypertensive therapy except ACE inhibitors and ARBs) | • Reduction in proteinuria<br>• Reduction in albuminuria |
| **ACE-I compared to ARB** | | | | | |
| Luño, 2002<br>N=46 | **CKD**<br>eGFR >50 mL/min/1.73m²<br>**Proteinuria**<br>Urinary protein excretion >2 g/24 h<br>**Age**<br>18 to 80 years | 6 months | Lisinopril (ACE-I) | Candesartan (ARB) | • Reduction in proteinuria |

| Author, year, sample size | Population | Follow-up | Intervention | Comparator | Outcome |
|---|---|---|---|---|---|
| Matsuda, 2003a<br>N=52 | **CKD**<br>Immunoglobulin A nephropathy; membranous nephropathy; focal segmental glomerulosclerosis ; and proliferative glomerulonephritis<br>**Proteinuria**<br>Urinary protein excretion >0.3 g/24 h<br>**Age**<br>Adults | 11 months | ACE-I | ARB | • Reduction in proteinuria |
| Matsuda, 2003b<br>N=62 | **CKD**<br>Underlying renal diseases: proliferative glomerulonephritis, membranous nephropathy, or focal segmental glomerulosclerosis<br>**Proteinuria**<br>Urinary protein excretion >0.5 g/24 h<br>**Age**<br>Adults | 22 months | Perindopril (ACE-I)<br>Or<br>Trandolapril (ACE-I) | Candesartan (ARB)<br>Or<br>Losartan (ARB) | • Reduction in proteinuria |
| **ARB compared to CCB** | | | | | |
| Iino, 2003<br>N=93 | **CKD**<br>serum creatinine ≥1.5 and <3.0 mg/dl in men of body weight 60 kg or more, and ≥1.3 and < 3.0 mg/dl in females or males of body weight <60 kg<br>**Proteinuria**<br>Urinary protein excretion ≥0.5 g/24 h<br>**Age**<br>20 to 75 years | 12 months | Losartan (ARB) | Amlodipine (CCB) | • Reduction in proteinuria<br>• Morbidity: non-fatal CV events |
| Praga, 2003<br>N=97 | **CKD**<br>chronic proteinuric nephropathy of non-diabetic cause<br>**Proteinuria** | 4.5 months | Losartan (ARB) | Amlodipine (CCB) | • Reduction in proteinuria |

| Author, year, sample size | Population | Follow-up | Intervention | Comparator | Outcome |
|---|---|---|---|---|---|
| | Urinary protein excretion >1.5 g/24 h<br>**Age**<br>≥18 years | | | | |
| **Subcutaneous insulin infusion compared to conventional insulin** | | | | | |
| Ciavarella, 1985<br>N=10 | **Diabetes**<br>Type 1<br>**CKD**<br>Diabetic nephropathy<br>**Proteinuria**<br>Urinary protein excretion >0.5 g/24 h<br>**Age**<br>Adults | 12 months | Subcutaneous insulin infusion | Conventional insulin | • Reduction in albuminuria |
| **ACE-I + ARB compared to ARB** | | | | | |
| Luño, 2002<br>N=46 | See above | 6 months | Candesartan (ARB) plus Lisinopril (ACE-I) | Candesartan (ARB) | See above |
| **ACE-I + ARB compared to ACE-I** | | | | | |
| Kanno, 2006<br>N=90 | **CKD**<br>chronic renal insufficiency<br>**Proteinuria**<br>Urinary protein excretion >1.0 g/24 h<br>**Age**<br>35 to 79 years | 3 years | Candesartan (ARB) plus ACE Inhibitor | ACE Inhibitors | • Reduction in proteinuria |
| Luño, 2002<br>N=46 | See above | 6 months | Candesartan (ARB) plus Lisinopril (ACE-I) | Lisinopril (ACE-I) | See above |
| **ARB + CCB compared to ARB** | | | | | |
| Ameen, 2016<br>N=140 | **CKD**<br>No details of CKD stage<br>**Proteinuria**<br>Urinary albumin/creatinine ratio >3.5 mg/mmol<br>**Age**<br>20 to 70 years | 6 months | Valsartan (ARB) and Amlodipine (ACE-I) | Valsartan (ARB) | • Reduction in albuminuria |
| **ARB + diuretic compared to ARB** | | | | | |
| Fujisaki, 2014<br>N=102 | **CKD**<br>eGFR ≥15 ml/min/1.73m² <br>**Proteinuria** | 12 months | Losartan plus Hydrochlorothiazide | Losartan | • Reduction in proteinuria |

| Author, year, sample size | Population | Follow-up | Intervention | Comparator | Outcome |
|---|---|---|---|---|---|
| | Urinary protein/creatinine ratio 30 mg/mmol (300 mg/g)[a]<br>**Age**<br>20 to 74 years | | | | |
| **Spironolactone + conventional therapy compared to conventional therapy** | | | | | |
| Bianchi, 2006<br>N=165 | **CKD**<br>eGFR 34 to 116 ml/min/ 1.73m²; clinical diagnosis of idiopathic chronic glomerulonephritis based on the presence of proteinuria (urinary protein/creatinine ratio >1.0 g/g) and no evidence of systemic diseases<br>**Proteinuria**<br>Urinary protein/creatinine ratio 100 to 390 mg/mmol (1.0 to 3.9 g/g)[a]<br>**Age**<br>Adults | 12 months | Conventional therapy plus spironolactone | Conventional therapy | • Reduction in proteinuria |

(a) *Original measure before conversion to mg/mmol (mg/g multiply by 0.113 to convert to mg/mmol; if needed, g/g was converted to mg/g multiplying g/g by 1000)*

*ACE-I: angiotensin-converting-enzyme inhibitors; ARB: angiotensin receptor blockers; CKD: chronic kidney disease; CV: cardiovascular*

See Appendix E for full evidence tables.

## 1.1.6 Summary of the effectiveness evidence

### 1.1.6.1 Adults with type 2 diabetes

**Table 3: Aldosterone antagonist vs Placebo**

| Aldosterone antagonist | Placebo | Effect size (95% CI) | Quality | Interpretation of effect[a] |
|---|---|---|---|---|
| **Urinary protein/creatinine ratio (mean percentage change) - Spironolactone vs placebo (type 2 diabetes) (Better indicated by lower values)** | | | | |
| 24 | 28 | MD 27.1 lower (58.75 lower to 4.55 higher) | VERY LOW | Could not differentiate |
| **Urinary albumin/creatinine ratio (mean percentage change) - Spironolactone vs placebo (at least 85% type 2 diabetes) (Better indicated by lower values)** | | | | |
| 51 | 55 | MD 29.13 lower (58.10 to 0.16 lower) | VERY LOW | There is an effect, but it is less than the defined MID |
| **Non-fatal CV events - Spironolactone vs placebo (85% type 2 diabetes)** | | | | |

| Aldosterone antagonist | Placebo | Effect size (95% CI) | Quality | Interpretation of effect[a] |
|---|---|---|---|---|
| 6/27 (22.2%) | 1/27 (3.7%) | RR 6 (0.77 to 46.55) | VERY LOW | Could not differentiate |
| **Hospitalisation - Spironolactone vs placebo (85% type 2 diabetes)** | | | | |
| 6/27 (22.2%) | 1/27 (3.7%) | RR 6 (0.77 to 46.55) | VERY LOW | Could not differentiate |

*a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: statistically significant and point estimate >MID; There is an effect, but it is less than the defined MID: statistically significant and point estimate <MID*

**Table 4: ARB vs Placebo**

| ARB | Placebo | Effect size (95% CI) | Quality | Interpretation of effect |
|---|---|---|---|---|
| **Urinary protein excretion (g/24 h) - Irbesartan vs placebo (type 2 diabetes) (Better indicated by lower values)** | | | | |
| 579 | 569 | MD 0.8 lower (1.18 to 0.42 lower) | MODERATE | There is an effect, but it is less than the defined MID |
| **Urinary albumin/creatinine ratio (mean percentage change) - Losartan vs placebo (85% type 2 diabetes) (Better indicated by lower values)** | | | | |
| 26 | 27 | MD 13.6 lower (70.73 lower to 43.53 higher) | LOW | Could not differentiate |
| **End stage kidney disease** | | | | |
| 219/1330 (16.5%) | 279/1331 (21%) | RR 0.79 (0.67 to 0.92) | LOW | Effect |
| **End stage kidney disease - Losartan vs placebo (type 2 diabetes)** | | | | |
| 147/751 (19.6%) | 194/762 (25.5%) | RR 0.77 (0.64 to 0.93) | LOW | Effect |
| **End stage kidney disease - Irbesartan vs placebo (type 2 diabetes)** | | | | |
| 72/579 (12.4%) | 85/569 (14.9%) | RR 0.83 (0.62 to 1.11) | LOW | Could not differentiate |
| **All-cause mortality** | | | | |
| 233/1330 (17.5%) | 233/1331 (17.5%) | RR 1.0 (0.85 to 1.18) | LOW | No meaningful difference |
| **All-cause mortality - Losartan vs placebo (type 2 diabetes)** | | | | |
| 158/751 (21%) | 155/762 (20.3%) | RR 1.03 (0.85 to 1.26) | LOW | Could not differentiate |
| **All-cause mortality - Irbesartan vs placebo (type 2 diabetes)** | | | | |
| 75/579 (13%) | 78/569 (13.7%) | RR 0.94 (0.7 to 1.27) | LOW | Could not differentiate |
| **Non-fatal CV events - Losartan vs placebo (at least 85% type 2 diabetes)** | | | | |
| 52/777 (6.7%) | 69/789 (8.7%) | RR 0.77 (0.54 to 1.08) | LOW | Could not differentiate |
| **Hospitalisation - Losartan vs placebo (at least 85% type 2 diabetes)** | | | | |
| 91/777 (11.7%) | 128/789 (16.2%) | RR 0.72 (0.56 to 0.93) | LOW | Effect |

*a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: statistically significant and point estimate >MID; There is an effect, but it is less than the defined MID: statistically significant and point estimate <MID*

**Table 5: CCB vs Placebo**

| CCB | Placebo | Effect size (95% CI) | Quality | Interpretation of effect |
|---|---|---|---|---|
| **Urinary protein excretion (g/24 h) - Amlodipine vs Placebo (type 2 diabetes) (Better indicated by lower values)** | | | | |
| 567 | 569 | MD 0.2 higher (0.23 lower to 0.63 higher) | MODERATE | No meaningful difference |
| **End stage kidney disease - Amlodipine vs Placebo (type 2 diabetes)** | | | | |
| 85/567 (15%) | 78/569 (13.7%) | RR 1.09 (0.82 to 1.45) | LOW | Could not differentiate |
| **All-cause mortality - Amlodipine vs Placebo (type 2 diabetes)** | | | | |
| 66/567 (11.6%) | 74/569 (13%) | RR 0.9 (0.66 to 1.22) | LOW | Could not differentiate |

*a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: statistically significant and point estimate >MID; There is an effect, but it is less than the defined MID: statistically significant and point estimate <MID*

**Table 6: ACE-I vs ARB**

| ACE-I | ARB | Effect size (95% CI) | Quality | Interpretation of effect |
|---|---|---|---|---|
| **Urinary protein/creatinine ratio (mg/mmol) - Enalapril vs Telmisartan (type 2 diabetes), 3 months (Better indicated by lower values)** | | | | |
| 40 | 40 | MD 46.33 higher (34.76 lower to 127.42 higher) | VERY LOW | Could not differentiate |
| **Urinary protein/creatinine ratio (mg/mmol) - Enalapril vs Telmisartan (type 2 diabetes), 6 months (Better indicated by lower values)** | | | | |
| 40 | 40 | MD 74.58 higher (6.72 lower to 155.88 higher) | VERY LOW | Could not differentiate |
| **End stage kidney disease - ACE-I vs ARB (95% type 2 diabetes)** | | | | |
| 6/413 (1.5%) | 2/414 (0.48%) | RR 3.01 (0.61 to 14.81) | VERY LOW | Could not differentiate |
| **All-cause mortality - ACE-I vs ARB (95% type 2 diabetes)** | | | | |
| 15/413 (3.6%) | 20/414 (4.8%) | RR 0.75 (0.39 to 1.45) | VERY LOW | Could not differentiate |
| **CV mortality - ACE-I vs ARB (95% type 2 diabetes)** | | | | |
| 6/413 (1.5%) | 7/414 (1.7%) | RR 0.86 (0.29 to 2.53) | VERY LOW | Could not differentiate |
| **Non-fatal CV events - ACE-I vs ARB (95% type 2 diabetes)** | | | | |
| 8/413 (1.9%) | 6/414 (1.4%) | RR 1.34 (0.47 to 3.82) | VERY LOW | Could not differentiate |
| **Adverse events (hypotension) - ACE-I vs ARB (95% type 2 diabetes)** | | | | |
| 3/413 (0.73%) | 2/414 (0.48%) | RR 1.5 (0.25 to 8.95) | VERY LOW | Could not differentiate |
| **Hospitalisation - ACE-I vs ARB (95% type 2 diabetes)** | | | | |
| 25/413 (6.1%) | 20/414 (4.8%) | RR 1.25 (0.71 to 2.22) | VERY LOW | Could not differentiate |

*a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: statistically significant and point estimate >MID; There is an effect, but it is less than the defined MID: statistically significant and point estimate <MID*

**Table 7: ARB vs Aldosterone antagonist**

| ARB | Aldosterone antagonist | Effect size (95% CI) | Quality | Interpretation of effect |
|---|---|---|---|---|
| **Urinary albumin/creatinine ratio (mean percentage change) - Losartan vs Spironolactone (85% type 2 diabetes) (Better indicated by lower values)** | | | | |
| 26 | 27 | MD 13.4 higher (28.72 lower to 55.52 higher) | LOW | Could not differentiate |
| **Non-fatal CV events - Losartan vs Spironolactone (85% type 2 diabetes)** | | | | |
| 2/26 (7.7%) | 6/27 (22.2%) | RR 0.35 (0.08 to 1.56) | VERY LOW | Could not differentiate |
| **Hospitalisation - Losartan vs Spironolactone (85% type 2 diabetes)** | | | | |
| 2/26 (7.7%) | 6/27 (22.2%) | RR 0.35 (0.08 to 1.56) | VERY LOW | Could not differentiate |

*a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: statistically significant and point estimate >MID; There is an effect, but it is less than the defined MID: statistically significant and point estimate <MID*

**Table 8: ARB vs CCB**

| ARB | CCB | Effect size (95% CI) | Quality | Interpretation of effect |
|---|---|---|---|---|
| **Urinary protein excretion (g/24 h) - Irbesartan vs Amlodipine (type 2 diabetes) (Better indicated by lower values)** | | | | |
| 579 | 567 | MD 1 lower (1.28 to 0.72 lower) | MODERATE | There is an effect, but it is less than the defined MID |
| **End stage kidney disease - Irbesartan vs Amlodipine (type 2 diabetes)** | | | | |
| 71/579 (12.3%) | 91/567 (16%) | RR 0.76 (0.57 to 1.02) | LOW | Could not differentiate |
| **All-cause mortality - Irbesartan vs Amlodipine (type 2 diabetes)** | | | | |
| 78/579 (13.5%) | 73/567 (12.9%) | RR 1.05 (0.78 to 1.41) | LOW | Could not differentiate |

*a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: statistically significant and point estimate >MID; There is an effect, but it is less than the defined MID: statistically significant and point estimate <MID*

**Table 9: Gliptin vs Placebo**

| Gliptin | Placebo | Effect size (95% CI) | Quality | Interpretation of effect |
|---|---|---|---|---|
| **Urinary albumin/creatinine ratio (mean percentage change) - Linagliptin vs Placebo (type 2 diabetes) (Better indicated by lower values)** | | | | |
| 182 | 178 | MD 5.9 lower (15.03 lower to 3.23 higher) | HIGH | No meaningful difference |
| **Hypoglycaemia - Linagliptin vs Placebo (type 2 diabetes)** | | | | |
| 24/182 (13.2%) | 10/178 (5.6%) | RR 2.35 (1.16 to 4.77) | MODERATE | Effect |

*a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: statistically significant and point estimate >MID; There is an effect, but it is less than the defined MID: statistically significant and point estimate <MID*

**Table 10: Thiazolidinedione vs Placebo**

| Thiazolidinedione | Placebo | Effect size (95% CI) | Quality | Interpretation of effect |
|---|---|---|---|---|
| **Urinary protein excretion (g/24 h) - Pioglitazone vs Placebo (Better indicated by lower values)** | | | | |

| Thiazolidinedione | Placebo | Effect size (95% CI) | Quality | Interpretation of effect |
|---|---|---|---|---|
| 21 | 20 | MD 1 lower (2.04 lower to 0.04 higher) | VERY LOW | Could not differentiate |

*a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: statistically significant and point estimate >MID; There is an effect, but it is less than the defined MID: statistically significant and point estimate <MID*

**Table 11: SGLT2 inhibitor vs placebo**

| SGLT2 inhibitor | Placebo | Effect size (95% CI) | Quality | Interpretation of effect |
|---|---|---|---|---|
| **Urinary albumin excretion (g/24 h) - Dapagliflozin vs Placebo (type 2 diabetes) (Better indicated by lower values [MID 71.44])** | | | | |
| 108 | 99 | MD 19.7 lower (56.39 lower to 16.99 higher) | HIGH | No meaningful difference |
| **End stage kidney disease** | | | | |
| 225/4354 (5.2%) | 326/4351 (7.5%) | RR 0.69 (0.59 to 0.81) | MODERATE | Effect |
| **End stage kidney disease - Canagliflozin vs Placebo (type 2 diabetes)** | | | | |
| 116/2202 (5.3%) | 165/2199 (7.5%) | RR 0.7 (0.56 to 0.88) | MODERATE | Effect |
| **End stage kidney disease - Dapagliflozin vs Placebo (67% with type 2 diabetes)** | | | | |
| 109/2152 (5.1%) | 161/2152 (7.5%) | RR 0.68 (0.53 to 0.86) | MODERATE | Effect |
| **All-cause mortality** | | | | |
| 270/4499 (6%) | 347/4499 (7.7%) | RR 0.78 (0.67 to 0.91) | HIGH | Effect |
| **All-cause mortality - Dapagliflozin vs Placebo (type 2 diabetes)** | | | | |
| 102/2297 (4.4%) | 146/2300 (6.3%) | RR 0.70 (0.55 to 0.89) | HIGH | Effect |
| **All-cause mortality - Canagliflozin vs Placebo (type 2 diabetes)** | | | | |
| 168/2202 (7.6%) | 201/2199 (9.1%) | RR 0.83 (0.69 to 1.02) | MODERATE | Could not differentiate |
| **All-cause mortality - Canagliflozin vs Placebo, microalbuminuria: urinary albumin/creatinine ratio 3 to 30 mg/mmol** | | | | |
| 23.5 patients with an event per 1000 patient-years | 22.9 patients with an event per 1000 patient-years | HR 1.00 (0.74 to 1.34) | MODERATE | Could not differentiate |
| **All-cause mortality - Canagliflozin vs Placebo, macroalbuminuria: urinary albumin/creatinine ratio >30 mg/mmol** | | | | |
| 37.3 patients with an event per 1000 patient-years | 57.5 patients with an event per 1000 patient-years | HR 0.63 (0.43, 0.92) | HIGH | Effect |
| **CV mortality** | | | | |
| 175/4354 (4%) | 220/4351 (5.1%) | RR 0.79 (0.65 to 0.96) | HIGH | Effect |
| **CV mortality - Canagliflozin vs Placebo (type 2 diabetes)** | | | | |

| SGLT2 inhibitor | Placebo | Effect size (95% CI) | Quality | Interpretation of effect |
|---|---|---|---|---|
| 110/2202 (5%) | 140/2199 (6.4%) | RR 0.78 (0.62 to 1) | MODERATE | Could not differentiate |
| **CV mortality - Dapagliflozin vs Placebo (67% with type 2 diabetes)** | | | | |
| 65/2152 (3%) | 80/2152 (3.7%) | RR 0.81 (0.59 to 1.12) | MODERATE | Could not differentiate |
| **CV mortality - Canagliflozin vs Placebo, microalbuminuria: urinary albumin/creatinine ratio 3 to 30 mg/mmol** | | | | |
| 16.0 patients with an event per 1000 patient-years | 15.8 patients with an event per 1000 patient-years | HR 0.98 (0.69 to 1.41) | MODERATE | Could not differentiate |
| **CV mortality - Canagliflozin vs Placebo, macroalbuminuria: urinary albumin/creatinine ratio >30 mg/mmol** | | | | |
| 31.3 patients with an event per 1000 patient-years | 42.6 patients with an event per 1000 patient-years | HR 0.70 (0.45 to 1.07) | MODERATE | Could not differentiate |
| **Acute kidney injury - Canagliflozin vs Placebo (type 2 diabetes)** | | | | |
| 86/2200 (3.9%) | 98/2197 (4.5%) | RR 0.88 (0.66 to 1.16) | MODERATE | Could not differentiate |
| **Minor hypoglycaemia - Dapagliflozin vs Placebo (type 2 diabetes)** | | | | |
| 35/145 (24.1%) | 29/148 (19.6%) | RR 1.23 (0.8 to 1.9) | LOW | Could not differentiate |
| **Major hypoglycaemia - Dapagliflozin vs Placebo (67% with type 2 diabetes)** | | | | |
| 14/2149 (0.65%) | 28/2149 (1.3%) | RR 0.50 (0.26 to 0.95) | MODERATE | Effect |
| **Hospitalisation - Canagliflozin vs Placebo (type 2 diabetes)** | | | | |
| 89/2202 (4%) | 141/2199 (6.4%) | RR 0.63 (0.49 to 0.82) | MODERATE | Effect |
| **Fractures - Dapagliflozin vs Placebo (67% with type 2 diabetes)** | | | | |
| 85/2149 (4%) | 69/2149 (3.2%) | RR 1.23 (0.9 to 1.68) | MODERATE | Could not differentiate |

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**Table 12: SGLT2 inhibitor + gliptin vs SGLT2 inhibitor**

| SGLT2 inhibitor + gliptin | SGLT2 inhibitor | Effect size (95% CI) | Quality | Interpretation of effect |
|---|---|---|---|---|
| **Urinary albumin excretion (mcg/min) - Dapagliflozin + Saxagliptin vs Dapagliflozin (type 2 diabetes) (Better indicated by lower values)** | | | | |
| 107 | 108 | MD 19.6 lower (48.4 lower to 9.2 higher) | HIGH | No meaningful difference |
| **All-cause mortality - Dapagliflozin + Saxagliptin vs Dapagliflozin (type 2 diabetes)** | | | | |
| 1/152 (0.66%) | 1/145 (0.69%) | RR 0.95 (0.06 to 15.11) | MODERATE | Could not differentiate |
| **Minor hypoglycaemia - Dapagliflozin + Saxagliptin vs Dapagliflozin (type 2 diabetes))** | | | | |
| 50/152 (32.9%) | 35/145 (24.1%) | RR 1.36 (0.94 to 1.97) | MODERATE | Could not differentiate |

| SGLT2 inhibitor + gliptin | SGLT2 inhibitor | Effect size (95% CI) | Quality | Interpretation of effect |
|---|---|---|---|---|
| **Any serious adverse events of hypoglycaemia - Dapagliflozin + Saxagliptin vs Dapagliflozin (type 2 diabetes)** | | | | |
| 2/152 (1.3%) | 0/145 (0%) | RR 4.77 (0.23 to 98.54) | LOW | Could not differentiate |

*a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: statistically significant and point estimate >MID; There is an effect, but it is less than the defined MID: statistically significant and point estimate <MID*

**Table 13: Exercise vs No intervention**

| Exercise | No intervention | Effect size (95% CI) | Quality | Interpretation of effect |
|---|---|---|---|---|
| **Urinary protein/creatinine ratio (mg/mmol) - Exercise vs No intervention (type 2 diabetes) (Better indicated by lower values)** | | | | |
| 7 | 6 | MD 12.66 lower (68.94 lower to 43.62 higher) | VERY LOW | Could not differentiate |
| **Urinary albumin/creatinine ratio (mg/mmol) - Exercise vs No intervention (type 2 diabetes) (Better indicated by lower values)** | | | | |
| 7 | 6 | MD 9.83 lower (52.64 lower to 32.97 higher) | VERY LOW | Could not differentiate |

*a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: statistically significant and point estimate >MID; There is an effect, but it is less than the defined MID: statistically significant and point estimate <MID*

**Table 14: Exercise vs Diet**

| Exercise | Diet | Effect size (95% CI) | Quality | Interpretation of effect |
|---|---|---|---|---|
| **Health-related quality of life - SF-36 PCS - Exercise vs Diet (type 2 diabetes), 3 months (Better indicated by higher values)** | | | | |
| 14 | 18 | MD 0.5 higher (6.66 lower to 7.66 higher) | VERY LOW | Could not differentiate |
| **Health-related quality of life - SF-36 PCS - Exercise vs Diet (type 2 diabetes), 12 months (Better indicated by higher values)** | | | | |
| 14 | 18 | MD 1.9 higher (4.62 lower to 8.42 higher) | VERY LOW | Could not differentiate |
| **Health-related quality of life - SF-36 MCS - Exercise vs Diet (type 2 diabetes), 3 months (Better indicated by higher values)** | | | | |
| 14 | 18 | MD 6.1 higher (0.94 lower to 13.14 higher) | VERY LOW | Could not differentiate |
| **Health-related quality of life - SF-36 MCS - Exercise vs Diet (type 2 diabetes), 12 months (Better indicated by higher values)** | | | | |
| 14 | 18 | MD 3.8 higher (3.66 lower to 11.26 higher) | VERY LOW | Could not differentiate |

*a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: statistically significant and point estimate >MID; There is an effect, but it is less than the defined MID: statistically significant and point estimate <MID*

**Table 15: ACE-I + ARB vs ARB**

| ACE-I + ARB | ARB | Effect size (95% CI) | Quality | Interpretation of effect |
|---|---|---|---|---|
| **End stage kidney disease (at least 95% type 2 diabetes)** | | | | |
| 31/1140 (2.7%) | 45/1138 (4%) | RR 0.69 (0.44 to 1.08) | LOW | Could not differentiate |

| ACE-I + ARB | ARB | Effect size (95% CI) | Quality | Interpretation of effect |
|---|---|---|---|---|
| **End stage kidney disease - Losartan + Lisinopril vs Losartan (at least 95% type 2 diabetes)** | | | | |
| 27/724 (3.7%) | 43/724 (5.9%) | RR 0.63 (0.39 to 1.0) | LOW | Could not differentiate |
| **End stage kidney disease - ACE-I + ARB vs ARB (at least 95% type 2 diabetes)** | | | | |
| 4/416 (0.96%) | 2/414 (0.48%) | RR 1.99 (0.37 to 10.81) | VERY LOW | Could not differentiate |
| **All-cause mortality - ACE-I + ARB vs ARB (at least 95% type 2 diabetes)** | | | | |
| 81/1140 (7.1%) | 80/1138 (7%) | RR 1.01 (0.75 to 1.36) | LOW | Could not differentiate |
| **All-cause mortality - Losartan + Lisinopril vs Losartan (at least 95% type 2 diabetes)** | | | | |
| 63/724 (8.7%) | 60/724 (8.3%) | RR 1.05 (0.75 to 1.47) | LOW | Could not differentiate |
| **All-cause mortality - ACE-I + ARB vs ARB (at least 95% type 2 diabetes)** | | | | |
| 18/416 (4.3%) | 20/414 (4.8%) | RR 0.9 (0.48 to 1.67) | VERY LOW | Could not differentiate |
| **CV mortality - ACE-I + ARB vs ARB (95% type 2 diabetes)** | | | | |
| 4/416 (0.96%) | 7/414 (1.7%) | RR 0.57 (0.17 to 1.93) | VERY LOW | Could not differentiate |
| **Non-fatal CV events (at least 95% type 2 diabetes)** | | | | |
| 149/1140 (13.1%) | 142/1138 (12.5%) | RR 1.39 (0.58 to 3.37) | VERY LOW | Could not differentiate |
| **Non-fatal CV events - Losartan + Lisinopril vs Losartan (at least 95% type 2 diabetes)** | | | | |
| 134/724 (18.5%) | 136/724 (18.8%) | RR 0.99 (0.79 to 1.22) | LOW | Could not differentiate |
| **Non-fatal CV events - ACE-I + ARB vs ARB (at least 95% type 2 diabetes)** | | | | |
| 15/416 (3.6%) | 6/414 (1.4%) | RR 2.49 (0.97 to 6.35) | VERY LOW | Could not differentiate |
| **Acute kidney injury - Losartan + Lisinopril vs Losartan (type 2 diabetes)** | | | | |
| 130/724 (18%) | 80/724 (11%) | RR 1.62 (1.25 to 2.1) | LOW | Effect |
| **Hypotension - ACE-I + ARB vs ARB (95% type 2 diabetes)** | | | | |
| 2/416 (0.48%) | 2/414 (0.48%) | RR 1 (0.14 to 7.03) | VERY LOW | Could not differentiate |
| **Hospitalisation - ACE-I + ARB vs ARB (95% type 2 diabetes)** | | | | |
| 34/416 (8.2%) | 20/414 (4.8%) | RR 1.69 (0.99 to 2.89) | VERY LOW | Could not differentiate |

*a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: statistically significant and point estimate >MID; There is an effect, but it is less than the defined MID: statistically significant and point estimate <MID*

**Table 16: ACE-I + ARB vs ACE-I**

| ACE-I + ARB | ACE-I | Effect size (95% CI) | Quality | Interpretation of effect |
|---|---|---|---|---|
| **End stage kidney disease - ACE-I + ARB vs ACE-I (95% type 2 diabetes)** | | | | |
| 4/416 (0.96%) | 6/413 (1.5%) | RR 0.66 (0.19 to 2.33) | VERY LOW | Could not differentiate |
| **All-cause mortality - ACE-I + ARB vs ACE-I (95% type 2 diabetes)** | | | | |
| 18/416 (4.3%) | 15/413 (3.6%) | RR 1.19 (0.61 to 2.33) | VERY LOW | Could not differentiate |

| ACE-I + ARB | ACE-I | Effect size (95% CI) | Quality | Interpretation of effect |
|---|---|---|---|---|
| **CV mortality - ACE-I + ARB vs ACE-I (95% type 2 diabetes)** | | | | |
| 4/416 (0.96%) | 6/413 (1.5%) | RR 0.66 (0.19 to 2.33) | VERY LOW | Could not differentiate |
| **Non-fatal CV events - ACE-I + ARB vs ACE-I (95% type 2 diabetes)** | | | | |
| 15/416 (3.6%) | 8/413 (1.9%) | RR 1.86 (0.8 to 4.34) | VERY LOW | Could not differentiate |
| **Hypotension - ACE-I + ARB vs ACE-I (95% type 2 diabetes)** | | | | |
| 2/416 (0.48%) | 3/413 (0.73%) | RR 0.66 (0.11 to 3.94) | VERY LOW | Could not differentiate |
| **Hospitalisation - ACE-I + ARB vs ACE-I (95% type 2 diabetes)** | | | | |
| 34/416 (8.2%) | 25/413 (6.1%) | RR 1.35 (0.82 to 2.22) | VERY LOW | Could not differentiate |

*a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: statistically significant and point estimate >MID; There is an effect, but it is less than the defined MID: statistically significant and point estimate <MID*

### 1.1.6.2 Adults without type 2 diabetes

**Table 17: ACE-I vs placebo**

| ACE-I | Placebo | Effect size (95% CI) | Quality | Interpretation of effect |
|---|---|---|---|---|
| **End stage kidney disease** | | | | |
| 46/384 (12%) | 78/377 (20.7%) | RR 0.59 (0.43 to 0.83) | VERY LOW | Effect |
| **End stage kidney disease – Ramipril vs Placebo** | | | | |
| 26/177 (14.7%) | 47/175 (26.9%) | RR 0.57 (0.37 to 0.87) | LOW | Effect |
| **End stage kidney disease - Captopril vs Placebo** | | | | |
| 20/207 (9.7%) | 31/202 (15.3%) | RR 0.63 (0.37 to 1.07) | VERY LOW | Could not differentiate |
| **All-cause mortality** | | | | |
| 10/285 (3.5%) | 15/290 (5.2%) | RR 0.66 (0.3 to 1.44) | VERY LOW | Could not differentiate |
| **All-cause mortality - Ramipril vs Placebo** | | | | |
| 2/78 (2.6%) | 1/88 (1.1%) | RR 2.26 (0.21 to 24.41) | LOW | Could not differentiate |
| **All-cause mortality - Captopril vs Placebo** | | | | |
| 8/207 (3.9%) | 14/202 (6.9%) | RR 0.56 (0.24 to 1.3) | VERY LOW | Could not differentiate |
| **CV mortality - Ramipril vs Placebo** | | | | |
| 2/177 (1.1%) | 0/175 (0%) | RR 2.99 (0.32 to 28.32) | LOW | Could not differentiate |
| **Non-fatal CV events - Ramipril vs Placebo** | | | | |
| 6/177 (3.4%) | 6/175 (3.4%) | RR 1.02 (0.34 to 3.05) | VERY LOW | Could not differentiate |

*a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: statistically significant and point estimate >MID; There is an effect, but it is less than the defined MID: statistically significant and point estimate <MID*

**Table 18: Aldosterone antagonist vs placebo**

| Aldosterone antagonist | Placebo | Effect size (95% CI) | Quality | Interpretation of effect |
|---|---|---|---|---|
| **Urinary albumin/creatinine ratio (mean percentage change) - Eplerenone vs Placebo (Better indicated by lower values)** | | | | |
| 158 | 146 | MD 27.6 lower (47.72 to 7.48 lower) | VERY LOW | There is an effect, but it is less than the defined MID |
| **All-cause mortality – Eplerenone vs Placebo** | | | | |
| 1/169 (0.59%) | 0/163 (0%) | RR 2.89 (0.12 to 70.53) | VERY LOW | Could not differentiate |
| **Non-fatal CV events – Eplerenone vs Placebo** | | | | |
| 1/169 (0.59%) | 1/163 (0.61%) | RR 0.96 (0.06 to 15.29) | VERY LOW | Could not differentiate |

*a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: statistically significant and point estimate >MID; There is an effect, but it is less than the defined MID: statistically significant and point estimate <MID*

**Table 19: ARB vs placebo**

| ARB | Placebo | Effect size (95% CI) | Quality | Interpretation of effect |
|---|---|---|---|---|
| **Urinary albumin excretion (g/24 h) – Valsartan vs Placebo, 3 months (Better indicated by lower values)** | | | | |
| 54 | 55 | MD 0.54 lower (1.12 lower to 0.04 higher) | VERY LOW | Could not differentiate |
| **Urinary albumin excretion (g/24 h) - Valsartan vs Placebo, 6 months (Better indicated by lower values)** | | | | |
| 54 | 55 | MD 0.81 lower (1.43 to 0.19 lower) | VERY LOW | There is an effect, but it is less than the defined MID |
| **Urinary albumin excretion (g/24 h) - Valsartan vs Placebo, 12 months (Better indicated by lower values)** | | | | |
| 54 | 55 | MD 0.16 lower (0.72 lower to 0.4 higher) | LOW | No meaningful difference |
| **Urinary albumin excretion (g/24 h) - Valsartan vs Placebo, 1.5 years (Better indicated by lower values)** | | | | |
| 54 | 55 | MD 0.22 lower (0.76 lower to 0.32 higher) | LOW | No meaningful difference |
| **Urinary albumin excretion (g/24 h) - Valsartan vs Placebo, 2 years (Better indicated by lower values)** | | | | |
| 54 | 55 | MD 0.19 lower (0.75 lower to 0.37 higher) | LOW | No meaningful difference |
| **Non-fatal CV events - Valsartan vs Placebo** | | | | |
| 0/54 (0%) | 1/55 (1.8%) | RR 0.34 (0.01 to 8.15) | VERY LOW | Could not differentiate |

*a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: statistically significant and point estimate >MID; There is an effect, but it is less than the defined MID: statistically significant and point estimate <MID*

**Table 20: ARB vs control (usual antihypertensive therapy except ACE inhibitors and ARBs)**

| ARB | Control | Effect size (95% CI) | Quality | Interpretation of effect |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| **Urinary protein creatinine ratio (mg/mmol) - Losartan, 12 months [MID 0.02] (Better indicated by lower values)** | | | | |
| 17 | 15 | MD 40.00 lower (79.41 to 0.59 lower) | VERY LOW | Could not differentiate |
| **Urinary protein creatinine ratio (mg/mmol) - Losartan, 24 months [MID 0.03] (Better indicated by lower values)** | | | | |
| 17 | 15 | MD 30.00 lower (65.23 lower to 5.23 higher) | VERY LOW | Could not differentiate |
| **Urinary albumin creatinine ratio (mg/mmol) - Losartan, 12 months [MID 0.02] (Better indicated by lower values)** | | | | |
| 17 | 15 | MD 30.00 lower (67.67 lower to 7.67 higher) | VERY LOW | Could not differentiate |
| **Urinary albumin creatinine ratio (mg/mmol) - Losartan, 24 months [MID 0.03] (Better indicated by lower values)** | | | | |
| 17 | 15 | MD 30.00 lower (67.79 lower to 7.79 higher) | VERY LOW | Could not differentiate |

1

2 **Table 21: ACE-I vs ARB**

| ACE-I | ARB | Effect size (95% CI) | Quality | Interpretation of effect |
|---|---|---|---|---|
| **Urinary protein/creatinine ratio (mg/mmol) - Lisinopril vs Candesartan, 3 months (Better indicated by lower values)** | | | | |
| 14 | 15 | MD 66.67 higher (12.68 to 120.66 higher) | LOW | Effect |
| **Urinary protein/creatinine ratio (mg/mmol) - Lisinopril vs Candesartan, 6 months (Better indicated by lower values)** | | | | |
| 14 | 15 | MD 4.52 higher (49.67 lower to 58.71 higher) | VERY LOW | Could not differentiate |
| **Urinary protein excretion (g/24h), Mean percentage reduction from baseline - ACE-I vs ARB (moderate proteinuria 1.1 to 6.9 g/24h), 3 months (Better indicated by lower values)** | | | | |
| 14 | 12 | MD 21 higher (15.49 to 26.51 higher) | LOW | Effect |
| **Urinary protein excretion (g/24h), Mean percentage reduction from baseline - ACE-I vs ARB (moderate proteinuria 1.1 to 6.9 g/24h), 11 months (Better indicated by lower values)** | | | | |
| 14 | 12 | MD 13 higher (8 to 18 higher) | LOW | Effect |
| **Urinary protein excretion (g/24h), Mean percentage reduction from baseline - Perindopril vs Candesartan, 3 months (Better indicated by lower values)** | | | | |
| 15 | 17 | MD 4 higher (0.42 to 7.58 higher) | VERY LOW | Effect |
| **Urinary protein excretion (g/24h), Mean percentage reduction from baseline - Perindopril vs Losartan, 3 months (Better indicated by lower values)** | | | | |
| 15 | 15 | MD 30 higher (26.61 to 33.39 higher) | LOW | Effect |
| **Urinary protein excretion (g/24h), Mean percentage reduction from baseline - Trandolapril vs Candesartan, 3 months (Better indicated by lower values)** | | | | |
| 15 | 17 | MD 1 lower (4.58 lower to 2.58 higher) | VERY LOW | Could not differentiate |
| **Urinary protein excretion (g/24h), Mean percentage reduction from baseline - Trandolapril vs Losartan, 3 months (Better indicated by lower values)** | | | | |
| 15 | 15 | MD 25 higher (21.61 to 28.39 higher) | LOW | Effect |
| **Urinary protein excretion (g/24h), Mean percentage reduction from baseline - Perindopril vs Candesartan, 22 months (Better indicated by lower values)** | | | | |
| 15 | 17 | MD 11 higher (6.73 to 15.27 higher) | LOW | Effect |

| ACE-I | ARB | Effect size (95% CI) | Quality | Interpretation of effect |
|---|---|---|---|---|
| **Urinary protein excretion (g/24h), Mean percentage reduction from baseline - Perindopril vs Losartan, 22 months (Better indicated by lower values)** | | | | |
| 15 | 15 | MD 24 higher (19.92 to 28.08 higher) | LOW | Effect |
| **Urinary protein excretion (g/24h), Mean percentage reduction from baseline - Trandolapril vs Candesartan, 22 months (Better indicated by lower values)** | | | | |
| 15 | 17 | MD 4 higher (0.27 lower to 8.27 higher) | VERY LOW | Could not differentiate |
| **Urinary protein excretion (g/24h), Mean percentage reduction from baseline - Trandolapril vs Losartan, 22 months (Better indicated by lower values)** | | | | |
| 15 | 15 | MD 17 higher (12.92 to 21.08 higher) | LOW | Effect |

*a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: statistically significant and point estimate >MID; There is an effect, but it is less than the defined MID: statistically significant and point estimate <MID*

**Table 22: ARB vs CCB**

| ARB | CCB | Effect size (95% CI) | Quality | Interpretation of effect |
|---|---|---|---|---|
| **Urinary protein excretion (g/24 h) - Losartan vs Amlodipine, 3 months (Better indicated by lower values)** | | | | |
| 26 | 28 | MD 27.38 lower (50.22 to 4.54 lower) | VERY LOW | Effect |
| **Urinary protein excretion (g/24 h) - Losartan vs Amlodipine (Better indicated by lower values)** | | | | |
| 50 | 47 | MD 1.7 lower (2.47 to 0.93 lower) | LOW | Effect |
| **Non-fatal CV events - Losartan vs Amlodipine** | | | | |
| 1/47 (2.1%) | 0/46 (0%) | RR 2.94 (0.12 to 70.3) | VERY LOW | Could not differentiate |

*a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: statistically significant and point estimate >MID; There is an effect, but it is less than the defined MID: statistically significant and point estimate <MID*

**Table 23: Subcutaneous insulin infusion vs Conventional insulin**

| Subcutaneous insulin infusion | Conventional insulin | Effect size (95% CI) | Quality | Interpretation of effect |
|---|---|---|---|---|
| **Urinary albumin excretion (mcg/min) - Type 1 diabetes (Better indicated by lower values)** | | | | |
| 5 | 5 | MD 195 lower (1353.56 lower to 963.56 higher) | VERY LOW | Could not differentiate |

*a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: statistically significant and point estimate >MID; There is an effect, but it is less than the defined MID: statistically significant and point estimate <MID*

**Table 24: ACE-I + ARB vs ARB**

| ACE-I + ARB | ARB | Relative (95% CI) | Quality | Interpretation of effect |
|---|---|---|---|---|
| **Urinary protein/creatinine ratio (mg/mmol) - Candesartan + Lisinopril vs Candesartan, 3 months (Better indicated by lower values)** | | | | |
| 16 | 15 | MD 29.38 lower (72.27 lower to 13.51 higher) | LOW | Could not differentiate |
| **Urinary protein/creatinine ratio (mg/mmol) - Candesartan + Lisinopril vs Candesartan, 6 months (Better indicated by lower values)** | | | | |

| ACE-I + ARB | ARB | Relative (95% CI) | Quality | Interpretation of effect |
|---|---|---|---|---|
| 16 | 15 | MD 111.87 lower (153.34 to 70.40) lower | MODERATE | Effect |

*a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: statistically significant and point estimate >MID; There is an effect, but it is less than the defined MID: statistically significant and point estimate <MID*

**Table 25: ACE-I + ARB vs ACE-I**

| ACE-I + ARB | ACE-I | Effect size (95% CI) | Quality | Interpretation of effect |
|---|---|---|---|---|
| **Urinary protein excretion (g/24 h) - Candesartan + ACE-I vs ACE-I (Better indicated by lower values)** | | | | |
| 45 | 45 | MD 0.83 lower (0.89 to 0.77 lower) | LOW | Effect |
| **Urinary protein/creatinine ratio (mg/mmol) - Candesartan + Lisinopril vs Lisinopril, 3 months (Better indicated by lower values)** | | | | |
| 16 | 14 | MD 96.05 lower (148.35 to 43.75 lower) | MODERATE | Effect |
| **Urinary protein/creatinine ratio (mg/mmol) - Candesartan + Lisinopril vs Lisinopril, 6 months (Better indicated by lower values)** | | | | |
| 16 | 14 | MD 116.39 lower (166.48 to 66.30 lower) | MODERATE | Effect |

*a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: statistically significant and point estimate >MID; There is an effect, but it is less than the defined MID: statistically significant and point estimate <MID*

**Table 26: ARB + CCB vs ARB**

| ARB + CCB | ARB | Effect size (95% CI) | Quality | Interpretation of effect |
|---|---|---|---|---|
| **Urinary albumin/creatinine ratio (mg/mmol) - Valsartan + Amlodipine vs Valsartan** | | | | |
| 70 | 70 | MD 9.83 lower (12.58 to 7.08 lower) | LOW | Effect |

*a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: statistically significant and point estimate >MID; There is an effect, but it is less than the defined MID: statistically significant and point estimate <MID*

**Table 27: ARB + Diuretic vs ARB**

| ARB + Diuretic | ARB | Effect size (95% CI) | Quality | Interpretation of effect |
|---|---|---|---|---|
| **Urinary protein/creatinine ratio (mg/mmol) - Losartan vs losartan + Hydrochlorothiazide, 3 months (Better indicated by lower values)** | | | | |
| 51 | 48 | MD 0.08 lower (0.12 to 0.05 lower) | LOW | Effect |
| **Urinary protein/creatinine ratio (mg/mmol) - Losartan vs losartan + Hydrochlorothiazide, 6 months (Better indicated by lower values)** | | | | |
| 51 | 48 | MD 0.06 lower (0.10 to 0.03 lower) | LOW | Effect |

*a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: statistically significant and point estimate >MID; There is an effect, but it is less than the defined MID: statistically significant and point estimate <MID*

**Table 28: Spironolactone + conventional therapy vs Conventional therapy**

| Spironolactone + conventional therapy | Conventional therapy | Effect size (95% CI) | Quality | Interpretation of effect |
|---|---|---|---|---|
| **Urinary protein/creatinine ratio (mg/mmol) - Spironolactone + conventional therapy vs Conventional therapy, 3 months (Better indicated by lower values)** | | | | |
| 83 | 82 | MD 91.53 lower (113.75 to 69.31 lower) | LOW | Effect |
| **Urinary protein/creatinine ratio (mg/mmol) - Spironolactone + conventional therapy vs Conventional therapy, 6 months (Better indicated by lower values)** | | | | |
| 83 | 82 | MD 106.22 lower (128.44 to 84.00 lower) | LOW | Effect |
| **Urinary protein/creatinine ratio (mg/mmol) - Spironolactone + conventional therapy vs Conventional therapy, 12 months (Better indicated by lower values)** | | | | |
| 83 | 82 | MD 149.16 lower (172.24 to 126.08 lower) | LOW | Effect |

*a) No meaningful difference: 95% CI completely between MIDs; Could not differentiate: 95% CI are not completely between MIDs and crossing line of no effect; Effect: statistically significant and point estimate >MID; There is an effect, but it is less than the defined MID: statistically significant and point estimate <MID*

See Appendix G for full GRADE tables.

### 1.1.7 Economic evidence

A systematic review was conducted to identify economic evaluations for this review question. The search returned 3,143 records which were sifted against the review protocol. Of these publications 3,109 were excluded based on title and abstract. On full paper inspection 10 studies were found to be duplicates and 21 did not to meet the inclusion criteria. Due to the number publications assessing the cost-effectiveness of antihypertensive therapy in people with kidney disease, inclusion was restricted to cost-utility analyses from OECD countries comparing interventions to lower proteinuria. For analyses of diet interventions, the criteria for inclusion was broadened as there was less evidence available. Fourteen published economic analyses were included in the evidence synthesis, 12 assessing the cost-effectiveness of antihypertensive agents and 2 on diet interventions.

#### 1.1.7.1 Included studies

A summary of the studies included in the cost-effectiveness review is given below. Detailed information on the studies identified from the review can be found in Appendix I, quality assessment in Appendix J, and the study selection is described in Appendix H.

Nine studies (including one conducted in the UK from an NHS perspective) looked at the timing of antihypertensive therapy, and in particular screening for moderately increased albuminuria (also called microalbuminuria) and subsequent treatment (in the general population, in people with hypertension, or in people with type 1 or type 2 diabetes) with no screening and either no treatment unless someone presents with a clinical indication, or with treating all included participants, without any prior screening. Although this review question was not specific to screening interventions, cost effectiveness analyses of programmes consisting of screening followed by treatment to lower proteinuria were still included. The committee agreed this was a reasonable approach as programmes deemed cost-effective after consideration of screening cost and consequences of false diagnoses, were likely to be cost-effective in a population with confirmed proteinuria.

The evidence consistently showed that screening followed by treatment (and hence also treatment in people already identified without additional screening costs) is highly likely to be

cost effective in people with hypertension or diabetes (both type 1 and type 2), and treatment (most commonly an ACE inhibitor) for all people with diabetes, without initially screening for microalbuminuria is likely to be more cost-effective than either screening or incidental detection.

One cost-utility analysis comparing ACE inhibitors to antihypertensives not acting on the renin-angiotensin system (Adarkwah 2013) found ACE inhibitors to be dominant, which supports their use in people with advanced kidney disease.

The 2 studies analysing the cost-effectiveness of diet interventions are only partially applicable and have very serious methodological limitations, having reduced value to inform recommendations.

## Timing of antihypertensive therapy

### *Farmer 2014*

| Study | Comparators[1] | Costs differences[2] | QALY differences | ICER | Uncertainty | Applicability | Limitations |
|---|---|---|---|---|---|---|---|
| **Farmer 2014**<br>Systematic review and cost utility analysis<br>NHS perspective<br>Individual patient simulation<br>Live time horizon | **Type 1 diabetes model (frequency of screening)** | | | | Univariate sensitivity analyses were conducted using the upper and lower levels of the confidence intervals for test cost, ACR progression, CVD and utility.<br>In both models, the results were sensitive to ACR progression, producing ICERs in excess of £40,000/QALY.<br><u>Type 1 diabetes</u><br>Annual screening had a 25% probability of being cost saving and an 80% probability of being cost-effective at a threshold below £30,000/QALY.<br><u>Type 2 diabetes</u><br>Annual screening had 97% probability of being cost-effective at a threshold below £30,000/QALY. | Partially applicable | Minor limitations |
| | 1-year versus 2-year | £2,837 | 0.26 | £11,203/QALY | | | |
| | 2-year versus 3-year | £2,222 | 0.39 | £5,766/QALY | | | |
| | 3-year versus 4-year | £672 | 0.15 | £2,943/QALY | | | |
| | 4-year versus 5-year | £337 | 0.08 | £4,215/QALY | | | |
| | **Type 2 diabetes model (frequency of screening)** | | | | | | |
| | 1-year versus 2-year | £244 | 0.42 | £707/QALY | | | |
| | 2-year versus 3-year | £131 | 0.11 | £575/QALY | | | |
| | 3-year versus 4-year | £82 | 0.24 | £386/QALY | | | |
| | 5-year versus 6-year | £83 | 0.09 | £890/QALY | | | |

*[1]Comparators consisted of different frequencies of screening for albuminuria in people with type 1 or type 2 diabetes. ACE inhibitor therapy was offered to people testing positive for micro/macroalbuminuria.*

*[2]Costs inflated from sterling 2011 to sterling 2020 using the EPPI Centre cost converter accessed 23/01/2020, inflation factor 0.857.*

1 ***Adarkwah 2011a***

| Study | Comparators[1] | Costs[2] | Effects | ICER | Uncertainty | Applicability | Limitations |
|---|---|---|---|---|---|---|---|
| **Adarkwah 2011**<br><br>People aged 50 with diabetes mellitus<br><br>Cost utility analysis<br><br>Dutch health system perspective<br><br>Lifetime horizon | ACE inhibitor at time of type 2 diabetes diagnosis (treat all) | €98,421 (£94,742) | 19.63 | Dominates | The most influential parameters in univariate sensitivity analysis were the baseline risk of progression from micro- to macroalbuminuria, the effect of ACE inhibition in preventing microalbuminuria and the discount rate.<br><br>When assuming a lower baseline risk of having macroalbuminuria, intervention 2 becomes dominant.<br><br>Compared to intervention 2, treating all patient has a 70% probability of producing savings. | Partially applicable | Potentially serious limitations |
| | ACE inhibitor if microalbuminuria | €101,140 (£97,359) | 19.54 | Dominated | | | |
| | ACE inhibitor if macroalbuminuria | €110,777 (£106,636) | 19.15 | Dominated | | | |

2 *[1]Normoalbuminuria – excretion <30 mg/day; microalbuminuria – excretion 30 to 300 mg/day; macroalbuminuria – excretion >300 mg/day; ESRD – treated with dialysis of renal*
3 *transplant.*

4 *[2]Euros 2010 converted to sterling 2019 using the EPPI Centre cost converter (accessed 11/12/2019), conversion factor 1.04.*

5 ***Adarkwah 2011b***

| Study | Comparators | Costs[1] | Effects | ICER | Uncertainty | Applicability | Limitations |
|---|---|---|---|---|---|---|---|
| **Adarkwah 2011**<br><br>People aged 44 with advanced renal insufficiency, proteinuria and hypertension<br><br>Cost utility analysis<br><br>German health system perspective | ACE inhibitor (treat all) | €172,676 (£177,233.60) | 8.26 | Dominates | All univariate sensitivity analyses showed that an ACE inhibitor is dominant. | Partially applicable | Potentially serious limitations |
| | No ACE inhibitor | €205,200 (£210,616.03) | 6.77 | Dominated | | | |

| Study | Comparators | Costs[1] | Effects | ICER | Uncertainty | Applicability | Limitations |
|---|---|---|---|---|---|---|---|
| Lifetime horizon | | | | | | | |

[1]*Euros 2011 converted to sterling 2019 using the EPPI Centre cost converter (accessed 30/10/2020), conversion factor 1.14.*

***Hoerger 2010***

| Study | Comparators | Costs[2] | QALYs | ICER[3] | Uncertainty | Applicability | Limitations |
|---|---|---|---|---|---|---|---|
| **Hoerger 2010**<br>Cost utility analysis<br>People aged >30 years<br>US health system<br>Lifetime horizon | **Total population screening** | | | | Univariate sensitivity analysis used a (+ -)25% variation on the rate of albuminuria, treatment adherence, costs of screening and discount rate, these being the most influential parameters in the model. This did not substantially change the conclusions of the analysis in the total population with annual screening being more effective and more expensive than usual care at over $55,000/QALY (£48,816/QALY).<br>Probabilistic sensitivity analysis was not conducted. | Partially applicable | Potentially serious limitations |
| | Universal: age 50 y only | $146,400 (£129,940) | 17.682 | | | | |
| | Usual care[1] | $146,500 (£130,029) | 17.685 | $33,333 (£29,586) | | | |
| | Universal: 10 y | $146,700 (£130,206) | 17.690 | $40,000 (£35,503) | | | |
| | Universal: 5 y | $146,800 (£130,295) | 17.691 | $100,000 (£88,757) | | | |
| | Universal: 2 y | $147,200 (£130,650) | 17.693 | $200,000 (£177,513) | | | |
| | Universal: 1 y | $147,900 (£131,271) | 17.695 | $350,000 (£310,649) | | | |
| | **Screening people with diabetes** | | | | | | |
| | Universal: age 50 y only | $179,400 (£159,230 ) | 16.078 | | | | |
| | Universal: 10 y | $180,100 (£159,851) | 16.119 | $17,073 (£15,154) | | | |
| | Usual care[1] | $180,300 (£160,028) | 16.128 | Dominated | | | |
| | Universal: 5 y | $180,300 (£160,028) | 16.135 | $12,500 (£11,095) | | | |
| | Universal: 2 y | $180,500 (£160,206) | 16.143 | $25,000 (£22,189) | | | |
| | Universal: 1 y | $181,000 | 16.146 | $166,667 (£147,928) | | | |
| | **Screening people with hypertension** | | | | | | |
| | Universal: age 50 y only | $148,500 (£131,804) | 17.177 | | | | |
| | Usual care[1] | $148,600 (£131,892) | 17.171 | Dominated | | | |
| | Universal: 10 y | $148,700 (£131,981) | 17.185 | $25,000 (£22,189) | | | |

| Study | Comparators | Costs[2] | QALYs | ICER[3] | Uncertainty | Applicability | Limitations |
|---|---|---|---|---|---|---|---|
| | Universal: 5 y | $148,800 (£132,070) | 17.189 | $25,000 (£22,189) | | | |
| | Universal: 2 y | $149,200 (£132,425) | 17.191 | $200,000 (£177,513) | | | |
| | Universal: 1 y | $149,800 (£132,958) | 17.189 | Dominated | | | |

[1]*Usual care assumed annual screening rates of 22% for people with diabetes, 2% for people with hypertension, 23% for people with both and 0% for people with neither.*

[2]*US dollars 2006 converted to sterling 2020 using the EPPI Centre cost converter (accessed 28/01/2020), conversion factor 1.127.*

[3]*In the original publication results were presented for each strategy compared to usual care in turn. Author also reported results using no treatment and no screening as the common comparator. These were not presented by the analyst as they were found not to be representative of the UK context were some degree of screening and treatment is in place. Analyst calculated full incremental analyses for the different populations considered in the study.*

***Howard 2010***

| Study | Comparators[1] | Costs[3] | Effects | ICER | Uncertainty | Applicability | Limitations |
|---|---|---|---|---|---|---|---|
| **Howard 2010**<br>Cost utility analysis<br>People aged >25 years with sub-optimally managed diabetes, hypertension and proteinuria<br>Australian healthcare provider perspective<br>Lifetime horizon | **"Treatment" model: Improved management in people with known risk factors** | | | | Probability cost effective[4] | Partially applicable | Minor limitations |
| | 1. Intensive glycaemic control in people with known type 2 diabetes | $40,144 (£23,530) | 9.942 | Dominant | 85% | | |
| | 1. Standard care | $40,277 (£23,608) | 9.867 | Dominated | - | | |
| | 2. Addition of ACE inhibitor in people with known type 2 diabetes | $37,781 (£22,145) | 10.111 | Dominant | 88% | | |
| | 2. Standard care | $38,606 (£22,629) | 9.987 | Dominated | - | | |
| | 3. Intensive blood pressure control in people with known hypertension | $39,716 (£23,279) | 10.070 | $2,588/QALY (£1,517/QALY | 82% | | |
| | 3. Standard care | $39,364 (£23,073) | 9.934 | | - | | |
| | **"Screening" model: Primary care screening for CKD risk factors[2]** | | | | | | |
| | 4. Screening for diabetes and intensive glycaemic control in | $17,832 (£10,452) | 12.798 | $13,866/QALY (£8,128/QALY) | 57% | | |

| Study | Comparators[1] | Costs[3] | Effects | ICER | Uncertainty | Applicability | Limitations |
|---|---|---|---|---|---|---|---|
| | known and screen-detected people with type 2 diabetes | | | | | | |
| | 4. Standard care | $16,487 (£9,664) | 12.701 | | - | | |
| | 5. Screening for hypertension and intensive hypertension control in known and screen-detected people with hypertension | $14,061 (£8,242) | 12.947 | $491/QALY (£288/QALY) | 55% | | |
| | 5. Standard care | $14,004 (8,208) | 12.831 | | - | | |
| | 6. Screening for proteinuria and addition of ACE inhibitor in people with known diabetes and screen-detected proteinuria | $16,974 (£9,949) | 12.763 | $4,781/QALY (£2,803/QALY) | 50% | | |
| | 6. Standard care | $16,821 (£9,860) | 12.731 | | - | | |

[1]*All strategies compared to standard care. Dominant means intervention if both cheaper and more effective than standard care.*

[2]*Screening was assumed to occur annually in a primary care setting, being offered to individuals aged 50 to 69 years*

[3]*Australian dollars 2008 converted to sterling 2019 using the EPPI Centre cost converter (accessed 17/12/2019), conversion factor 1.71*

[4]*Probability of interventions being cost effectiveness at a $50,000/QALY (£29,307/QALY) threshold*

***Dong 2004***

| Study | Comparators | Costs[2] | Effects | ICER | Uncertainty | Applicability | Limitations |
|---|---|---|---|---|---|---|---|
| **Dong 2004**<br>People with type 1 diabetes<br>Cost utility analysis<br>US single payer perspective | ACE inhibitor 1 year after diagnosis of type 1 diabetes (Early) | $130,460 (£136,558) | 20.456 | $27,192 (£28,463)/QALY | Increasing the age at diagnosis and decreasing the level of HbA1c would raise the ICER but did not change conclusions of the analysis. This was explored in bivariate scenario analysis. For people diagnosed at age 20 and with HbA1c of 9%, the early ACE inhibitor intervention was associated with an ICER of $13, 814 (£14,460)/QALY. For those diagnosed at 30 years with HbA1c of 7% Early | Partially applicable | Potentially serious limitations |
| | Annual screening for microalbuminuria[1] | $127,768 (£133,740) | 20.357 | | | | |

| Study | Comparators | Costs[2] | Effects | ICER | Uncertainty | Applicability | Limitations |
|---|---|---|---|---|---|---|---|
| Lifetime horizon<br>Individual patient simulation | + ACE inhibitor (Standard) | | | | administration of ACE inhibitors was priced at $32,972 (£34,513)/QALY.<br>Univariate sensitivity analyses used alternative discount rate, cost and accuracy of the screening test, efficacy and costs of ACE inhibition. The results were particularly sensitive to ACE inhibitor efficacy. A relative risk reduction of 10% (instead of 24%) gives an ICER of $75,276 (£78,794) per QALY. A relative risk reduction of 50% originated an ICER of $8,814 (£9,226) per QALY.<br>The results were overall robust to one-way sensitivity analysis.<br>Probabilistic sensitivity analysis was not conducted. | | |

[1]*Details of albuminuria screening were not provided by the author, sensitivity and specificity assumed to be 100%.*

[2]*US dollars 1999 converted to sterling 2020 using the EPPI Centre cost converter (accessed 22/01/2020), conversion factor 0.955*

***Boulware 2003***

| Study | Comparators | Costs[2] | QALYs | ICER[3] | Uncertainty | Applicability | Limitations |
|---|---|---|---|---|---|---|---|
| **Boulware 2003**<br>Cost utility analysis<br>US adults aged 50<br>Societal perspective | **People without hypertension or diabetes** | | | | Results were not sensitive to starting age for screening.<br>Screening less frequently was associated with lower ICERs, $120,727 (£124,657) if done every 5 years and $80,700 (£83,327) if done every 10 years.<br>Screening was associated with a 1.5% probability of being cost-effective at a threshold of less than $50,000 (£51,628) per QALY. | Partially applicable | Minor limitations |
| | Screening + ACE inhibitor or ARB[1] | $13,745 (£14,192) | 19.461 | $280,000 (£289,114)/QALY | | | |
| | No screening | $13,129 (£13,556) | 19.459 | | | | |
| | **People with hypertension** | | | | Screening was cost-effective irrespectively of the age at which screening was started (range 30 to | | |

| Study | Comparators | Costs[2] | QALYs | ICER[3] | Uncertainty | Applicability | Limitations |
|---|---|---|---|---|---|---|---|
| Lifetime horizon | Screening + ACE inhibitor or ARB[1] | $23,927 (£24,706) | 17.241 | $18,594 (£19,999)/QALY | 70 years). After the age of 40, screening was associated with a cost of $18,589 (£19,194) per QALY, decreasing thereafter.<br>The screening strategy remained cost-effective with less frequent screening produced lower ICERs.<br>Screening was associated with a 50.3% probability of being cost-effective at a threshold less than $50,000 (£51,628) per QALY). | | |
| | No screening | $23,451 (£24,214) | 17.215 | | | | |

[1]*Initial screening for proteinuria consisted of a urine dipstick. Positive results were followed by a second physician appointment to assess protein levels using albumin to creatinine ratio or timed urine specimens in addition to serum creatinine level and eGFR. Screening occurred annually until age 75, development of ESRD or death.*

[2]*US dollars 2002 converted to sterling 2020 using the EPPI Centre cost converter (accessed 22/01/2020), conversion factor 0.968.*

[3]*The author assumed an ICERs below $50,000/QALY (£51,628/QALY) to be highly favourable, between $50,000 and $100,000/QALY (£103,255/QALY) moderately favourable and greater than $100,000/QALY unfavourable*

***Golan 1999***

| Study | Comparators | Costs | Effects | ICER | Uncertainty | Applicability | Limitations |
|---|---|---|---|---|---|---|---|
| **Golan 1999**<br>Cost utility analysis<br>50-year-old people with type 2 diabetes<br>Lifetime horizon<br>US Societal perspective | Treat all with ACE inhibitor (no screening) | $15,240 (£15,874) | 11.82 QALYs | $7500/QALY (£7,812/QALY) | In univariate sensitivity analysis the ICER was sensitive to age at diagnosis of diabetes, drug costs, effectiveness and quality of life associated with ACE inhibitor.<br>This did not change the overall conclusions of the analysis. | Partially applicable | Very serious limitations |
| | ACE inhibitor if microalbuminuria | $14,940 (£15,562) | 11.78 QALYs | | | | |
| | ACE inhibitor if gross proteinuria | $19,520 (£20,333) | 11.59 QALYs | Dominated | | | |

[1]*Normoalbuminuria –excretion < 30 mg/day; microalbuminuria – excretion 30 to 100 mg/day; gross proteinuria – excretion > 300 mg/day*

[2]*US dollars 1998 converted to sterling 2019 using the EPPI Centre cost converter (accessed 17/12/2019), conversion factor 0.96*

***Kiberd 1998***

| Study | Comparators | Costs[3] | Effects | ICER | Uncertainty | Applicability | Limitations |
|---|---|---|---|---|---|---|---|
| Cost utility analysis<br><br>People with type 1 diabetes<br><br>US third party<br><br>60-year time horizon | **Intervention 1:** Current recommendations (annual screening for microalbuminuria plus ACE inhibitor)[1] | $29,350 (£32,646) | 19.15 | Dominated | The analysis was robust to univariate sensitivity analyses.<br><br>No probabilistic sensitivity analysis was conducted. | Partially applicable | Very serious limitations |
| | **Intervention 2:** Routine treatment of all people 5 years after diagnosis of diabetes | $29,180 (£32,457) | 19.34 | Dominates | | | |
| | **Intervention 3:** Treat people at high risk 5 years after diagnosis of diabetes and screen people at low risk and treat with ACE inhibitor accordingly[2] | $29,236 (£32,520) | 19.17 | Dominated | | | |

*[1]Screening in people with diagnosis of diabetes for more than 5 years and treatment with the equivalent to captopril 25 mg 3 times a day if 2 of 3 tests were positive (>20 mcg/min or 30 mg albumin/g creatinine)*

*[2]People with low risk were screened for hypertension and macroproteinuria (dipstick >0.3 g/L or positive albustick confirmed with >3000 mg/day or >200 mcg/min proteinuria)*

*[3]US dollars 1995 converted to sterling 2020 using the EPPI Centre cost converter (accessed 14/01/2020), conversion factor 0.90*

## Comparison of antihypertensive therapies

***Adarkwah 2013***

| Study | Comparators | Costs[1] | Effects | ICER | Uncertainty | Applicability | Limitations |
|---|---|---|---|---|---|---|---|
| **Adarkwah 2013**<br><br>People with advanced renal disease<br><br>Cost utility analysis<br><br>Dutch health system perspective | ACE inhibitor | €183, 535 (£176,674) | 14.66 | Dominates | Parameters with largest impact in univariate sensitivity analysis were the effectiveness of ACE inhibitor, cost of ESRD and discount rate. The conclusions of the analysis did not change when these were varied.<br><br>The probability of producing savings was 83%. | Partially applicable | Potentially serious limitations |
| | No treatment (Antihypertensives not acting on the renin-angiotensin-system) | €220,942 (£212,683) | 13.38 | Dominated | | | |

| Study | Comparators | Costs[1] | Effects | ICER | Uncertainty | Applicability | Limitations |
|---|---|---|---|---|---|---|---|
| Lifetime horizon | | | | | | | |

[1]*Euros 2010 converted to sterling 2019 using the EPPI Centre cost converter (accessed 11/12/2019), conversion factor 1.04.*

***Delea 2009***

| Study | Comparators | Costs[1] | Effects | ICER | Uncertainty | Applicability | Limitations |
|---|---|---|---|---|---|---|---|
| **Delea (2009)**<br>People with type 2 diabetes and microalbuminuria<br>Cost utility analysis<br>US health system<br>Lifetime horizon | Aliskiren 300 mg/day plus losartan 100 mg/day | $64,746 (£53,849) | 5.9775 QALYs | $30,527/QALY (£25,390/QALY) | In univariate sensitivity analysis the results were sensitive to the duration of effect and price of aliskiren but the intervention remained cost-effective at the $50,000 to $100,000/QALY (£41,585 to £83,170/QALY) threshold.<br>Interventions 1 had a 60% probability of being cost-effective at a $50,000/QALY threshold and a 72% probability of being cost-effective at a threshold of $100,000. | Partially applicable | Potentially serious limitations |
| | Losartan 100 mg/day | $61,794 (£51,394) | 5.8808 QALYs | | | | |

[1]*US dollars 2008 converted to sterling 2019 using the EPPI Centre cost converter (accessed 17/12/2019), conversion factor 1.20.*

***Smith 2004***

| Study | Comparators | Costs[1] | QALYs | ICER | Uncertainty | Applicability | Limitations |
|---|---|---|---|---|---|---|---|
| **Smith 2004**<br>Cost utility analysis<br>People with type 2 diabetes<br>US third party perspective<br>8-year time horizon, 3-month cycles | Valsartan | $92,058 (£92,231) | 6.390 | dominates | The results were robust to univariate sensitivity analyses on discount rate, health state costs, and medication costs<br><br>Probabilistic sensitivity analysis was not conducted. | Partially applicable | Very serious limitations |
| | Amlodipine | $124,470 (£124,703) | 5.835 | | | | |

[1]*US dollars 1995 converted to sterling 2020 using the EPPI Centre cost converter (accessed 15/01/2020), conversion factor 0.998*

## Diet interventions

### *You 2015*

| Study | Comparators | Costs[4] | QALYs | ICER[5] | Uncertainty | Applicability | Limitations |
|---|---|---|---|---|---|---|---|
| **You 2015**<br>Cost utility analysis<br>People with CKD stage 4[1]<br>Taiwanese health system<br>10-year time horizon | Low protein diet[2] + supplementation with ketoanalogues[3] in people with CKD stage 4 | $564,637 (£430,741) | 3.926 | Dominates | The analysis was robust to univariate sensitivity analysis of the treatment efficacy parameter.<br>Probabilistic sensitivity analysis used 10,000 iterations of each of the model's parameters using a triangular distribution. This analysis suggested a statistically significant difference in cost and QALYs between comparators. | Partially applicable | Very serious limitations |
| | Low protein diet and watchful waiting (CKD stage 4) + supplementation with ketoanalogues if CKD stage 5 | $914,236 (£697,437) | 3.787 | Dominated | | | |

*[1]CKD stage 4 defined as estimated glomerular filtration rate (eGFR) 15 – 29 mL/min/1.73 m$^2$ and CKD stage 5 defined as eGFR < 15 mL/min/1.73 m$^2$.*

*[2]Defined as a protein intake of ≤ 0.6 g/kg/day*

*[3]Combination of essential amino acids and essential amino acid analogues*

*[4]US dollars 2015 converted to sterling 2020 using the EPPI Centre cost converter (accessed 27/01/2020), conversion factor 1.311.*

*[5]The analysis used the threshold for cost-effectiveness defined by the World Health Organisation, 3-fold the gross domestic product (GDP) per capita. In Taiwan this value was calculated as US $20,726 (£15,811)*

### *Mennini 2014*

| Study | Comparators | Costs[2] | QALYs | ICER | Uncertainty | Applicability | Limitations |
|---|---|---|---|---|---|---|---|
| **Mennini 2014**<br>Cost utility analysis<br>People with CKD stage 4 or 5<br>Italian NHS<br>2,3,5 and 10-year time horizon | Very low protein diet[1] | €55,109 (£56,391) | 4.75 | Dominates | The analysis was robust to univariate analysis of discount rates, transition probability to ESRD, probability of death from ESRD, utility parameters, cost of dialysis and cost of diet.<br>In probabilistic sensitivity analysis the very low protein diet had 100% probability of being cost-effective (dominant). | Partially applicable | Very serious limitations |
| | Moderately low protein diet[2] | €65,483 (£67,007) | 4.77 | Dominated | | | |

*[1]Low protein diet defined as 0.6 g/kg/day; very low protein diet defined as 0.3 g/kg/day.*

*[2]Euros 2014 converted to sterling 2020 using the EPPI Centre cost converter (accessed 27/01/2020), conversion factor 0.977.*

#### 1.1.7.2 Excluded studies

A list of studies excluded at full text from the cost-effectiveness review can be found in Appendix L.

### 1.1.8 The committee's discussion and interpretation of the evidence

#### 1.1.8.1 The outcomes that matter most

The committee agreed that the key outcomes for adults, children and young people with suspected or diagnosed CKD and proteinuria or albuminuria were mortality (all-cause and cardiovascular), CKD progression (occurrence of end stage kidney disease), morbidity (non-fatal cardiovascular events), and hospitalisation (as an adverse outcome). Health-related quality of life was a key outcome but only reported by 1 RCT. Other morbidities and adverse outcomes were also important outcomes, but shortage of evidence on these outcomes made harder to use them for decision making. The committee agreed that reducing proteinuria would have an effect on the key outcomes (reducing chronic kidney disease progression and reducing cardiovascular risk). The committee also discussed the implications of recommending blood pressure medications for the reduction of proteinuria or albuminuria and agreed that blood pressure control is more important than reduction of proteinuria or albuminuria. The committee also highlighted that there is an increased risk for acute kidney injury when prescribing ACE-I and ARB together. Most of the outcomes were reported by the included studies apart from advancement of renal bone disease, vascular calcification, and anaemia which are listed in the protocol as specific morbidities.

#### 1.1.8.2 The quality of the evidence

Overall, the quality of the evidence varied from high to very low (most of the studies were of low and very low quality), with the main reasons for downgrading being due to imprecision of the evidence on the relative effectiveness of different medications to lower proteinuria or albuminuria and due to risk of bias of included RCTs. In most of the comparisons, imprecision was considered to be serious or very serious. Most of the comparisons were reported by single studies and 14 of the 32 included studies had sample sizes of 100 participants or fewer. Risk of bias for some of the included RCTs was due to lack of detailed reporting of the randomisation process, lack of information on the type of analysis (intention-to-treat or per-protocol analysis), and lack of reporting that protocols were pre-registered.

None of the included RCTs reported evidence for endothelin antagonists and dietary interventions (NaCl, protein) as interventions to reduce proteinuria or albuminuria. There were 2 RCTs reporting exercise interventions, 6 RCTs reported diabetes medications and the rest of the RCTs reported blood pressure medications. The committee did not make specific research recommendations on endothelin antagonists, dietary (NaCl, protein) or exercise interventions. because they were aware of ongoing trials targeting these areas, and did not think that they were priority areas for research. Evidence on these interventions is expected to be found in the future, if any, with further updates of this review question. The evidence was analysed by class of medication (see 1.1.3 Methods and ).

There were 2 RCTs reporting on aliskiren (direct renin inhibitor) but the committee agreed to exclude both RCTs from the evidence for this review because of the restricted use in people with CKD in the UK (see British National Formulary).The committee also noted that aliskiren is not widely use in clinical practice.

Pairwise analysis was sub-grouped within class by drug to investigate any potential intra-class effect. The committee looked at these subgroups and concluded that there was no intra-class effect on any of the interventions.

None of the included studies reported results for children and young people.

#### 1.1.8.3 Benefits and harms

The committee discussed the evidence for adults with type 2 diabetes separately from the evidence for adults without diabetes. The committee also noted that not all studies were specific for adults with high blood pressure but many of the study participants had hypertension and most of the evidence was for blood pressure medications. The committee also discussed the implications of recommending blood pressure medications for the reduction of proteinuria or albuminuria and agreed that blood pressure control is more important than reduction of proteinuria or albuminuria and made sure that there were no contradictions when recommending blood pressure medications for blood pressure control or for reduction of proteinuria or albuminuria.

The committee highlighted that in their experience, adults with CKD might not want to have more medications prescribed if they have high levels of proteinuria or albuminuria and they are not already taking the medications recommended here. The committee noted that adults with CKD and diabetes have their albumin levels revised/screened annually as set out in the Quality and Outcomes Framework (QoF) system. The committee acknowledged that testing albuminuria might be an implementation issue.

The committee agreed to replace the recommendation for the use of 'a low-cost renin–angiotensin system antagonist' for the use of 'ACE inhibitor or ARB' because the evidence was strongest for these 2 medications and it is more helpful to have the specific classes in the recommendation and because the evidence showed a class effect. It was agreed to remove the text referring to the cost of medications because both ACE inhibitors and ARBs are low cost renin–angiotensin system antagonists.

The committee agreed that it was important to monitor CKD progression in adults, children and young people who were taking medications to lower proteinuria and made specific recommendations for each age group to highlight and refer back to recommendations on frequency of monitoring and recommendations on referral criteria for specialist assessment.

##### 1.1.8.3.1 Adults with type 2 diabetes

**Blood pressure medications**

The committee discussed the evidence for blood pressure medications in adults with type 2 diabetes and noted that there was a clinically meaningful risk reduction for end stage kidney disease, and first hospitalisation for heart failure with ARBs compared to placebo:

- End stage kidney disease (RR 0.79 [95% CI 0.67, 0.92], 3.4 years follow-up, low quality of evidence, losartan and irbesartan [ARB])
- First hospitalisation for heart failure (RR 0.72 [95% CI 0.56, 0.93], 3.4 years follow-up, low quality of evidence, losartan [ARB])

The committee noted that the evidence could not differentiate the effect of ACE-I compared to ARB in adults with type 2 diabetes on the following outcomes: reduction of proteinuria, end stage kidney disease, all-cause mortality, CV mortality, non-fatal CV events, adverse events (hypotension), and hospitalisation. There was no evidence comparing ACE-I with placebo in this population but there was evidence showing a reduction of end stage renal disease with ACE-I compared to placebo in adults without type 2 diabetes. Based on this evidence and the thresholds for ACR in the previous version of the guideline, the committee agreed to recommend both ACE inhibitors and ARBs for adults with type 2 diabetes and proteinuria or albuminuria (ACR ≥3 mg/mmol) and for adults with ACR ≥70 mg/mmol with or without hypertension or cardiovascular disease. The previous version of the guideline recommended ACE-I or ARB to adults with CKD and proteinuria with or without hypertension or

cardiovascular disease at the same thresholds based on economic evaluations which showed that ACE-I or ARB were cost saving compared to placebo in this population.

The committee also discussed the evidence for harms from combined treatments and noted that there was a clinically meaningful increased risk for acute kidney injury with ACE-I (lisinopril) and ARB (losartan) prescribed together compared to ARB (losartan) prescribed alone (RR 1.62 [95% CI 1.25, 2.1], 2.2 years follow-up, low quality of evidence). Therefore, the committee agreed that this evidence was in line with the 2014 recommendation of 'do not offer a combination of renin-angiotensin system antagonists to people with CKD'.

The committee also noted that there was some evidence for blood pressure medications showing a clinically meaningful effect at reducing proteinuria or albuminuria at 2 years. However, the committee agreed that long-term outcomes (such as CKD progression and mortality) were the key outcomes to make recommendations of interventions to lower proteinuria or albuminuria. Therefore, data on reducing proteinuria or albuminuria was not used to make recommendations.

There were studies reporting on other interventions which did not show an effect on most of the outcomes when compared to placebo (spironolactone [aldosterone antagonist], amlodipine [CCB]) or between different interventions (losartan [ARB] compared to spironolactone; irbesartan [ARB ] compared to amlodipine [CCB]) or the effect was on the reduction of albuminuria or proteinuria (spironolactone compared to placebo; irbesartan compared to amlodipine).

**Diabetes medications**

The committee discussed the evidence for diabetes medications and noted that there was a clinically meaningful risk reduction for end stage kidney disease, all-cause mortality and hospitalisation for heart failure with canagliflozin and dapagliflozin (both of these medications are SGLT2 inhibitors) compared to placebo:

- End stage kidney disease in adults with ACR 20 mg/mmol and higher (RR 0.69 [95% CI 0.59, 0.81], up to 2.4 years follow-up, moderate quality of evidence)
- All-cause mortality (RR 0.78 [95% CI 0.68, 0.91], up to 2.4 years follow-up, high quality of evidence)
- All-cause mortality in adults with macroalbuminuria (HR 0.63 [95% CI 0.43, 0.92], 6 years follow-up, high quality of evidence, only reported for canagliflozin)
- Cardiovascular mortality (RR 0.79 [95% CI 0.65, 0.96], up to 2.4 years follow-up, high quality of evidence)
- Hospitalisation for heart failure (RR 0.63 [95% CI 0.49, 0.82], 6 months follow-up, moderate quality of evidence, only reported for canagliflozin)

There was evidence showing an increased risk for hypoglycaemia with gliptins compared to placebo (RR 2.35 [95% CI 1.16, 4.77], 6 months follow-up, moderate quality of evidence).

The committee agreed that evidence on canagliflozin and dapagliflozin was robust, showed an effect on key outcomes and the quality was high to moderate which meant that SGLT2 inhibitors could be recommended as a class of medications to lower proteinuria. The committee also agreed that this recommendation was for adults with ACR 30 mg/mmol or more because the risk of dying was lowest in adults with macroalbuminuria (ACR >30 mg/mmol).

The committee noted that the RCTs reporting on SGLT2 inhibitors used different thresholds of proteinuria to recruit participants:

- Heerspink, 2020 (n=4304): 20 to 50 mg/mmol
- Neuen, 2019 (n=2266): 3 to 30 mg/mmol
- Neuen, 2019 (n=760): ≥30 mg/mmol

- Perkovic, 2019 (n=4401): >30 to 500 mg/mmol
- Pollock, 2019 (n=461): 3 to 350 mg/mmol

Most of these studies included participants with CKD based on their eGFR levels apart from Neuen 2019 which included participants with microalbuminuria or macroalbuminuria irrespective of their eGFR levels.

Overall, the committee agreed that a threshold of ≥30 mg/mmol was a sensible threshold that broadly represented the inclusion criteria of the trials and was consistent with other recommendations in the guideline.

There were studies reporting on other interventions which did not show an effect on most of the outcomes when compared to placebo (pioglitazone [thiazolidinedione]) or between different interventions (dapagliflozin [SGLT2] + saxagliptin [gliptin] compared to dapagliflozin; exercise compared to no intervention or to diet).

#### 1.1.8.3.2 Adults without type 2 diabetes

**Blood pressure medications**

The committee discussed the evidence for blood pressure medications and noted that there was a clinically meaningful risk reduction for end stage kidney disease with ACE-I compared to placebo (RR 0.59 [95% CI 0.43, 0.83], up to 6 years follow-up, very low quality). The committee also noted that most of the evidence for blood pressure medications showed a clinically meaningful effect at reducing proteinuria or albuminuria at different time points ranging from 3 months to 3 years. However, the committee agreed that long-term outcomes (such as CKD progression and mortality) were the key outcomes to make recommendations for interventions to lower proteinuria or albuminuria. Based on this evidence and evidence from adults with type 2 diabetes, the committee agreed to recommend ARBs and ACE-I for adults without type 2 diabetes and proteinuria or albuminuria (ACR ≥30 mg/mmol).

There were studies reporting on other interventions which did not show an effect on most of the outcomes when compared to placebo (eplerenone [aldosterone antagonist]) or between different interventions (losartan [ARB] compared to amlodipine [CCB]) or the effect was on the reduction of albuminuria or proteinuria (eplerenone compared to placebo; losartan compared to amlodipine; losartan + hydrochlorothiazide (diuretic) compared to losartan; spironolactone [aldosterone antagonist] + conventional therapy [ACE-I, ARB or diuretic] compared to conventional therapy).

**Adults aged over 75 years**

The committee highlighted that most of the studies did not include adults aged over 75 years. The committee agreed that clinical expertise would have to guide decisions on how to treat proteinuria or albuminuria in adults aged over 75 years as no evidence was found for this group. The committee noted that multimorbidity and frailty are important characteristics to take into account when prescribing medications to reduce proteinuria/albuminuria in adults aged over 75 years and that health professionals might choose to discuss treatment with a specialist if appropriate. Therefore, a new recommendation was made which refers to the NICE guideline on medicines optimisation and to seek specialist advice if needed.

**Research recommendations**

The committee agreed that there was not enough evidence to recommend ACE-I over ARB or the other way around and made a research recommendation to investigate the effectiveness of ACE-I compared to ARBs. There was evidence on this comparison but it was very low quality and could not differentiate between ACE-I and ARB for end stage renal disease (CKD progression), all-cause mortality, cardiovascular mortality, non-fatal CV events, adverse events, and hospitalisation. There was also low quality evidence showing an increase in proteinuria with ACE-I compared to ARBs. However, the committee agreed that

long-term outcomes (such as CKD progression and mortality) were the key outcomes to make recommendations of interventions to lower proteinuria or albuminuria.

#### 1.1.8.4 Cost effectiveness and resource use

The committee noted there was robust evidence (including evidence from the UK) that screening for proteinuria followed by treatment in those identified was cost effective in people with hypertension or diabetes (both type 1 and type 2). They agreed that screening was not within the scope of this question, but that such a screening strategy could only be cost effective if treatment was also cost effective, and therefore this provided evidence to support the recommendations made for the use of ACE inhibitors and ARBs in this population. The majority of the cost effectiveness evidence was for treatment with ACE inhibitors, but there was a study that also considered ARBs. Further, the committee noted that there was no evidence of differences in clinical effectiveness between the two classes, and the prices of both are low, so were confident treatment with either class of drugs would be cost effective.

The committee noted there was not equivalent cost effectiveness evidence for people without either hypertension or diabetes. However, they noted that there was clinical evidence that the treatments were also effective in this group and were therefore confident that the treatments would still be cost effective, in particular given the higher threshold for treatment specified in people without hypertension or diabetes.

The committee agreed the 2 studies looking at cost-effectiveness of diet interventions were of low quality, and in the absence of strong clinical evidence in this area either, agreed it was not possible to make any recommendations in this area.

The committee noted that there were no published cost-effectiveness studies for SGLT2 inhibitors; this is likely due to all the licences until recently containing contraindications for people with CKD. They also noted that it was not practical to conduct original cost-effectiveness modelling within this guideline, as to appropriately model this would involve modelling both renal and diabetes outcomes, including modelling of future intensification of diabetes treatments, which was not practical within this guideline. They agreed that such modelling was more appropriate to undertake within an update of the diabetes guideline, particularly as many people in this population would develop diabetes first, and therefore already be on a diabetes treatment pathway before CKD is diagnosed.

The committed noted there were already a number of published technology appraisals on SGLT2 inhibitors, demonstrating them to be cost-effective for certain indications (in populations without CKD). In particular, these TAs find SGLT2s to be cost-effective first-line in people where metformin, sulfonylurea and pioglitazone are not appropriate, or as part of dual and triple therapies in people where earlier lines of therapy are not sufficient. These appraisals were mostly conducted before the publications of recent large RCTs directly looking at cardiovascular events and mortality, and were therefore based on extrapolations from intermediate endpoints (in particular HbA1c). The committee noted the impact of their recommendations would be to bring forward the potential use of these drugs to an earlier point in time for some patients (specifically those who develop CKD and proteinuria before the point they would meet the criteria for an SGLT2 based solely on their diabetes).

The committee noted that the doses of SGLT2 used in people with diabetes and CKD were lower than the doses used in people without renal impairment. They were nonetheless confident these drugs would still be effective for blood glucose control in this population, and would therefore provide similar benefits on diabetes control to those in the non-CKD population. In addition, there would then be further benefits on renal outcomes, as demonstrated in the RCTs included in this review, and therefore the overall clinical benefit in a population of people with diabetic kidney disease would be larger than the benefit estimated in the technology appraisals for people with diabetes but not CKD. They therefore felt confident that, with a larger benefit for a similar cost, it was appropriate that these drugs

be available earlier in the treatment pathway for people with diabetes and CKD, and that this would represent a cost-effective use of NHS resources.

The committee noted that two of the drugs from the class (canagliflozin and dapagliflozin) now had positive RCTs for this indication, and trials in other SGLT2 inhibitors were ongoing. They therefore felt it was appropriate to make a class level recommendation, to cover any future SGLT2 inhibitors which might get a similar license extension to cover people with diabetes and CKD.

#### 1.1.8.5 Other factors the committee took into account

The committee highlighted that an ongoing trial (EMPA-KIDNEY) may provide additional evidence about SGLT2 inhibitors. EMPA-KIDNEY is a randomised controlled trial testing the effects of empagliflozin 10mg versus placebo on kidney disease progression endpoints and cardiovascular death among patients at risk of progressive chronic kidney disease. This information has been passed to the NICE Surveillance team to follow-up publication of the trial.

### 1.1.9 Recommendations supported by this evidence review

This evidence review supports recommendations 1.6.5 – 1.6.11 and the research recommendation on the effect of ACE-I compared to ARB for lowering proteinuria.

### 1.1.10 References – included studies

#### 1.1.10.1 Effectiveness

Ameen; Kashif, M.A.; Sumreen (2016) To compare anti-albumin urea effects of valsartan alone with combination of valsartan and amlodipine in patients of chronic kidney disease. Pakistan Journal of Medical Sciences 32(3): 613-616

Ando, Katsuyuki, Ohtsu, Hiroshi, Uchida, Shunya et al. (2014) Anti-albuminuric effect of the aldosterone blocker eplerenone in non-diabetic hypertensive patients with albuminuria: a double-blind, randomised, placebo-controlled trial. The lancet. Diabetes & endocrinology 2(12): 944-53

Anonymous (1997) Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). Lancet (London, England) 349(9069): 1857-63

Bianchi, S; Bigazzi, R; Campese, V M (2006) Long-term effects of spironolactone on proteinuria and kidney function in patients with chronic kidney disease. Kidney international 70(12): 2116-23

Brenner, B M, Cooper, M E, de Zeeuw, D et al. (2001) Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. The New England journal of medicine 345(12): 861-9

Ciavarella, A, Vannini, P, Flammini, M et al. (1985) Effect of long-term near-normoglycemia on the progression of diabetic nephropathy. Diabete & metabolisme 11(1): 3-8

Fried, Linda F, Emanuele, Nicholas, Zhang, Jane H et al. (2013) Combined angiotensin inhibition for the treatment of diabetic nephropathy. The New England journal of medicine 369(20): 1892-903

Fujisaki, Kiichiro, Tsuruya, Kazuhiko, Nakano, Toshiaki et al. (2014) Impact of combined losartan/hydrochlorothiazide on proteinuria in patients with chronic kidney disease and

hypertension. Hypertension research : official journal of the Japanese Society of Hypertension 37(11): 993-8

Groop, P.-H., Cooper, M.E., Perkovic, V. et al. (2017) Linagliptin and its effects on hyperglycaemia and albuminuria in patients with type 2 diabetes and renal dysfunction: the randomized MARLINA-T2D trial. Diabetes, Obesity and Metabolism 19(11): 1610-1619

Heerspink, Hiddo J.L., Stefánsson, Bergur V., Correa-Rotter, Ricardo et al. (2020) Dapagliflozin in Patients with Chronic Kidney Disease. New England Journal of Medicine

Iino, Yasuhiko, Hayashi, Matsuhiko, Kawamura, Tetsuya et al. (2003) Interim evidence of the renoprotective effect of the angiotensin II receptor antagonist losartan versus the calcium channel blocker amlodipine in patients with chronic kidney disease and hypertension: a report of the Japanese Losartan Therapy Intended for Global Renal Protection in Hypertensive Patients (JLIGHT) Study. Clinical and experimental nephrology 7(3): 221-30

Kanjanabuch, T., Sukhato, W., Katavetin, P. et al. (2009) Beneficial effect of pioglitazone in proteinuric IgA nephropathy with concomitant ACEI/ARB treatment. Asian Biomedicine 3(6): 645-652

Kanno, Yoshihiko, Takenaka, Tsuneo, Nakamura, Tsukasa et al. (2006) Add-on angiotensin receptor blocker in patients who have proteinuric chronic kidney diseases and are treated with angiotensin-converting enzyme inhibitors. Clinical journal of the American Society of Nephrology : CJASN 1(4): 730-7

Krairittichai, Udom and Chaisuvannarat, Viranya (2009) Effects of dual blockade of renin-angiotensin system in type 2 diabetes mellitus patients with diabetic nephropathy. Journal of the Medical Association of Thailand = Chotmaihet thangphaet 92(5): 611-7

Lee, Yu-Ji, Cho, Seong, Kim, Sung Rok et al. (2011) Effect of losartan on proteinuria and urinary angiotensinogen excretion in non-diabetic patients with chronic kidney disease. Postgraduate medical journal 87(1032): 664-9

Leehey, David J, Collins, Eileen, Kramer, Holly J et al. (2016) Structured Exercise in Obese Diabetic Patients with Chronic Kidney Disease: A Randomized Controlled Trial. American journal of nephrology 44(1): 54-62

Leehey, David J, Moinuddin, Irfan, Bast, Joseph P et al. (2009) Aerobic exercise in obese diabetic patients with chronic kidney disease: a randomized and controlled pilot study. Cardiovascular diabetology 8: 62

Lewis, Edmund J., Hunsicker, Lawrence G., Bain, Raymond P. et al. (1993) The Effect of Angiotensin-Converting-Enzyme Inhibition on Diabetic Nephropathy. New England Journal of Medicine 329(20): 1456-1462

Lewis, Edmund J., Hunsicker, Lawrence G., Clarke, William R. et al. (2001) Renoprotective Effect of the Angiotensin-Receptor Antagonist Irbesartan in Patients with Nephropathy Due to Type 2 Diabetes. New England Journal of Medicine 345(12): 851-860

Li, Philip Kam-Tao, Leung, Chi Bon, Chow, Kai Ming et al. (2006) Hong Kong study using valsartan in IgA nephropathy (HKVIN): a double-blind, randomized, placebo-controlled study. American journal of kidney diseases : the official journal of the National Kidney Foundation 47(5): 751-60

Luño, José, Barrio, Vicente, Goicoechea, Maria Ángeles et al. (2002) Effects of dual blockade of the renin-angiotensin system in primary proteinuric nephropathies. Kidney International 62: 47-s52

Matsuda, H; Hayashi, K; Saruta, T (2003) Distinct time courses of renal protective action of angiotensin receptor antagonists and ACE inhibitors in chronic renal disease. Journal of human hypertension 17(4): 271-6

Matsuda, Hiroto, Hayashi, Koichi, Homma, Koichiro et al. (2003) Differing anti-proteinuric action of candesartan and losartan in chronic renal disease. Hypertension research : official journal of the Japanese Society of Hypertension 26(11): 875-80

Mehdi, Uzma F, Adams-Huet, Beverley, Raskin, Philip et al. (2009) Addition of angiotensin receptor blockade or mineralocorticoid antagonism to maximal angiotensin-converting enzyme inhibition in diabetic nephropathy. Journal of the American Society of Nephrology : JASN 20(12): 2641-50

Neuen, B.L., Ohkuma, T., Neal, B. et al. (2019) Effect of canagliflozin on renal and cardiovascular outcomes across different levels of albuminuria: Data from the CANVAS program. Journal of the American Society of Nephrology 30(11): 2229-2242

Perkovic, Vlado, Jardine, Meg J, Neal, Bruce et al. (2019) Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. The New England journal of medicine 380(24): 2295-2306

Pollock, C., Stefansson, B., Reyner, D. et al. (2019) Albuminuria-lowering effect of dapagliflozin alone and in combination with saxagliptin and effect of dapagliflozin and saxagliptin on glycaemic control in patients with type 2 diabetes and chronic kidney disease (DELIGHT): a randomised, double-blind, placebo-controlled trial. The Lancet Diabetes and Endocrinology 7(6): 429-441

Praga, Manuel, Andrade, Carlos Fernandez, Luno, Jose et al. (2003) Antiproteinuric efficacy of losartan in comparison with amlodipine in non-diabetic proteinuric renal diseases: a double-blind, randomized clinical trial. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 18(9): 1806-13

Ruggenenti, P, Perna, A, Gherardi, G et al. (1999) Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. Lancet (London, England) 354(9176): 359-64

Saglimbene, Valeria, Palmer, Suetonia C, Ruospo, Marinella et al. (2018) The Long-Term Impact of Renin-Angiotensin System (RAS) Inhibition on Cardiorenal Outcomes (LIRICO): A Randomized, Controlled Trial. Journal of the American Society of Nephrology : JASN 29(12): 2890-2899

van den Meiracker, Anton H, Baggen, Rini Ga, Pauli, Sacha et al. (2006) Spironolactone in type 2 diabetic nephropathy: Effects on proteinuria, blood pressure and renal function. Journal of hypertension 24(11): 2285-92

#### 1.1.10.2 Economic

Adarkwah CC, Gandjour A, Akkerman M et al (2011a) Cost-effectiveness of angiotensin-converting enzyme inhibitors for the prevention of diabetic nephropathy in the Netherlands: a Markov model. PLOS ONE 10: e26139

Adarkwah CC, Gandjour A, (2011b) Cost-effectiveness of angiotensin-converting enzyme inhibitors in nondiabetic advanced renal disease. Expert Rev Pharmacoecon Outcomes Res. 2011 Apr;11(2):215-23. doi: 10.1586/erp.11.18.

Adarkwah CC, Gandjour A, Akkerman M et al. (2013) To treat or not to treat? Cost-effectiveness of ace inhibitors in non-diabetic advanced renal disease: a Dutch perspective. Kidney and Blood Pressure Research 37: 168-180

Boulware LE, Jaar BG, Brancati FL et al. (2003) Screening for proteinuria in US adults: a cost-effectiveness analysis. JAMA 23: 3101-3114

Delea TE, Sofrygin O, Palmer JL et al. (2009) Cost-effectiveness of aliskiren in type 2 diabetes, hypertension, and albuminuria. Journal of the American Society of Nephrology 20: 2205-13

Dong FB, Sorensen SW, Manninen DL et al. (2004) Cost effectiveness of ACE inhibitor treatment for patients with Type 1 diabetes mellitus. Pharmacoeconomics 22(15): 1015-1027

Farmer AJ, Stevens R, Hirst J et al. (2014) Optimal strategies for identifying kidney disease in diabetes: Properties of screening tests, progression of renal dysfunction and impact of treatment - Systematic review and modelling of progression and cost-effectiveness. Health Technology Assessment 18(14): 1-127

Golan L, Birkmeyer JD and Welch HG (1999) The cost-effectiveness of treating all patients with type 2 diabetes with angiotensin-converting enzyme inhibitors. Annals of Internal Medicine 131: 660-667

Hoerger TJ, Wittenborn JS, Segel JE et al. (2010) A health policy model of CKD. Part 2: The cost-effectiveness of microalbuminuria screening. American Journal of Kidney Diseases 55(3): 463-473

Howard K, White S, Salkeld G et al. (2010) Cost-effectiveness of screening and optimal management for diabetes, hypertension, and chronic kidney disease: a modeled analysis. Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research 13: 196-208

Kiberd BA and Jindal KK (1998) Routine treatment of insulin-dependent diabetic patients with ACE inhibitors to prevent renal failure: an economic evaluation. American Journal of Kidney Diseases 31: 49-54

Mennini FS, Russo S, Marcellusi A et al. (2014) Economic effects of treatment of chronic kidney disease with low-protein diet. Journal of renal nutrition: the official journal of the Council on Renal Nutrition of the National Kidney Foundation 24: 313-21

Smith DG, Nguyen AB, Peak CN et al. (2004) Markov modeling analysis of health and economic outcomes of therapy with valsartan versus amlodipine in patients with Type 2 diabetes and microalbuminuria. Journal of Managed Care Pharmacy 10: 26-32

You JHS, Ming WK, Lin WA et al. (2015) Early supplemented low-protein diet restriction for chronic kidney disease patients in Taiwan - A cost-effectiveness analysis. Clinical nephrology 88:189-96

#### 1.1.10.3 Other – clinical data informing the economic papers

APD Context, Inc (2001) Physician Fees. Roseland, NJ

Adarkwah CC and Gandjour A (2010) Cost-effectiveness of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers in newly diagnosed type 2 diabetes in Germany. Int J Technol Assess Health Care 26(1): 62–70

American Heart Association (1999) Heart and stroke facts: statistical supplement. Dallas (TX): American Heart Association

Arnesen T, and Trommald M (2004) Roughly right or precisely wrong? Systematic review of quality-of-life weights elicited with the time trade-off method. J Health Serv Res Policy 9: 43–50

Australian Bureau of Statistics (2003) Population Projections: Australia. Canberra, Report No.: ABS Catalogue number 3222.0

Boulware LE, Jaar BG, Tarver-Carr Meet al. (2003) Screening for proteinuria in US adults: a cost effectiveness analysis. JAMA 290(23): 3101-3114

Brand FN, Smith RT and Brand PA (1977) Effect of economic barriers to medical care patients' noncompliance. Public Health Rep 92: 72-8

Brazier J, Roberts J and Deverill M (2002) The estimation of a preference-based measure of health from the SF-36. J Health Econ 21: 271–92

Brenner BM, Cooper ME, De Zeeuw D et al. (2001) Effects of Losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 345 (12): 861-69

Briganti EM, Shaw JE, Chadban SJ et al. (2003) Untreated hypertension among Australian adults: the 1999-2000 Australian Diabetes, Obesity and Lifestyle Study (AusDiab). Med J Aust 179: 135–9

Brown GC, Brown MM, Sharma S et al. (2000) Quality of life associated with diabetes mellitus in an adult population. J Diabetes Complications 14: 18–24

Brown JB, Pedula KL and Bakst AW (1999) The progressive cost of complications in type 2 diabetes mellitus. Arch Intern Med 159 (16): 1873-80

Canadian Organ Replacement Register (1996) Dialysis and renal transplantation - Vol 1 & 2 Annual report. Ottawa: Canadian Institute for Health Information; Mar 1996

Cass A, Chadban SJ, Craig JC et al. (2006) The economic impact of end-stage kidney disease in Australia. Available from: www.kidney.org.au/assets/documents/Economic%20Impact%20of%20ESKD%20in%20Australia%20Published%202006.pdf [Accessed July 2009]

Centers for Disease Control and Prevention (1998) The cost-effectiveness of screening for type 2 diabetes JAMA 280: 1757–1763

Centers for Medicare & Medicaid Services (2007) Clinical diagnostic laboratory fee schedule—07CLAB **http://www.cms.hhs.gov/ClinicalLabFeeSched/02_clinlab.asp#TopOfPage [Accessed July 20, 2007]**

Centers for Medicare & Medicaid Services (2007) Physician fee schedule search, 2007. http://www.cms.hhs.gov/pfslookup/02_PFSsearch.asp [Accessed July 20, 2007]

Centers for Medicare and Medicaid Services (2003) Clinical diagnostic laboratory fee schedule. Available at: http://cms.hhs.gov/providers/pufdownload/default.asp#pfsrelative. [Accessed February 15, 2003]

Centers for Medicare and Medicaid Services (2003a) National physician fee schedule relative value file. Avail-able at: http://cms.hhs.gov/providers/pufdownload /default.asp#pfsrelative. ]Accessed February 21, 2003]

Centro Studi Investimenti Sociali, CENSIS (2009) I trattamenti sostitutivi della funzione renale in Italia, aspetti clinici,economici e sociali 2009. Available at www.censis.it. [Accessed March 2013.]

Chadban SJ, Briganti EM, Kerr PG et al. (2003) Prevalence of kidney damage in Australian adults: the AusDiab kidney study. J Am Soc Nephrol 14 (Suppl. 2): S131–8

Chang JH, Kim DK, Park JT et al. (2009) Influence of ketoanalogs supplementation on the progression in chronic kidney disease patients who had training on low-protein diet. Nephrology (Carlton) 14: 750-757

Cherry DK and Woodwell DA (2002) National Ambulatory Medical Care Survey: 2000 Summary. Hyatts-ville, Md: National Center for Health Statistics, US Department of Health and Human Services

Churchill DN, Torrance GW, Taylor DW et al. (1987) Measurement of quality of life in end-stage renal disease: the time trade-off approach. Clin Invest Med 10: 14-20

Cianciaruso B, Pota A, Pisani A et al. (2008) Metabolic effects of two low protein diets in chronic kidney disease stage 4-5–a randomized controlled trial. Nephrol Dial Transplant 23: 636-644

Clarke P, Gray A, Legood R et al. (2002) The impact of diabetes-related complications on healthcare costs: results from the United Kingdom Prospective Diabetes Study (UKPDS Study No. 65). Diabet Med 20: 442–50

Clarke P, Kelman C, Colagiuri S et al. (2006) Factors influencing the cost of hospital care for people with diabetes in Australia. J Diabetes Complications 20: 349–55

Clarke PM, Gray AM, Briggs A et al. (2004) A model to estimate the lifetime health outcomes of patients with type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68). Diabetologia 47: 1747–59

Coffey JT, Brandle M, Zhou H et al (2002) Valuing health-related quality of life in diabetes. Diabetes Care 25: 2238–2243

Colagiuri S, Hussain Z, Zimmet P et al. (2004) Screening for type 2 diabetes and impaired glucose metabolism: the Australian experience. Diabetes Care 27: 367–71

Colhoun HM, Betteridge DJ, Durrington PN et al. (2004) Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative AtoRvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 364: 685

Consumer Price Index for Canada (1972–1996) Statistics Canada: p. 11. Cat no 62010XPB

Coresh J, Astor BC, Greene T et al. (2003) Prevalence of chronic kidney disease and de-creased kidney function in the adult US population. Am J Kidney Dis 41: 1-12

Curtis L (2010) Unit costs of health and social care 2010. Canterbury: Personal Social Services Research Unit, University of Kent

Dasbach EJ, Fryback DG, Thornbury JR (1992) Health utility preference differences [abstract]. Med Decis Making 12: 4

De Nicola L, Dal Canton A, Research Group CARHES (2010) Epidemiology of chronic kidney disease in Italy: the CARHES study [Article in Italian]. G Ital Cardiol (Rome) 11(5 Suppl 3):106S-108S. PubMed PMID: 20879494

de Wit GA, Merkus MP, Krediet RT et al. (2002) Health profiles and health preferences of dialysis patients. Nephrol Dial Transplant 17: 86-92

de Wit GA, Ramsteijn PG and de Charro FT (1998) Economic evaluation of end stage renal disease treatment. Health Policy 44: 215-232

Diabetes and Digestive and Kidney Diseases, Bethesda, MD, April 1995. Am J Kidney Dis 26: S140-S156

Diabetes Control and Complications Trial Research Group (1995) Resource utilization and costs of care in the Diabetes Control and Complications Trial. Diabetes Care 18: 1468-78

Diabetes Control and Complications Trial Research Group (1996) Lifetime benefits and costs of intensive therapy as practiced in the Diabetes Control and Complications Trial. JAMA 276: 1409-15

DiMatteo RM, Giordani PJ, Lepper HS et al. (2002) Patient adherence and medical treatment out-comes: a meta-analysis. Med Care 40: 794-811

Drug Topics Red Book (1993) Oradell, NJ, Medical Economics Publishing

Drug Topics Red Book (2001) Montvale, NJ: Thomson Medical Economics

Drug Topics Redbook (2007) Oradell, NJ: Medical Economics Co

Dutch End-Stage Renal Disease Registry (Registratie Nierfunktievervanging Nederland) (2011). Available: https://www.renine.nl/page?id=home&lang=en. Accessed 18 October 2011.

Dutch End-Stage Renal Disease Registry (Registratie Nierfunktievervanging Nederland) (2011a) Available: https://www.renine.nl/page?id=home&lang=en [Accessed 13 April 2011]

Eckman MH, Greenfield S, Mackey WC et al. (1995) Foot infections in diabetic patients: decision and cost-effectiveness analysis. JAMA 273: 712-20

Finne P, Reunanen A, Stenman S et al. (2005) Incidence of end-stage renal disease in patients with type 1 diabetes. JAMA 294: 1782–7

Fouque D, Laville M (2009) Low protein diets for chronic kidney disease in non diabetic adults. Cochrane Database Syst Rev CD001892

Fryback DG, Dasbach ED, Klein R et al. (1992) Health assessment by SF-36, quality of well-being index, and time trade-offs: Predicting one measure from another. Med Decis Making 12:348

Fryback DG, Dasbach EJ, Klein R et al. (1993) The Beaver Dam Health Outcomes Study: initial catalog of health-state quality factors. Med Decis Making 13: 89-102

Gambaro G, Yabarek T, Graziani MS et al. (2010) INCIPE Study Group. Prevalence of CKD in northeastern Italy: results of the INCIPE study and comparison with NHANES. Clin J Am Soc Nephrol 5: 1946-1953

Garg AX, Kiberd BA, Clark WF et al. (2002) Albuminuria and renal insufficiency prevalence guides population screening: results from the NHANES III. Kidney Int 61: 2165-2175

Gerstein HC, Mann JF, Yi Q et al. (2001) Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA 286:421-426

Goeree R, Manalich J, Grootendorst P et al. (1995) Cost analysis of dialysis treatments for end-stage renal disease (ESRD). Clin Invest Med 18: 455-64

Gorodetskaya I, Zenios S, McCulloch CE et al. (2005) Health-related quality of life and estimates of utility in chronic kidney disease. Kidney Int 68: 2801-2808

Gray A, Raikou M, McGuire A et al. (2000) Cost effectiveness of an intensive blood glucose control policy in patients with type 2 diabetes: economic analysis alongside randomised controlled trial (UKPDS 41). United Kingdom Prospective Diabetes Study Group. BMJ 320:1373–8

Group (1996) Lifetime benefits and costs of intensive therapy as practiced in the diabetes control and complications trial. JAMA 276:1409-1415

Hayes AJ, Leal J, Kelman CW et al. (2011) Risk equations to predict life expectancy of people with type 2 diabetes mellitus following major complications: a study from Western Australia. Diabet Med 28: 428–35

Health Care Financing Administration (1999) Health research report: end-stage renal disease, 1993–1995. Baltimore

Hemmelgarn BR, Manns BJ, Lloyd A et al. (2010) Kidney Disease Network: Relation between kidney function, proteinuria, and adverse outcomes. JAMA 303: 423-429

Hilleman DE, Mohiuddin SM, Lucas BD et al. (1994) Cost-minimization analysis of initial antihypertensive therapy in patients with mild-to-moderate essential diastolic hypertension. Clin Ther 16: 88-102

Hoerger TJ, Wittenborn JS, Segel JE et al. (2010) Centers for Disease Control and Prevention CKD Initiative: A health policy model of CKD: 2. The cost-effectiveness of microalbuminuria screening. Am J Kidney Dis 55: 463-473

Hogan TJ, Elliott WJ, Seto AH et al. (2002) Antihypertensive treatment with and without benazepril in patients with chronic renal insufficiency: a US economic evaluation. Pharmacoeconomics 20(1):37-47

Hou FF, Zhang X, Zhang GH et al. (2006) Efficacy and safety of benazepril for advanced chronic renal insufficiency. N Engl J Med 354: 131-140

Hwang SJ, Yang WC, Lin MY et al. (2010) Taiwan Society of Nephrology. Impact of the clinical conditions at dialysis initiation on mortality in incident haemodialysis patients: a national cohort study in Taiwan. Nephrol Dial Transplant 25: 2616-2624

Ihle BU, Whitworth JA, Shahinfar S et al. (1996) Angiotensin-converting enzyme inhibition in nondiabetic progressive renal insufficiency: a controlled double-blind trial. Am J Kidney Dis 27:489-495

IMS Health National Prescription Audit (2008) Available at http://us.imshealth.com/nextgen/enh_NPA.htm Accessed August 2008

Jafar TH, Schmid CH, Landa M et al. (2001) Angiotensin-converting enzyme inhibitors and progression of non-diabetic renal disease: a meta-analysis of patient-level data. Ann Intern Med 135: 73-87

Kelly PK, Clarke PM, Hayes AJ et al. (2011) Predicting the mortality of people with type 2 diabetes mellitus following a major complication: a study using Swedish Nation Diabetes Register Data. Diabetologia 54(Suppl. 1): S1–542

Kiberd BA and Jindal KK (1995) Screening to prevent renal failure in insulin dependent diabetic patients: An economic evaluation. BMJ 311:1595-1599

Laupacis A, Keown P, Pus N et al. (1996) A study of the quality of life and cost-utility of renal transplantation. Kidney Int 50: 235-42

Lee AJ, Morgan CL, Conway P et al. (2005) Characterisation and comparison of health-related quality of life for patients with renal failure. Curr Med Res Opin 21:1777–83

Lewis EJ, Hunsicker LG, Bain RP et al. (1993) The effect of angiotensinconverting enzyme inhibition on diabetic nephropathy. N Engl J Med 329: 1456–62

Lewis EJ, Hunsicker LG, Clarke WR et al. (2001) Reno-protective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type2 diabetes. N Engl J Med 345:851-860

Lindholm LH, Ibsen H, Dahlof B et al. (2002) Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention for Endpoint Reduction in Hypertension Study (LIFE): a randomised trial against atenolol. Lancet 359:1004-1010

Lovell HG (1998) Are angiotensin-converting enzyme inhibitors useful for normotensive diabetic patients with microalbuminuria? The Cochrane Database of Systematic Reviews 3

Lung TW, Hayes AJ, Hayen A et al (2011) A meta-analysis of health state valuations for people with diabetes: explaining the variation across methods and implications for economic evaluation. Qual Life Res 20: 1669–78

Microalbuminuria Captopril Study Group (1996) Captopril reduces the risk of nephropathy in IDDM patients with microalbuminuria. Diabetologia 39:587-593

Nathan DM, Cleary PA, Backlund JY et al. (2005) Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 353: 2643–53

National Center for Health Statistics (1995) Health, United States, 1994. Hyattsville, MD, Public Health Service

National Institute for Health and Care Excellence (2008) Chronic kidney disease costing report: implementing NICE guidance. London

Nease RF, Kneeland T, O'Connor GT et al. (1995) Variation in patient utilities for outcomes of the management of chronic stable angina. JAMA 273(15): 1185-1190

O'Hare AM, Bertenthal D, Covinsky KE et al. (2006) Mortality risk stratification in chronic kidney disease: one size for all ages? J Am Soc Nephrol 17:846-853. Epub 2006 Feb 1. PubMed PMID: 16452492

Oke J, Stevens RJ, Perera R et al. (2010) Current and alternative programmes for monitoring renal function in type 1 diabetes: modelling study based on the Oxford Regional Prospective Study. Prim Health Care Res Dev 11(Suppl. 1):43

Palmer AJ, Annemans L, Roze S et al. (2004) Cost-effectiveness of early irbesartan treatment versus control (standard antihypertensive medications excluding ACE inhibitors, other angiotensin-2 receptor antagonists, and dihydropyridine calcium channel blockers) or late irbesartan treatment in patients with type 2 diabetes, hypertension, and renal disease. Diabetes Care 27: 1897–1903, 2004

Parving HH, Lehnert H, Brochner-Mortensen J et al. (2001) The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 345 (8): 70-78

Parving HH, Persson F, Lewis JB et al. (2008) Aliskiren combined with losartan in type 2 diabetes and nephropathy. N Engl J Med 358: 2433–2446

Patel A, MacMahon, Chalmers JS et al. (2008) Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes (ADVANCE). N Engl J Med 358:2560–72

Portuese E and Orchard T (1995) Mortality in insulin-dependent diabetics, in National Diabetes Data Group: Diabetes in America (ed 2). Bethesda, MD, National Institutes of Health: 221-232

Ravid M, Brosh D, Levi Z et al. (1998) Use of enalapril to attenuate decline in renal function in normotensive, normoalbuminuric patients with type 2 diabetes mellitus. A randomized, controlled trial. Ann Intern Med 128: 982-8

Ravid M, Savin H, Jutrin I, Bental T eta l. (1993) M. Long-term stabilizing effect of angiotensin-converting enzyme inhibition on plasma creatinine and on proteinuria in normotensive type II diabetic patients. Ann Intern Med 118: 577-81

Red Book (2000) Montvale (NJ): Medical Economics Company Inc.

Rossing P, Hougaard P, Borch-Johnsen K et al. (1996) Predictors of mortality in insulin dependent diabetes: 10 Year observational follow up study. BMJ 313:779-784

Sarafidis PA, Riehle J, Bogojevic Z et al. (2008) A comparative evaluation of various methods for microalbuminuria screening. Am J Nephrol 28(2): 324-329

Schultz CJ, Konopelska-Bahu T, Dalton RN et al. (1999) Microalbuminuria prevalence varies with age, sex, and puberty in children with type 1 diabetes followed from diagnosis in a longitudinal study. Oxford Regional Prospective Study Group. Diabetes Care 22:495–502

Smith DH, Nichols GA, Gullion CM et al. (2007) Predicting costs of care in chronic kidney disease: the role of comorbid conditions. Internet J Nephrol 4(1)

Strippoli GF, Craig M, Deeks JJ et al. (2004) Effects of angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists on mortality and renal outcomes in diabetic nephropathy: systematic review. BMJ 329: 828

Strippoli GFM, Bonifati C, Craig M et al. (2006) Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease. Cochrane Database Syst Rev CD006257

Strippoli GFM, Craig M and Craig JC (2005) Antihypertensive agents for preventing diabetic kidney disease. Cochrane Database Syst Rev CD004136

Syne Qua Non Ltd (2001) A Multicentre, Randomized, Double Blind, Amlodipine Controlled, Parallel Group Study of Valsartan in Patients with Type 2 Diabetes Mellitus and Microalbuminuria. Frimley/Camberley, Surrey, UK: Novartis Pharmaceuticals UK, Ltd. Clinical Study Report Val D 902; May 16

Taiwan National Health Insurance (2014) Website (assessed on 1 September 2014): http://www.nih.gov.tw

Tengs TO and Wallace A (2000) One thousand health-related quality-of-life estimates. Med Care 38: 583-637

Terajima T, Yamagata S, Satoh N et al (2003) Meta-analysis: effect of ACE-inhibitors on outcomes in patients with renal insufficiency. Pharm Ther 28: 98-112

The Diabetes Control and Complications Trial Research Group (1996) Lifetime benefits and costs of intensive therapy as practiced in the Diabetes Control and Complications Trial. JAMA 276: 1409–1415

Thomas MC and Atkins R (2009) Assessment and management of hypertension in patients with type 2 diabetes. Intern Med J 39: 143–9

Tsevat J, Goldman L, Soukup JR et al. (1993) Stability of time-trade-off utilities in survivors of myocardial infarction. Med Decis Making 13(2): 161-165

United States Renal Data System (1998) Patient mortality and survival. Am J Kidney Dis 32 (2 Suppl 1): S69-80

US Department of Labor (2002) National Compensation Survey 2001. Washington, DC: US Dept of Labor, Bureau of Labor Statistics; 2002

US Renal Data System (1995) Annual Report. The National Institutes of Health

US Renal Data System (2002) Annual Data Report: Atlas of End-Stage Renal Disease in the United States. Available at: http://www.usrds.org/adr.htm. Accessed March 30, 2003

US Renal Data System (2003) Available at: ttp://www.usrds.org. Accessed January 20 2003.

US Renal Data System (2006) Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases 53; Fig 1.8. http://www.usrds.org/2006/pdf/01_ckd_06.pdf. Accessed July 30, 2009

US Renal Data System (2007) Annual Data Report: Atlas of End-Stage Renal Disease in the United States, Bethesda, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases

US Renal Data System. USRDS 2006 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. 2006:208; Fig 11.3. http://www.usrds.org/2006/pdf/01_ckd_06.pdf Accessed July 30,2009

Viberti G, Wheeldon NM, for the MicroAlbuminuria Reduction with VALsartan (MARVAL) Study Investigators (2002) Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: a blood pressure-independent effect. Circulation 106: 672-78

Walters DP, Gatling W, Houston AC et al. (1994) Mortality in diabetic subjects: an eleven-year follow-up of a community-based population. Diabet Med 10: 968-73

Warram JH, Dong F and Krolewski AS (1995) Bimodal distribution of the incidence rate of microalbuminuria according to duration of IDDM. JAm Soc Nephrol 6:457 (abstract)

Weng SC, Tarng DC, Chen CM et al. (2014) CKDBHPDH investigators. Estimated glomerular filtration rate decline is a better risk factor for outcomes of systemic disease-related nephropathy than for outcomes of primary renal diseases. PLoS ONE 9: e92881

World Health Organization (2008) Life Tables for WHO Member States. Available at: http://apps.who.int/whois/database/life_tables/life_tables.cfm Accessed April 9 2008

Zoccali C, Mallamaci F, Parlongo S et al. (2002) Plasma norepinephrine predicts survival and incident cardiovascular events in patients with end-stage renal disease. Circulation 105: 1354–9

#### 1.1.10.4 Other

Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney inter., Suppl. 2013; 3: 1–150.

Norman GR, Sloan JA, Wyrwich KW (2003) Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care. 2003 May;41(5):582-92.

Pergola PE, Pecoits-Filho R, Winkelmayer WC, et al. (2019) Economic Burden and Health-Related Quality of Life Associated with Current Treatments for Anaemia in Patients with CKD not on Dialysis: A Systematic Review. Pharmacoecon Open. 2019 Apr 9 [Epub ahead of print]

# Appendices

## Appendix A – Review protocols

**Review protocol for 2.3 For adults, children and young people with suspected or diagnosed CKD, what is the effect of interventions to lower proteinuria?**

| ID | Field | Content |
|---|---|---|
| 0. | PROSPERO registration number | CRD42019162559 |
| 1. | Review title | The effectiveness of interventions to lower proteinuria in adults children and young people with suspected or diagnosed CKD |
| 2. | Review question | For adults, children and young people with suspected or diagnosed CKD, what is the effect of interventions to lower proteinuria? |
| 3. | Objective | To determine the effect of interventions to lower proteinuria in adults, children and young people. |
| 4. | Searches | The following databases will be searched:<br>• Cochrane Central Register of Controlled Trials (CENTRAL)<br>• Cochrane Database of Systematic Reviews (CDSR)<br>• Embase<br>• MEDLINE |

| | | |
|---|---|---|
| | | Searches will be restricted by:<br>• English language<br>• Human studies<br><br>Searches will not be limited by date.<br><br>The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion.<br><br>The full search strategies for MEDLINE database will be published in the final review. |
| 5. | Condition or domain being studied | Chronic Kidney Disease |

| | | |
|---|---|---|
| 6. | Population | Adults, children and young people with suspected or diagnosed chronic kidney disease stages 1 to 5 and proteinuria/albuminuria.<br><br>Exclusion:<br>• people receiving renal replacement therapy (RRT)<br>• people with acute kidney injury combined with rapidly progressive glomerulonephritis<br>• people receiving palliative care. |
| 7. | Intervention/Exposure/Test | Interventions to lower proteinuria<br>• Blood pressure medication<br>• Diabetes medication<br>• Weight loss/Exercise<br>• Dietary interventions (NaCl, protein)<br>• Endothelin antagonists |
| 8. | Comparator/Reference standard/Confounding factors | • No intervention<br>• Placebo<br>• Other intervention in class to lower proteinuria (for diabetes and blood pressure medication)<br>• Other interclass intervention |

| | | |
|---|---|---|
| 9. | Types of study to be included | • RCTs<br>• Systematic reviews of RCTs |
| 10. | Other exclusion criteria | • Population:<br>  ○ people receiving renal replacement therapy (RRT)<br>  ○ people with acute kidney injury combined with rapidly progressive glomerulonephritis<br>  ○ pregnant women<br>  ○ people receiving palliative care.<br>• Abstracts, conference presentations and theses<br>• Non-human studies<br>• Non-English language studies |
| 11. | Context | NICE guideline CG182 chronic kidney disease in adults: assessment and management will be updated by this question. This guideline will be combined with guidelines CG157 chronic kidney disease (stage 4 or 5): management of hyperphosphataemia and NG 8 chronic kidney disease: managing anaemia. The guideline will be extended to cover the assessment and management of chronic kidney disease in children and young people. |
| 12. | Primary outcomes (critical outcomes) | Over the follow up of the study: |

| | | |
|---|---|---|
| | | • Reduction in proteinuria<br>• CKD progression: occurrence of end stage kidney disease (ESRD or ESKD as reported by the study)<br>• Mortality (all-cause and cardiovascular)<br>• Specific morbidity:<br>  ○ fractures,<br>  ○ advancement of renal bone disease,<br>  ○ vascular calcification,<br>  ○ cardiovascular impact,<br>  ○ anaemia<br>  ○ health-related quality of life<br>• Adverse outcome:<br>  ○ AKI,<br>  ○ drug specific (hypotension/falls, hypoglycaemia, hospitalisation)<br><br>Where follow up times are close to coinciding they will be grouped together, for example 11 week data and 3 month data will be grouped. Any uncertainty about grouping data will be explored with the committee. |

| | | |
|---|---|---|
| | | Outcomes will be stratified by diabetic and non-diabetic populations. |
| 13. | Secondary outcomes (important outcomes) | None |
| 14. | Data extraction (selection and coding) | The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. Data will be extracted from the included studies for assessment of study quality and evidence synthesis. Extracted information will include: study setting; study population and participant demographics and baseline characteristics; details of the test and reference standard used; study methodology; recruitment and study completion rates; outcomes and times of measurement and information for assessment of the risk of bias.<br><br>Study investigators may be contacted for missing data where time and resources allow. |
| 15. | Risk of bias (quality) assessment | Risk of bias will be assessed using the Cochrane RoB 2.0 checklist as described in Developing NICE guidelines: the manual. |
| 16. | Strategy for data synthesis | Meta-analyses of primary and secondary outcome data will be conducted for all comparators that are reported by more than one study, with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).<br><br>Fixed- and random-effects models (der Simonian and Laird) will be fitted for all comparators, with the presented analysis dependent on |

| | | |
|---|---|---|
| | | the degree of heterogeneity in the assembled evidence. Fixed-effects models will be the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model is clearly not met, even after appropriate pre-specified subgroup analyses is conducted, random-effects results are presented. Fixed-effects models are deemed to be inappropriate if one or both of the following conditions was met:<br>• Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis.<br>• The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.<br>Meta-analyses will be performed in Cochrane Review Manager V5.3.<br>If data allow, the technical team will consider running Bayesian Network Meta-analysis using WinBugs. |
| 17. | Analysis of sub-groups | Where it is possible to disambiguate data, subgroup analyses will explore the effects of ethnicity. |
| 18. | Type and method of review | ☒ Intervention<br>☐ Diagnostic |

| | | | | |
|---|---|---|---|---|
| | | ☐ Prognostic<br>☐ Qualitative<br>☐ Epidemiologic<br>☐ Service Delivery<br>☐ Other (please specify) | | |
| 19. | Language | English | | |
| 20. | Country | England | | |
| 21. | Anticipated or actual start date | December 2019 | | |
| 22. | Anticipated completion date | March 2020 | | |
| 23. | Stage of review at time of this submission | **Review stage** | **Started** | **Completed** |
| | | Preliminary searches | ☐ | ☐ |
| | | Piloting of the study selection process | ☐ | ☐ |

| | | | | |
|---|---|---|---|---|
| | | Formal screening of search results against eligibility criteria | ☐ | ☐ |
| | | Data extraction | ☐ | ☐ |
| | | Risk of bias (quality) assessment | ☐ | ☐ |
| | | Data analysis | ☐ | ☐ |
| 24. | Named contact | **5a. Named contact**<br>NICE Guideline Updates Team<br><br>**5b Named contact e-mail**<br>GUTprospero@nice.org.uk<br><br>**5e Organisational affiliation of the review**<br>National Institute for Health and Care Excellence (NICE) | | |
| 25. | Review team members | From the Guideline Updates Team:<br>• Mr Chris Carmona<br>• Dr Yolanda Martinez | | |

| | | |
|---|---|---|
| | | • Ms Hannah Nicholas<br>• Ms Lynda Ayiku<br>• Mr Rui Martins |
| 26. | Funding sources/sponsor | This systematic review is being completed by the Guideline Updates Team which is part of NICE. |
| 27. | Conflicts of interest | All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline. |
| 28. | Collaborators | Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website. |
| 29. | Other registration details | |
| 30. | Reference/URL for published protocol | |

| | | |
|---|---|---|
| 31. | Dissemination plans | NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:<br>• notifying registered stakeholders of publication<br>• publicising the guideline through NICE's newsletter and alerts<br>• issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE. |
| 32. | Keywords | Chronic kidney disease, proteinuria |
| 33. | Details of existing review of same topic by same authors | |
| 34. | Current review status | ☒ Ongoing<br>☐ Completed but not published<br>☐ Completed and published<br>☐ Completed, published and being updated<br>☐ Discontinued |

| | | |
|---|---|---|
| 35.. | Additional information | |
| 36. | Details of final publication | www.nice.org.uk |

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# Appendix B – Methods

## Evidence synthesis and meta-analyses of pair-wise data

Where possible, meta-analyses were conducted to combine the results of quantitative studies for each outcome. For continuous outcomes analysed as mean differences, where change from baseline data were reported in the trials and were accompanied by a measure of spread (for example standard deviation), these were extracted and used in the meta-analysis. Where measures of spread for change from baseline values were not reported, the corresponding values at study end were used and were combined with change from baseline values to produce summary estimates of effect. These studies were assessed to ensure that baseline values were balanced across the treatment groups; if there were significant differences at baseline these studies were not included in any meta-analysis and were reported separately. For continuous outcomes analysed as standardised mean differences, where only baseline and final time point values were available, change from baseline standard deviations were estimated, assuming a correlation coefficient of 0.5. In cases where SMDs were used they were back converted to a single scale to aid interpretation by the committee where possible.

## Evidence of effectiveness of interventions

### *Quality assessment*

Individual RCTs were quality assessed using the Cochrane Risk of Bias Tool. Each individual study was classified into one of the following groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the following areas: population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

### *Methods for combining intervention evidence*

Meta-analyses of interventional data were conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).

Where different studies presented continuous data measuring the same outcome but using different numerical scales (e.g. a 0-10 and a 0-100 visual analogue scale), these outcomes were all converted to the same scale before meta-analysis was conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, data were analysed using standardised mean differences (Hedges' g).

A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event, and a pooled incidence rate ratio was calculated for dichotomous outcomes reporting total numbers of events. Both relative and absolute risks were presented, with absolute risks calculated by applying the relative risk to the risk in the comparator arm of the meta-analysis (calculated as the total number events in the comparator arms of studies in the meta-analysis divided by the total number of participants in the comparator arms of studies in the meta-analysis).

Fixed- and random-effects models (der Simonian and Laird) were fitted for all syntheses, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if one or both of the following conditions was met:

- Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. This decision was made and recorded before any data analysis was undertaken.
- The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.

However, in cases where the results from individual pre-specified subgroup analyses are less heterogeneous (with $I^2 < 50\%$) the results from these subgroups will be reported using fixed effects models. This may lead to situations where pooled results are reported from random-effects models and subgroup results are reported from fixed-effects models.

In situations where subgroup analyses were conducted, pooled results and results for the individual subgroups are reported when there was evidence of between group heterogeneity, defined as a statistically significant test for subgroup interactions (at the 95% confidence level). Where no such evidence as identified, only pooled results are presented.

In any meta-analyses where some (but not all) of the data came from studies at high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from indirect studies, a sensitivity analysis was conducted, excluding those studies from the analysis.

Meta-analyses were performed in Cochrane Review Manager V5.3, with the exception of incidence rate ratio analyses which were carried out in R version 3.3.4.

***Minimal clinically important differences (MIDs)***

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline. Identified MIDs were assessed to ensure they had been developed and validated in a methodologically rigorous way, and were applicable to the populations, interventions and outcomes specified in this guideline. In addition, the Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus MID could be defined from their experience. In particular, any questions looking to evaluate non-inferiority (that one treatment is not meaningfully worse than another) required an MID to be defined to act as a non-inferiority margin. Confidence intervals were taken into account for clinical importance and uncertainty around the effect to make final decisions for recommendations.

MIDs found through this process and used to assess imprecision in the guideline are given in Table 29.

**Table 29: Identified MIDs**

| Outcome | MID | Source |
|---|---|---|
| Quality of life: SF-12/36 | 4 | Pergola PE (2019) |
| Quality of life: KDQoL-12/36 | 4 | Pergola PE (2019) |
| Quality of life: KDQ | 0.5 | Pergola PE (2019) |
| Quality of life: EQ-5D | 0.07 | Pergola PE (2019) |
| Quality of life: LASA | 15 | Pergola PE (2019) |
| Quality of life: FACIT-Fatigue scale | 3.0 | Pergola PE (2019) |
| Quality of life: FACT-Fatigue scale | 3.0 | Pergola PE (2019) |

For continuous outcomes expressed as a mean difference where no other MID was available, an MID of 0.5 of the median standard deviations of the comparison group arms was used (Norman et al. 2003). For continuous outcomes expressed as a standardised mean difference where no other MID was available, an MID of 0.5 was used. For relative risks where no other MID was available, a default MID interval for dichotomous outcomes of 0.8 to 1.25 was used. For dichotomous outcomes relating to mortality, the line of no effect was used.

When decisions were made in situations where MIDs were not available, the 'Evidence to Recommendations' section of that review makes explicit the committee's view of the expected clinical importance and relevance of the findings. In particular, this includes consideration of whether the whole effect of a treatment (which may be felt across multiple independent outcome domains) would be likely to be clinically meaningful, rather than simply whether each individual sub outcome might be meaningful in isolation.

***GRADE for pairwise meta-analyses of interventional evidence***

GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'Developing NICE guidelines: the manual (2014)'. Data from randomised controlled trials were initially rated as high quality. The quality of the evidence for each outcome was downgraded or not from this initial point, based on the criteria given in Table 30.

**Table 30: Rationale for downgrading quality of evidence for intervention studies**

| GRADE criteria | Reasons for downgrading quality |
|---|---|
| Risk of bias | Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded.<br>Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level.<br>Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels.<br>Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias. |
| Indirectness | Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded.<br>Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level.<br>Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels.<br>Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies. |

| GRADE criteria | Reasons for downgrading quality |
|---|---|
| Inconsistency | Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the $I^2$ statistic.<br>N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study.<br>Not serious: If the $I^2$ was less than 33.3%, the outcome was not downgraded.<br>Serious: If the $I^2$ was between 33.3% and 66.7%, the outcome was downgraded one level.<br>Very serious: If the $I^2$ was greater than 66.7%, the outcome was downgraded two levels.<br>Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes. |
| Imprecision | If an MID other than the line of no effect was defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID.<br>If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected.<br>Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios. |

# Health economics

Literature reviews seeking to identify published cost–utility analyses of relevance to the issues under consideration were conducted for all questions. In each case, the search undertaken for the clinical review was modified, retaining population and intervention descriptors, but removing any study-design filter and adding a filter designed to identify relevant health economic analyses. In assessing studies for inclusion, population, intervention and comparator, criteria were always identical to those used in the parallel clinical search; only cost–utility analyses were included. Economic evidence profiles, including critical appraisal according to the Guidelines manual, were completed for included studies.

Economic studies identified through a systematic search of the literature are appraised using a methodology checklist designed for economic evaluations (NICE guidelines manual; 2014). This checklist is not intended to judge the quality of a study per se, but to determine whether an existing economic evaluation is useful to inform the decision-making of the committee for a specific topic within the guideline.

There are 2 parts of the appraisal process. The first step is to assess applicability (that is, the relevance of the study to the specific guideline topic and the NICE reference case); evaluations are categorised according to the criteria in Table 31.

**Table 31 Applicability criteria**

| Level | Explanation |
|---|---|
| Directly applicable | The study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness |

| Level | Explanation |
|---|---|
| Partially applicable | The study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness |
| Not applicable | The study fails to meet one or more applicability criteria, and this is likely to change the conclusions about cost effectiveness. These studies are excluded from further consideration |

In the second step, only those studies deemed directly or partially applicable are further assessed for limitations (that is, methodological quality); see categorisation criteria in Table 32.

**Table 32 Methodological criteria**

| Level | Explanation |
|---|---|
| Minor limitations | Meets all quality criteria, or fails to meet one or more quality criteria but this is unlikely to change the conclusions about cost effectiveness |
| Potentially serious limitations | Fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness |
| Very serious limitations | Fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies should usually be excluded from further consideration |

Where relevant, a summary of the main findings from the systematic search, review and appraisal of economic evidence is presented in an economic evidence profile alongside the clinical evidence.

# Appendix C – Literature search strategies

## The effectiveness of interventions to lower proteinuria in adults, children and young people with suspected or diagnosed CKD

### Background to the search

A NICE information specialist conducted the literature searches for the evidence review. The searches were originally run on the 7th of January 2020 and updated on the 7th of September 2020. This search report is compliant with the requirements of PRISMA-S.

The principal search strategy was developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

The MEDLINE strategy below was quality assured (QA) by trained NICE information specialist. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2016 PRESS Checklist.

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess 'low-probability' matches. All decisions made for the review can be accessed via the deduplication history.

English language limits were applied in adherence to standard NICE practice and the review protocol.

Limits to exclude conferences, letters and notes in Embase were applied in adherence to standard NICE practice.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from: Dickersin, K., Scherer, R., & Lefebvre, C. (1994). Systematic Reviews: Identifying relevant studies for systematic reviews. *BMJ*, 309(6964), 1286.

### Clinical searches

| Databases | Date searched | Version/files | No. retrieved |
|---|---|---|---|
| Cochrane Central Register of Controlled Trials (CENTRAL) | 7th Jan 2020 | Issue 1 of 12, January 2020 | 3062 |
| Cochrane Database of Systematic Reviews (CDSR) | 7th Jan 2020 | Issue 1 of 12, January 2020 | 58 |
| Database of Abstracts of Reviews of Effect (DARE) | 7th Jan 2020 | Up to 2015 | 135 |
| Embase (Ovid) | 7th Jan 2020 | Embase <1974 to 2020 Week 01> | 4237 |

| | | | |
|---|---|---|---|
| MEDLINE (Ovid) | 7th Jan 2020 | Ovid MEDLINE(R) <1946 to January 06, 2020> | 2873 |
| MEDLINE In-Process (Ovid) | 7th Jan 2020 | Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to January 06, 2020> | 274 |
| MEDLINE Epub Ahead of Print[a] | 7th Jan 2020 | Ovid MEDLINE(R) Epub Ahead of Print <January 06, 2020 | 36 |

The following search filters were applied in MEDLINE and Embase to identify RCTs and systematic reviews:

- RCT filters:
  - McMaster Therapy – Medline - "best balance of sensitivity and specificity" version.

    Haynes RB et al. (2005) Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. *BMJ*, 330, 1179-1183.

  - McMaster Therapy – Embase "best balance of sensitivity and specificity" version.

    Wong SSL et al. (2006) Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. Journal of the Medical Library Association, 94(1), 41-47.

- Systematic reviews filters:
  - Lee, E. et al. (2012) An optimal search filter for retrieving systematic reviews and meta-analyses. *BMC Medical Research Methodology,* 12(1), 51.

    In MEDLINE, the standard NICE modifications were used: pubmed.tw added; systematic review.pt added from MeSH update 2019.

    In Embase, the standard NICE modifications were used: pubmed.tw added to line medline.tw.

| **Search strategies** |
|---|
| Database: Ovid MEDLINE(R) <1946 to January 06, 2020><br><br>Search Strategy:<br><br>----------<br><br>1 exp Renal Insufficiency, Chronic/ (111773) |

[a] Please search for both development and re-run searches

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (71808)

3 ((kidney* or renal*) adj1 insufficien*).tw. (21175)

4 ckd*.tw. (22546)

5 ((kidney* or renal*) adj1 fail*).tw. (86008)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (34922)

7 (esrd* or eskd*).tw. (14067)

8 "Chronic Kidney Disease-Mineral and Bone Disorder"/ (3435)

9 or/1-8 (211281)

10 exp Proteinuria/ (38575)

11 Proteins/ (202512)

12 exp dietary proteins/ (97336)

13 protein*.tw. (2680399)

14 Albumins/ (19261)

15 albumin*.tw. (139304)

16 or/10-15 (2867417)

17 9 and 16 (37305)

18 (MEDLINE or pubmed).tw. (152526)

19 systematic review.tw. (110770)

20 systematic review.pt. (118884)

21 meta-analysis.pt. (109366)

22 intervention$.ti. (118249)

23 or/18-22 (357890)

24 randomized controlled trial.pt. (497838)

25 randomi?ed.mp. (773096)

26 placebo.mp. (190793)

27 or/24-26 (824015)

28 23 or 27 (1079124)

29 17 and 28 (3197)

30 limit 29 to english language (3032)

31 animals/ not humans/ (4627622)

32 30 not 31 (2873)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to January 06, 2020>

Search Strategy:

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1 exp Renal Insufficiency, Chronic/ (0)

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (9154)

3 ((kidney* or renal*) adj1 insufficien*).tw. (1088)

4 ckd*.tw. (4308)

5 ((kidney* or renal*) adj1 fail*).tw. (6220)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (4641)

7 (esrd* or eskd*).tw. (1915)

8 "Chronic Kidney Disease-Mineral and Bone Disorder"/ (0)

9 or/1-8 (17908)

10 exp Proteinuria/ (0)

11 Proteins/ (0)

12 exp dietary proteins/ (0)

13 protein*.tw. (227663)

14 Albumins/ (0)

15 albumin*.tw. (12018)

16 or/10-15 (234702)

17 9 and 16 (3374)

18 (MEDLINE or pubmed).tw. (32629)

19 systematic review.tw. (26658)

20 systematic review.pt. (576)

21 meta-analysis.pt. (39)

22 intervention$.ti. (19642)

23 or/18-22 (62513)

24 randomized controlled trial.pt. (276)

25 randomi?ed.mp. (69001)

26 placebo.mp. (17015)

27 or/24-26 (75069)

28 23 or 27 (123678)

29 17 and 28 (275)

30 limit 29 to english language (274)

31 animals/ not humans/ (0)

32 30 not 31 (274)

Database: Ovid MEDLINE(R) Epub Ahead of Print <January 06, 2020>

Search Strategy:

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1 exp Renal Insufficiency, Chronic/ (0)

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (1384)

3 ((kidney* or renal*) adj1 insufficien*).tw. (157)

4 ckd*.tw. (721)

5 ((kidney* or renal*) adj1 fail*).tw. (735)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (671)

7 (esrd* or eskd*).tw. (282)

8 "Chronic Kidney Disease-Mineral and Bone Disorder"/ (0)

9 or/1-8 (2557)

10 exp Proteinuria/ (0)

11 Proteins/ (0)

12 exp dietary proteins/ (0)

13 protein*.tw. (31226)

14 Albumins/ (0)

15 albumin*.tw. (1619)

16 or/10-15 (32204)

17 9 and 16 (484)

18 (MEDLINE or pubmed).tw. (6706)

19 systematic review.tw. (6507)

20 systematic review.pt. (25)

21 meta-analysis.pt. (23)

22 intervention$.ti. (3973)

23 or/18-22 (13284)

24 randomized controlled trial.pt. (1)

25 randomi?ed.mp. (12981)

26 placebo.mp. (3005)

27 or/24-26 (13966)

28 23 or 27 (24113)

29 17 and 28 (36)

30 limit 29 to english language (36)

31 animals/ not humans/ (0)

32 30 not 31 (36)

Database: Embase <1974 to 2020 Week 01>

Search Strategy:

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1 exp kidney failure/ (345985)

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (120783)

3 ((kidney* or renal*) adj1 insufficien*).tw. (29830)

4 ckd*.tw. (48319)

5 ((kidney* or renal*) adj1 fail*).tw. (131006)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (57177)

7 (esrd* or eskd*).tw. (26744)

8 or/1-7 (437234)

9 exp *proteinuria/ (19412)

10 *protein/ (136872)

11 *protein intake/ (12236)

12 *egg protein/ or *milk protein/ (5545)

13 protein*.tw. (3478122)

14 *albumin/ (22091)

15 albumin*.tw. (201186)

16 or/9-15 (3626081)

17 8 and 16 (66728)

18 (MEDLINE or pubmed).tw. (241849)

19 exp systematic review/ or systematic review.tw. (276199)

20 meta-analysis/ (178169)

21 intervention$.ti. (190237)

22 or/18-21 (618585)

23 random:.tw. (1488577)

24 placebo:.mp. (445939)

25 double-blind:.tw. (205060)

26 or/23-25 (1740414)

27 22 or 26 (2164654)

28 17 and 27 (6938)

29 limit 28 to english language (6589)

30 nonhuman/ not human/ (4528327)

31 29 not 30 (6002)

32 limit 31 to (conference abstract or conference paper or "conference review" or erratum or letter or note or tombstone) (1765)

33 31 not 32 (4237)

Cochrane Library

#1 MeSH descriptor: [Renal Insufficiency, Chronic] this term only 2050

#2 (((chronic* or progressi*) near/1 (renal* or kidney*))):ti,ab,kw 10095

#3 (((kidney* or renal*) near/1 insufficien*)):ti,ab,kw 4869

#4 (ckd*):ti,ab,kw 4708

#5 (((kidney* or renal*) near/1 fail*)):ti,ab,kw 16189

#6 (((endstage* or end-stage* or "end stage*") near/1 (renal* or kidney*))):ti,ab,kw 4428

#7 ((esrd* or eskd*)):ti,ab,kw 2009

#8 MeSH descriptor: [Chronic Kidney Disease-Mineral and Bone Disorder] this term only 83

#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 25438

#10 MeSH descriptor: [Proteinuria] explode all trees 2211

#11 MeSH descriptor: [Proteins] this term only 837

#12 MeSH descriptor: [Dietary Proteins] explode all trees 3892

#13 (protein*):ti,ab 58789

#14 MeSH descriptor: [Albumins] this term only 622

#15 (albumin*):ti,ab12819

#16 #10 or #11 or #12 or #13 or #14 or #15 68850

#17 #9 and #16 4918

#18 "conference":pt or (clinicaltrials or trialsearch):so 446661

#19 #17 not #18 3124 (58 CDSR, 3062 CENTRAL, 4 other databases)

CRD databases

1 (MeSH DESCRIPTOR Renal Insufficiency, Chronic EXPLODE ALL TREES) 538 Delete

2 ((chronic* or progressi*) near1 (renal* or kidney*)) 489 Delete

3 ((kidney* or renal*) near1 insufficien*) 320 Delete

4 (ckd*) 93 Delete

5 ((kidney* or renal*) near1 fail*) 836 Delete

6 ((endstage* or end-stage* or "end stage*") near1 (renal* or kidney)) 354 Delete

7 (esrd* or eskd*) 150 Delete

8 (MeSH DESCRIPTOR Chronic Kidney Disease-Mineral and Bone Disorder) 0 Delete

9 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8) 1407 Delete

10 (MeSH DESCRIPTOR Proteinuria EXPLODE ALL TREES) 145 Delete

11 (MeSH DESCRIPTOR Proteins) 17 Delete

12 (MeSH DESCRIPTOR Dietary Proteins ) 46 Delete

13 (protein*) 2636 Delete

14 MeSH DESCRIPTOR albumins 59 Delete

15 (albumin*) 353 Delete

16 (#10 or #11 or #12 or #13 or #14 or #15) 2888 Delete

| | | | |
|---|---|---|---|
| 17 | #9 AND #16 | 234 | Delete |
| 18 | (#9 AND #16) IN DARE | 135 | Delete |
| 19 | (#9 AND #16) IN NHSEED | 80 | Delete |
| 20 | (#9 AND #16) IN HTA | 19 | Delete |

Notes:

Embase: Protein-related Emtree headings are focused to produce manageable result sizes.

Cochrane Library: ti,ab used for protein and albumin free-text term to produce manageable result sizes

### Cost-effectiveness searches

| Databases | Date searched | Version/files | No. retrieved |
|---|---|---|---|
| MEDLINE (Ovid) | 7th Jan 2020 | Ovid MEDLINE(R) <1946 to January 06, 2020> | 1607 |
| MEDLINE in Process (Ovid) | 7th Jan 2020 | Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to January 06, 2020> | 194 |
| MEDLINE epub (Ovid) | 7th Jan 2020 | Ovid MEDLINE(R) Epub Ahead of Print <January 06, 2020> | 25 |
| Embase (Ovid) | 7th Jan 2020 | Embase <1974 to 2020 Week 01> | 2407 |
| EconLit (Ovid) | 7th Jan 2020 | Econlit <1886 to December 26, 2019> | 1 |
| NHS Economic Evaluation Database (NHS EED) (legacy database) | 7th Jan 2020 | Up to 2015 | 80 |
| CRD HTA | 7th Jan 2020 | Up to 2018 | 19 |

The following search filters were applied to the search strategies in MEDLINE and Embase to identify cost-effectiveness studies:

- Glanville J et al. (2009) Development and Testing of Search Filters to Identify Economic Evaluations in MEDLINE and EMBASE. Alberta: Canadian Agency for Drugs and Technologies in Health (CADTH)

  Several modifications have been made to these filters over the years that are standard NICE practice.

**Search strategies**

Database: Ovid MEDLINE(R) <1946 to January 06, 2020>

Search Strategy:

---

1 exp Renal Insufficiency, Chronic/ (111773)

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (71808)

3 ((kidney* or renal*) adj1 insufficien*).tw. (21175)

4 ckd*.tw. (22546)

5 ((kidney* or renal*) adj1 fail*).tw. (86008)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (34922)

7 (esrd* or eskd*).tw. (14067)

8 "Chronic Kidney Disease-Mineral and Bone Disorder"/ (3435)

9 or/1-8 (211281)

10 exp Proteinuria/ (38575)

11 Proteins/ (202512)

12 exp dietary proteins/ (97336)

13 protein*.tw. (2680399)

14 Albumins/ (19261)

15 albumin*.tw. (139304)

16 or/10-15 (2867417)

17 9 and 16 (37305)

18 Economics/ (27118)

19 exp "Costs and Cost Analysis"/ (231460)

20 Economics, Dental/ (1908)

21 exp Economics, Hospital/ (24133)

22 exp Economics, Medical/ (14151)

23 Economics, Nursing/ (3996)

24 Economics, Pharmaceutical/ (2904)

25 Budgets/ (11213)

26 exp Models, Economic/ (14629)

27 Markov Chains/ (13905)

28 Monte Carlo Method/ (27625)

29 Decision Trees/ (10850)

30 econom$.tw. (229102)

31 cba.tw. (9683)

32 cea.tw. (20096)

33 cua.tw. (970)

34 markov$.tw. (17355)

35 (monte adj carlo).tw. (29088)

36 (decision adj3 (tree$ or analys$)).tw. (12737)

37 (cost or costs or costing$ or costly or costed).tw. (443915)

38 (price$ or pricing$).tw. (32356)

39 budget$.tw. (23039)

40 expenditure$.tw. (47794)

41 (value adj3 (money or monetary)).tw. (2021)

42 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (3425)

43 or/18-42 (896639)

44 "Quality of Life"/ (186515)

45 quality of life.tw. (219790)

46 "Value of Life"/ (5681)

47 Quality-Adjusted Life Years/ (11737)

48 quality adjusted life.tw. (10310)

49 (qaly$ or qald$ or qale$ or qtime$).tw. (8466)

50 disability adjusted life.tw. (2534)

51 daly$.tw. (2316)

52 Health Status Indicators/ (23145)

53 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (21770)

54 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1290)

55 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (4672)

56 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (28)

57 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (375)

58 (euroqol or euro qol or eq5d or eq 5d).tw. (8365)

59 (qol or hql or hqol or hrqol).tw. (41899)

60 (hye or hyes).tw. (60)

61 health$ year$ equivalent$.tw. (38)

62 utilit$.tw. (164961)

63 (hui or hui1 or hui2 or hui3).tw. (1252)

64 disutili$.tw. (366)

65 rosser.tw. (92)

66 quality of wellbeing.tw. (13)

67 quality of well-being.tw. (375)

68 qwb.tw. (187)

69 willingness to pay.tw. (4201)

70 standard gamble$.tw. (773)

71 time trade off.tw. (1007)

72 time tradeoff.tw. (227)

73 tto.tw. (873)

74 or/44-73 (474097)

75 43 or 74 (1304996)

76 17 and 75 (1830)

77 limit 76 to english language (1669)

78 animals/ not humans/ (4627622)

79 77 not 78 (1607)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to January 06, 2020>

Search Strategy:

---

1 exp Renal Insufficiency, Chronic/ (0)

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (9154)

3 ((kidney* or renal*) adj1 insufficien*).tw. (1088)

4 ckd*.tw. (4308)

5 ((kidney* or renal*) adj1 fail*).tw. (6220)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (4641)

7 (esrd* or eskd*).tw. (1915)

8 "Chronic Kidney Disease-Mineral and Bone Disorder"/ (0)

9 or/1-8 (17908)

10 exp Proteinuria/ (0)

11 Proteins/ (0)

12 exp dietary proteins/ (0)

13 protein*.tw. (227663)

14 Albumins/ (0)

15 albumin*.tw. (12018)

16 or/10-15 (234702)

17 9 and 16 (3374)

18 Economics/ (0)

19 exp "Costs and Cost Analysis"/ (0)

20 Economics, Dental/ (0)

21 exp Economics, Hospital/ (0)

22 exp Economics, Medical/ (0)

23 Economics, Nursing/ (0)

24 Economics, Pharmaceutical/ (0)

25 Budgets/ (0)

26 exp Models, Economic/ (0)

27 Markov Chains/ (0)

28 Monte Carlo Method/ (0)

29 Decision Trees/ (0)

30 econom$.tw. (42531)

31 cba.tw. (405)

32 cea.tw. (1803)

33 cua.tw. (195)

34 markov$.tw. (5381)

35 (monte adj carlo).tw. (16430)

36 (decision adj3 (tree$ or analys$)).tw. (2270)

37 (cost or costs or costing$ or costly or costed).tw. (91018)

38 (price$ or pricing$).tw. (5564)

39 budget$.tw. (4763)

40 expenditure$.tw. (6121)

41 (value adj3 (money or monetary)).tw. (342)

42 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (518)

43 or/18-42 (157960)

44 "Quality of Life"/ (0)

45 quality of life.tw. (36389)

46 "Value of Life"/ (0)

47 Quality-Adjusted Life Years/ (0)

48 quality adjusted life.tw. (1564)

49 (qaly$ or qald$ or qale$ or qtime$).tw. (1330)

50 disability adjusted life.tw. (490)

51 daly$.tw. (448)

52 Health Status Indicators/ (0)

53 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (2548)

54 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (741)

55 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (704)

56 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (5)

57 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (20)

58 (euroqol or euro qol or eq5d or eq 5d).tw. (1579)

59 (qol or hql or hqol or hrqol).tw. (6975)

60 (hye or hyes).tw. (5)

61 health$ year$ equivalent$.tw. (2)

62 utilit$.tw. (29486)

63 (hui or hui1 or hui2 or hui3).tw. (167)

64 disutili$.tw. (70)

65 rosser.tw. (4)

66 quality of wellbeing.tw. (7)

67 quality of well-being.tw. (27)

68 qwb.tw. (12)

69 willingness to pay.tw. (879)

70 standard gamble$.tw. (58)

71 time trade off.tw. (119)

72 time tradeoff.tw. (16)

73 tto.tw. (120)

74 or/44-73 (68170)

75 43 or 74 (217173)

76 17 and 75 (196)

77 limit 76 to english language (194)

78 animals/ not humans/ (0)

79 77 not 78 (194)

Database: Ovid MEDLINE(R) Epub Ahead of Print <January 06, 2020>

Search Strategy:

---

1 exp Renal Insufficiency, Chronic/ (0)

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (1384)

3 ((kidney* or renal*) adj1 insufficien*).tw. (157)

4 ckd*.tw. (721)

5 ((kidney* or renal*) adj1 fail*).tw. (735)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (671)

7 (esrd* or eskd*).tw. (282)

8 "Chronic Kidney Disease-Mineral and Bone Disorder"/ (0)

9 or/1-8 (2557)

10 exp Proteinuria/ (0)

11 Proteins/ (0)

12 exp dietary proteins/ (0)

13 protein*.tw. (31226)

14 Albumins/ (0)

15 albumin*.tw. (1619)

16 or/10-15 (32204)

17 9 and 16 (484)

18 Economics/ (0)

19 exp "Costs and Cost Analysis"/ (0)

20 Economics, Dental/ (0)

21 exp Economics, Hospital/ (0)

22 exp Economics, Medical/ (0)

23 Economics, Nursing/ (0)

24 Economics, Pharmaceutical/ (0)

25 Budgets/ (0)

26 exp Models, Economic/ (0)

27 Markov Chains/ (0)

28 Monte Carlo Method/ (0)

29 Decision Trees/ (0)

30 econom$.tw. (5861)

31 cba.tw. (59)

32 cea.tw. (322)

33 cua.tw. (17)

34 markov$.tw. (715)

35 (monte adj carlo).tw. (1174)

36 (decision adj3 (tree$ or analys$)).tw. (383)

37 (cost or costs or costing$ or costly or costed).tw. (12238)

38 (price$ or pricing$).tw. (843)

39 budget$.tw. (535)

40 expenditure$.tw. (1149)

41 (value adj3 (money or monetary)).tw. (63)

42 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (45)

43 or/18-42 (20034)

44 "Quality of Life"/ (0)

45 quality of life.tw. (6857)

46 "Value of Life"/ (0)

47 Quality-Adjusted Life Years/ (0)

48 quality adjusted life.tw. (394)

49 (qaly$ or qald$ or qale$ or qtime$).tw. (335)

50 disability adjusted life.tw. (93)

51 daly$.tw. (84)

52 Health Status Indicators/ (0)

53 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (460)

54 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (40)

55 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (159)

56 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (0)

57 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (3)

58 (euroqol or euro qol or eq5d or eq 5d).tw. (343)

59 (qol or hql or hqol or hrqol).tw. (1357)

60 (hye or hyes).tw. (3)

61 health$ year$ equivalent$.tw. (0)

62 utilit$.tw. (4699)

63 (hui or hui1 or hui2 or hui3).tw. (24)

64 disutili$.tw. (12)

65 rosser.tw. (0)

66 quality of wellbeing.tw. (1)

67 quality of well-being.tw. (8)

68 qwb.tw. (5)

69 willingness to pay.tw. (167)

70 standard gamble$.tw. (7)

71 time trade off.tw. (21)

72 time tradeoff.tw. (4)

73 tto.tw. (20)

74 or/44-73 (11800)

75 43 or 74 (30069)

76 17 and 75 (25)

77 limit 76 to english language (25)

78 animals/ not humans/ (0)

79 77 not 78 (25)

Database: Econlit <1886 to December 26, 2019>

Search Strategy:

---

1 [exp Renal Insufficiency, Chronic/] (0)

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (21)

3 ((kidney* or renal*) adj1 insufficien*).tw. (3)

4 ckd*.tw. (5)

5 ((kidney* or renal*) adj1 fail*).tw. (32)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (54)

7 (esrd* or eskd*).tw. (31)

8 ["Chronic Kidney Disease-Mineral and Bone Disorder"/] (0)

9 or/1-8 (100)

10 [exp Proteinuria/] (0)

11 [Proteins/] (0)

12 [exp dietary proteins/] (0)

13 protein*.tw. (609)

14 albumin*.tw. (4)

15 or/10-14 (612)

16 9 and 15 (1)

Database: Embase <1974 to 2020 Week 01>

Search Strategy:

---

1 exp kidney failure/ (345985)

2 ((chronic* or progressi*) adj1 (renal* or kidney*)).tw. (120783)

3 ((kidney* or renal*) adj1 insufficien*).tw. (29830)

4 ckd*.tw. (48319)

5 ((kidney* or renal*) adj1 fail*).tw. (131006)

6 ((endstage* or end-stage* or "end stage*") adj1 (renal* or kidney*)).tw. (57177)

7 (esrd* or eskd*).tw. (26744)

8 or/1-7 (437234)

9 exp *proteinuria/ (19412)

10 *protein/ (136872)

11 *protein intake/ (12236)

12 *egg protein/ or *milk protein/ (5545)

13 protein*.tw. (3478122)

14 *albumin/ (22091)

15 albumin*.tw. (201186)

16 or/9-15 (3626081)

17 8 and 16 (66728)

18 exp Health Economics/ (826819)

19 exp "Health Care Cost"/ (285341)

20 exp Pharmacoeconomics/ (199640)

21 Monte Carlo Method/ (38571)

22 Decision Tree/ (12062)

23 econom$.tw. (351609)

24 cba.tw. (12556)

25 cea.tw. (33684)

26 cua.tw. (1442)

27 markov$.tw. (28986)

28 (monte adj carlo).tw. (46295)

29 (decision adj3 (tree$ or analys$)).tw. (22072)

30 (cost or costs or costing$ or costly or costed).tw. (737751)

31 (price$ or pricing$).tw. (55195)

32 budget$.tw. (37279)

33 expenditure$.tw. (72008)

34 (value adj3 (money or monetary)).tw. (3337)

35 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (8486)

36 or/18-35 (1696460)

37 "Quality of Life"/ (449240)

38 Quality Adjusted Life Year/ (25473)

39 Quality of Life Index/ (2702)

40 Short Form 36/ (27454)

41 Health Status/ (123868)

42 quality of life.tw. (417832)

43 quality adjusted life.tw. (18772)

44 (qaly$ or qald$ or qale$ or qtime$).tw. (19251)

45 disability adjusted life.tw. (3796)

46 daly$.tw. (3742)

47 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (40107)

48 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (2315)

49 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (9029)

50 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (57)

51 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (441)

52 (euroqol or euro qol or eq5d or eq 5d).tw. (19306)

53 (qol or hql or hqol or hrqol).tw. (92064)

54 (hye or hyes).tw. (131)

55 health$ year$ equivalent$.tw. (41)

56 utilit$.tw. (276873)

57 (hui or hui1 or hui2 or hui3).tw. (2186)

58 disutili$.tw. (888)

59 rosser.tw. (118)

60 quality of wellbeing.tw. (42)

61 quality of well-being.tw. (469)

62 qwb.tw. (243)

63 willingness to pay.tw. (8275)

64 standard gamble$.tw. (1086)

65 time trade off.tw. (1669)

66 time tradeoff.tw. (286)

67 tto.tw. (1603)

68 or/37-67 (946416)

69 36 or 68 (2492404)

70 17 and 69 (4083)

71 limit 70 to english language (3835)

72 nonhuman/ not human/ (4528327)

73 71 not 72 (3709)

74 limit 73 to (conference abstract or conference paper or "conference review" or letter or note or tombstone) (1302)

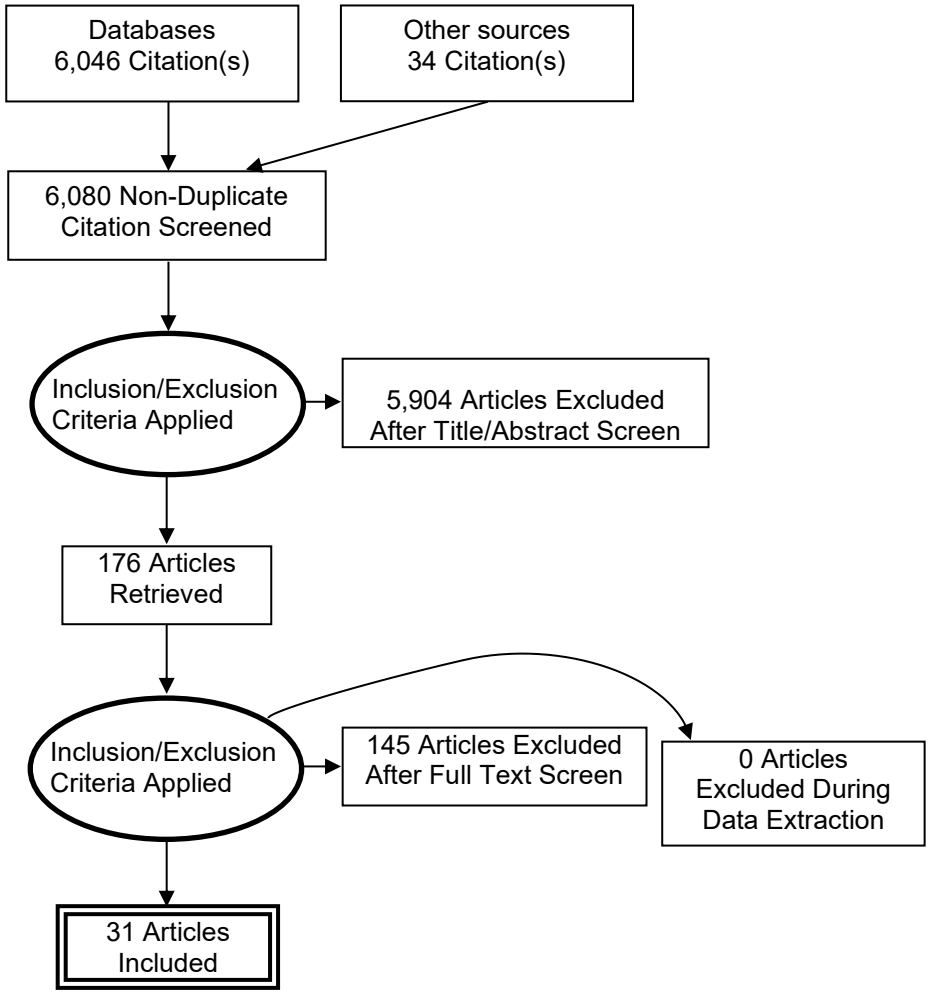
75 73 not 74 (2407)

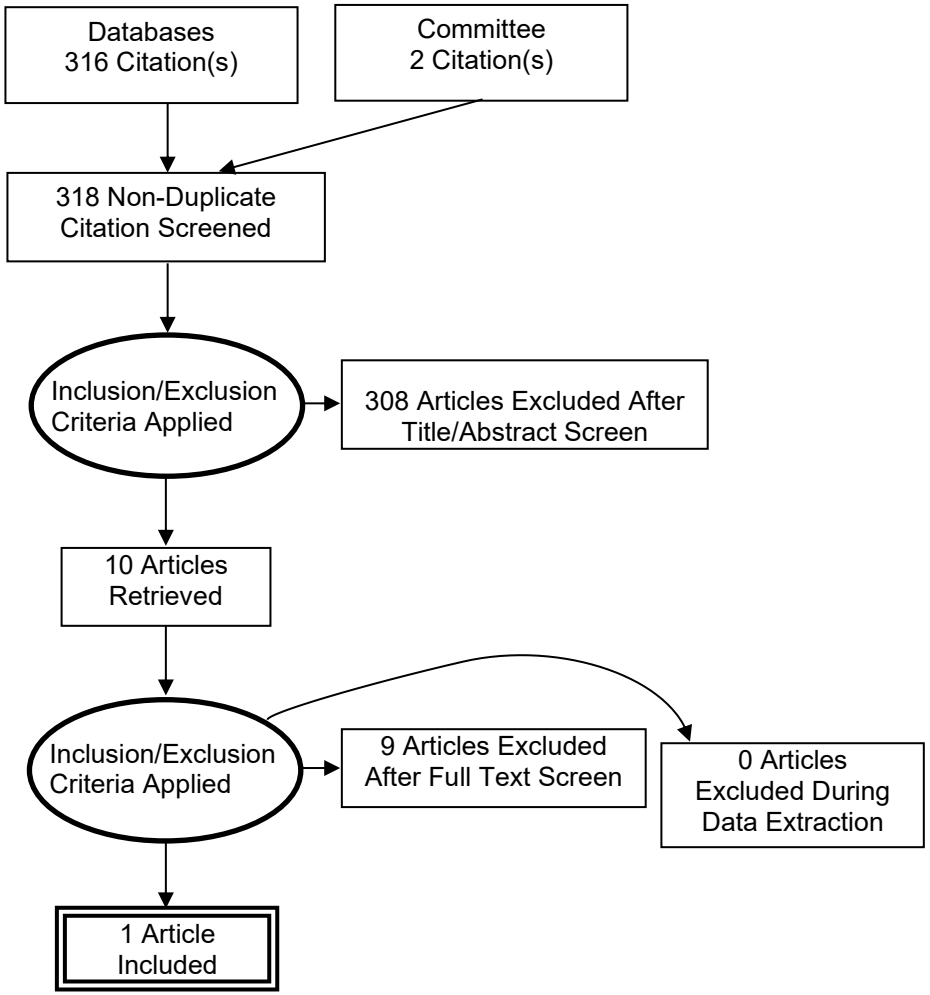
CRD databases

| | | | |
|---|---|---|---|
| 1 | (MeSH DESCRIPTOR Renal Insufficiency, Chronic EXPLODE ALL TREES) | 538 | Delete |
| 2 | ((chronic* or progressi*) near1 (renal* or kidney*)) | 489 | Delete |
| 3 | ((kidney* or renal*) near1 insufficien*) | 320 | Delete |
| 4 | (ckd*) | 93 | Delete |
| 5 | ((kidney* or renal*) near1 fail*) | 836 | Delete |
| 6 | ((endstage* or end-stage* or "end stage*") near1 (renal* or kidney)) | 354 | Delete |
| 7 | (esrd* or eskd*) | 150 | Delete |
| 8 | (MeSH DESCRIPTOR Chronic Kidney Disease-Mineral and Bone Disorder) | 0 | Delete |
| 9 | (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8) | 1407 | Delete |
| 10 | (MeSH DESCRIPTOR Proteinuria EXPLODE ALL TREES) | 145 | Delete |
| 11 | (MeSH DESCRIPTOR Proteins) | 17 | Delete |
| 12 | (MeSH DESCRIPTOR Dietary Proteins ) | 46 | Delete |
| 13 | (protein*) | 2636 | Delete |
| 14 | MeSH DESCRIPTOR albumins | 59 | Delete |
| 15 | (albumin*) | 353 | Delete |
| 16 | (#10 or #11 or #12 or #13 or #14 or #15) | 2888 | Delete |
| 17 | #9 AND #16 | 234 | Delete |
| 18 | (#9 AND #16) IN DARE | 135 | Delete |
| 19 | (#9 AND #16) IN NHSEED | 80 | Delete |
| 20 | (#9 AND #16) IN HTA | 19 | Delete |

1

# Appendix D – Effectiveness evidence study selection



# Appendix E – Effectiveness evidence – evidence tables and risk of bias

## Ameen, 2016

| | |
|---|---|
| **Bibliographic Reference** | Ameen; Kashif, M.A.; Sumreen; To compare anti-albumin urea effects of valsartan alone with combination of valsartan and amlodipine in patients of chronic kidney disease; Pakistan Journal of Medical Sciences; 2016; vol. 32 (no. 3); 613-616 |

**Study details**

| | |
|---|---|
| **Study type** | Randomised controlled trial (RCT) |
| **Study location** | Pakistan |
| **Study setting** | Department of Medicine, Combined Military Hospital Bahawalpur |
| **Study dates** | 2014 |
| **Duration of follow-up** | 6 months |
| **Sources of funding** | None |
| **Inclusion criteria** | CKD<br>No details of CKD stage<br><br>Albuminuria<br>urinary albumin: creatinine ratio >3.5 mg/mmol<br><br>Age<br>20 to 70 years |

| | |
|---|---|
| | Hypertension<br>persistant uncontrolled hypertension: BP more than 140/90 mmHg |
| **Exclusion criteria** | Other conditions<br>history of heart failure, angina, myocardial infarction in last six months, endocrine hypertension and uncontrolled diabetes with ketoacidosis<br><br>Treatment<br>immunosuppressive therapy |
| **Sample size** | 140 |
| **% Female** | 44.2 |
| **Interventions** | Blood pressure medication<br>Valsartan vs Valsartan and Amlodipine<br><br>Additional notes<br>The target BP level was < 130/80 mmHg |
| **Outcome measures** | Reduction in albuminuria<br>Urinary albumin creatinine ratio (mg/mmol) at baseline and follow-up |

**Study arms**

**Valsartan (N = 70)**
80 mg once a day; doses were not be altered during the study period

| | |
|---|---|
| Loss to follow-up | None |
| Mean age (SD) | 56.3 (8.2) |
| Condition specific characteristics | Baseline albuminuria<br>Urinary albumin creatinine ratio (mg/mmol): mean 28.2 (SD 6.7) |

**Valsartan and Amlodipine (N = 70)**
Valsartan 80 mg and Amlodipine 10 mg once a day; doses were not be altered during the study period

| | |
|---|---|
| Loss to follow-up | None |
| Mean age (SD) | 53.0 (9.8) |
| Condition specific characteristics | Baseline albuminuria<br>Urinary albumin creatinine ratio (mg/mmol): mean 43.4 (SD 7.5) |

**Domain 1: Bias arising from the randomisation process**

*Risk of bias judgement for the randomisation process*

High

*(Urinary albumin creatinine ratio was different between the groups at baseline)*

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

High

*(No information on the type of analysis (intention-to-treat or per-protocol analyses))*

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

High

*(No information about an appropriate analysis to estimate the effect of participants adherence)*

**Domain 3. Bias due to missing outcome data**

*Risk-of-bias judgement for missing outcome data*

Low

**Domain 4. Bias in measurement of the outcome**

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*Risk-of-bias judgement for selection of the reported result*

Low

**Overall bias and Directness**

*Risk of bias judgement*

High

*Overall Directness*

Directly applicable

## Ando, 2014

| | |
|---|---|
| **Bibliographic Reference** | Ando, Katsuyuki; Ohtsu, Hiroshi; Uchida, Shunya; Kaname, Shinya; Arakawa, Yoshihiro; Fujita, Toshiro; EVALUATE Study, Group; Anti-albuminuric effect of the aldosterone blocker eplerenone in non-diabetic hypertensive patients with albuminuria: a double-blind, randomised, placebo-controlled trial.; The lancet. Diabetes & endocrinology; 2014; vol. 2 (no. 12); 944-53 |

**Study details**

| | |
|---|---|
| **Study type** | Randomised controlled trial (RCT) |
| **Study location** | Japan |
| **Study setting** | Clinics and hospitals |
| **Study dates** | 2009 - 2012 |
| **Duration of follow-up** | 52 weeks |
| **Sources of funding** | Pfizer |
| **Inclusion criteria** | CKD<br>eGFR 50 mL/min per 1.73 m² or more<br><br>Albuminuria<br>pre-treatment urinary albumin creatinine ratio in the fi rst morning void urine (a mean of three measurements in three consecutive visits) of 30–599 mg/g<br><br>Age<br>20 to 79 years<br><br>Hypertension<br>systolic blood pressures of 130–179 mm Hg or diastolic blood pressures of 80–99 mm Hg<br><br>Treatment<br>Patients had received an angiotensin-converting enzyme inhibitor, an angiotensinreceptor blocker, or both, for at least 8 weeks |
| **Exclusion criteria** | Diabetes<br>fasting blood glucose concentration ≥126 mg/dL or treatment with anti-diabetic drugs<br><br>Other conditions<br>hypertensive emergencies that required intravenous administration of antihypertensive agents; serum potassium concentrations of 5.0 mmol/L or more; severe liver damage (Child-Pugh score: class C); severe heart failure (New York Heart Association class ≥III); severe arrhythmia (frequent ventricular or atrial extrasystole, prolonged ventricular tachycardia, atrial tachyarrhythmia with severe tachycardia, atrial fibrillation or fl utter with severe tachycardia, sick sinus syndrome with severe bradycardia, or atrioventricular block with severe bradycardia); angina; myocardial infarction or cerebrovascular disease within 6 months before registration; pregnancy, possibility of pregnancy, or a desire to become pregnant; a history of severe adverse eff ects from mineralocorticoid receptor antagonists, angiotensinconverting enzyme inhibitors, or angiotensin-receptor blockers<br><br>Treatment |

| | |
|---|---|
| | administration of a mineralocorticoid receptor antagonist less than 8 weeks before registration; taking contraindicated drugs (including adreno corticosteroidal drugs, immuno suppressants, potassium-sparing diuretics, potassium supplementation, itra conazole, riton avir, and nelfi navir); and treatment for more than 2 weeks with nonsteroidal anti-infl ammatory drugs at registration |
| **Sample size** | 336 |
| **Interventions** | Blood pressure medication<br>Eplerenone<br><br>Placebo |
| **Outcome measures** | Reduction in albuminuria<br>Mean percentage change from baseline for urinary albumin creatinine ratio<br><br>Mortality: all cause<br><br>Morbidity<br>atrial fibrillation and cerebrovascular infarction |

**Study arms**

**Eplerenone (N = 170)**
50 mg/day; added to standard therapy with an angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, or both

| | |
|---|---|
| Loss to follow-up | 12 |
| % Female | 30.0 |
| Mean age (SD) | 58.6 (13.0) |
| Condition specific characteristics | Baseline albuminuria<br>Urinary albumin creatinine ratio (mg/g): mean 163.1 (SD 148.0)<br><br>eGFR<br>mean 67.7 (SD 14.3) mL/min/1.73m² |

**Placebo (N = 166)**
Added to standard therapy with an angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, or both

| | |
|---|---|
| Loss to follow-up | 20 |
| % Female | 34.0 |
| Mean age (SD) | 58.6 (13.8) |
| Condition specific characteristics | Baseline albuminuria<br>Urinary albumin creatinine ratio (mg/g): mean 156.8 (SD 133.6)<br><br>eGFR<br>mean 68.6 (SD 13.6) mL/min/1.73m² |

**Domain 1: Bias arising from the randomisation process**

*Risk of bias judgement for the randomisation process*

Low

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

High

*(No information on the type of analysis (intention-to-treat or per-protocol analyses))*

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

High

*(No information on the type of analysis (intention-to-treat or per-protocol analyses))*

**Domain 3. Bias due to missing outcome data**

*Risk-of-bias judgement for missing outcome data*

Low

**Domain 4. Bias in measurement of the outcome**

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*Risk-of-bias judgement for selection of the reported result*

Low

**Overall bias and Directness**

*Risk of bias judgement*

High

*Overall Directness*

Directly applicable

## Anonymous, 1997

| | |
|---|---|
| **Bibliographic Reference** | Anonymous; Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia).; Lancet (London, England); 1997; vol. 349 (no. 9069); 1857-63 |

**Study details**

| | |
|---|---|
| **Study type** | Randomised controlled trial (RCT)<br>This paper reports stratum 2 of this RCT which contains participants with proteinuria ≥3 g/24 h. Stratum 1 is reported by Ruggenenti 1999b |
| **Study location** | Italy |
| **Study setting** | Not reported |
| **Duration of follow-up** | 3 years |
| **Sources of funding** | Grant from Hoechst Marion Roussel Cinical Research Institute, Frankfurt am Main, Germany |
| **Inclusion criteria** | CKD<br>creatinine clearance 20-70 mL/min per 1.73m² with variation of <30% during the previous 3 months<br><br>Proteinuria<br>Urinary protein excretion >1 g/24 h for at least 3 months without evidence of urinary-tract infection or overt heart failure (New York Heart Association class III or more)<br><br>Age<br>18 to 70 years<br><br>Hypertension<br>Normotensive or hypertensive patients defined as diastolic and systolic blood pressure <140 mm Hg and 90 mm Hg, without antihypertensive therapy |
| **Exclusion criteria** | Other conditions<br>acute myocardial infarction or cerebrovascular accident in the previous 6 months; severe uncontrolled hypertension (diastolic blood pressure ≥115 and/or systolic blood pressure ≥220 mm Hg); evidence or suspicion of renovascular disease, obstructive uropathy, insulin-dependent diabetes mellitus, collagen disease, cancer, higher serum aminotransferase concentrations, or chronic cough; drug or alcohol abuse; pregnancy breast feeding; and ineffective contraception<br><br>Treatment<br>corticosteroids, non-steroidal anti-inflammatory drugs, or immunosuppressive drugs |
| **Sample size** | 166 |
| **Condition specific characteristics** | Additional notes<br>This paper reports stratum 2 which contains participants with proteinuria ≥3 g/24 h |

| | |
|---|---|
| **Interventions** | Blood pressure medication<br>Ramipril<br><br>Placebo<br><br>Additional notes<br>Antihypertensive agents (but not ACE inhibitors) were introduced, and their doses adjusted appropriately to achieve and maintain diastolic blood pressure <90 mm Hg. In patients already receiving antihypertensive agents, the study-drug dose was increased and the dose of other antihypertensive drugs progressively reduced to avoid symptomatic hypotension. In each patient, the broad aim was to adjust the dose of the study drugs to achieve and maintain the target blood pressure with the minimum dose of concomitant antihypertensive agents. ACE inhibitors or antagonists to angiotensin-II receptor could not be added to the study drugs during the study period. All patients were recommended to limit their sodium intake, and to eat 0.6-0.8 g protein per kg body-weight daily. |
| **Outcome measures** | Reduction in proteinuria<br>Median percentage change from baseline for urinary protein excretion (g/24 h) at 1, 3, 6, 12, 24, 36 months<br><br>CKD progression: occurrence of end stage kidney disease<br>Requirement of dialysis or renal transplantation<br><br>Mortality: all cause<br><br>Mortality: cardiovascular<br><br>Morbidity<br>Myocardial infarction |

**Study arms**

**Ramipril (N = 78)**

1.25 mg capsules; increased every 2 weeks until diastolic blood pressure was reduced to under 90 mm Hg

| | |
|---|---|
| Loss to follow-up | 22 |
| % Female | 15.0 |
| Mean age (SD) | 48.9 (13.6) |

| | |
|---|---|
| Condition specific characteristics | Baseline proteinuria<br>Urinary protein excretion (g/24 h): mean 5.6 (SD 2.8)<br><br>eGFR<br>mean 40.2 (SD 19.0) mL/min/1.73m² |

**Placebo (N = 88)**

| | |
|---|---|
| Loss to follow-up | 27 |
| % Female | 27.0 |
| Mean age (SD) | 49.7 (13.6) |
| Condition specific characteristics | Baseline proteinuria<br>Urinary protein excretion (g/24 h): mean 5.1 (SD 2.0)<br><br>eGFR<br>mean 37.4 (SD 17.5) mL/min/1.73m² |

**Domain 1: Bias arising from the randomisation process**

*Risk of bias judgement for the randomisation process*

Low

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

Some concerns

*(Randomisation became open at 27 months)*

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

Some concerns

*(No information about adherence)*

**Domain 3. Bias due to missing outcome data**

*Risk-of-bias judgement for missing outcome data*

Low

**Domain 4. Bias in measurement of the outcome**

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*Risk-of-bias judgement for selection of the reported result*

Some concerns

*(Protocol was not reported)*

**Overall bias and Directness**

*Risk of bias judgement*

Some concerns

*Overall Directness*

Directly applicable

## Bianchi, 2006

| | |
|---|---|
| **Bibliographic Reference** | Bianchi, S; Bigazzi, R; Campese, V M; Long-term effects of spironolactone on proteinuria and kidney function in patients with chronic kidney disease.; Kidney international; 2006; vol. 70 (no. 12); 2116-23 |

**Study details**

| | |
|---|---|
| **Study type** | Randomised controlled trial (RCT) |
| **Study location** | US |
| **Study setting** | Outpatient clinic |
| **Study dates** | Not reported |
| **Duration of follow-up** | 12 months |
| **Sources of funding** | This study was supported with private funding. No support was received by pharmaceutical companies |
| **Inclusion criteria** | CKD<br>eGFR ranging from 34 to 116 ml/min/ 1.73m²; clinical diagnosis of idiopathic chronic glomerulonephritis based on the presence of proteinuria (urinary protein/creatinine ratio >1.0 g/g) and no evidence of systemic diseases<br><br>Proteinuria<br>Urinary protein/creatinine ratio (g/g) ranging from 1.0 to 3.9 |
| **Exclusion criteria** | Diabetes<br><br>Other conditions<br>renovascular or malignant hypertension, secondary glomerular disease, malignancies, myocardial infarction, or cerebrovascular accident within the 6 months preceding the study, congestive heart failure, hepatic dysfunction, serum potassium >5 mEq/l, eGFR <30 ml/min/1.73m², and a history of allergy to ACEIs or ARBs<br><br>Treatment<br>steroids, nonsteroidal anti-inflammatory drugs, or immunosuppressive agents |

| | |
|---|---|
| **Sample size** | 165 |
| **Interventions** | Blood pressure medication<br>Conventional therapy plus spironolactone vs Conventional therapy<br><br>Additional notes<br>Other antihypertensive drugs were used as needed to achieve a target BP of <125/75mmHg, and 74 patients achieved this target. The doses of ACEIs and ARBs were not changed after randomization and inclusion in the study. The dose of diuretics was increased in patients who developed hyperkalemia in an attempt to control serum potassium before deciding to withdraw patients from the study. Seventy-two patients in the conventional therapy group and 74 in the spironolactone group received atorvastatin (20–40 mg/day) for at least 1 year before the initiation of this study. Patients were advised to ingest a diet with approximately 2–3 g sodium per day, and if eGFR was lower than 60 ml/min/1.73m², they were counseled to ingest a protein intake of 0.8 g/kg/day. We did not measure urinary sodium and urea excretion to assess compliance with these dietary restrictions |
| **Outcome measures** | Reduction in proteinuria<br>Percentage change compared to baseline and mean baseline, 1, 3, 6, 9 and 12 months for urinary protein/creatinine ratio (g/g) |

**Study arms**

**Conventional therapy plus spironolactone (N = 83)**

28 were treated with ACEIs, 17 with ARBs and 38 with a combination of ACEIs and ARBs; 60 received hydrochlorothiazide or furosemide

| | |
|---|---|
| Loss to follow-up | 5 |
| % Female | 32.5 |
| Mean age (SD) | 55.0 (1.2) |
| Condition specific characteristics | Baseline proteinuria<br>Urinary protein/creatinine ratio (g/g): mean 2.1 (SEM 0.08)<br><br>eGFR<br>mean 62.4 (SD 2.4) mL/min/1.73m² |

**Conventional therapy (N = 82)**

21 were treated with ACEIs, 18 with ARBs, and 43 with a combination of these two classes of drugs; 56 received hydrochlorothiazide or furosemide

| | |
|---|---|
| Loss to follow-up | 4 |
| % Female | 39.0 |
| Mean age (SD) | 54.4 (1.2) |
| Condition specific characteristics | Baseline proteinuria<br>Urinary protein/creatinine ratio (g/g): mean 2.0 (SEM 0.07)<br><br>eGFR<br>mean 62.2 (SD 2.1) mL/min/1.73m² |

**Domain 1: Bias arising from the randomisation process**

*Risk of bias judgement for the randomisation process*

Some concerns

*(No information about allocation concealment)*

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

High

*(No information on the type of analysis (intention-to-treat or per-protocol analyses))*

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

High

*(No information about an appropriate analysis to estimate the effect of participants adherence)*

**Domain 3. Bias due to missing outcome data**

*Risk-of-bias judgement for missing outcome data*

Low

**Domain 4. Bias in measurement of the outcome**

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*Risk-of-bias judgement for selection of the reported result*

Some concerns

*(Protocol was not reported)*

**Overall bias and Directness**

*Risk of bias judgement*

High

*Overall Directness*

Directly applicable

## Brenner, 2001

| | |
|---|---|
| **Bibliographic Reference** | Brenner, B M; Cooper, M E; de Zeeuw, D; Keane, W F; Mitch, W E; Parving, H H; Remuzzi, G; Snapinn, S M; Zhang, Z; Shahinfar, S; RENAAL Study, Investigators; Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy.; The New England journal of medicine; 2001; vol. 345 (no. 12); 861-9 |

**Study details**

| | |
|---|---|
| **Study type** | Randomised controlled trial (RCT) |
| **Study location** | 250 centers in 28 countries in Asia, Europe, Central America, South America, and North America |
| **Study setting** | Not reported |
| **Study dates** | 2001 |
| **Duration of follow-up** | 3.4 years (range 2.3 to 4.6) |
| **Sources of funding** | Merck and Company |
| **Inclusion criteria** | CKD<br>Nephropathy defined by the presence on 2 occasions of urinary albumin/creatinine ratio (mg/g) from a first morning specimen of at least 300 (or a rate of urinary protein excretion of at least 0.5 g per day) and serum creatinine values between 1.3 and 3.0 mg per deciliter (115 and 265 µmol per liter), with a lower limit of 1.5 mg per deciliter (133 µmol per liter) for male patients weighing more than 60 kg<br><br>Proteinuria<br>rate of urinary protein excretion of at least 0.5 g per day<br><br>Albuminuria<br>urinary albumin/creatinine ratio (mg/g) of at least 300<br><br>Age<br>31 to 70 years<br><br>Diabetes<br>type 2 diabetes |

| | |
|---|---|
| **Exclusion criteria** | Diabetes<br>type 1 diabetes<br><br>Other conditions<br>Nondiabetic renal disease, including renal-artery stenosis, myocardial infarction or undergone coronary-artery bypass grafting within the previous month, cerebrovascular accident or undergone percutaneous transluminal coronary angioplasty within the previous six months, transient ischemic attack within the previous year, or history of heart failure before enrolment |
| **Sample size** | 1513 |
| **Interventions** | Blood pressure medication<br>Losartan<br><br>Placebo<br><br>Additional notes<br>Conventional antihypertensive therapy included open-label medications (diuretics, calcium-channel antagonists, alpha- or betablockers, centrally acting agents, or some combination of these types of medication). After an additional eight weeks, antihypertensive agents (but not angiotensin-I–converting enzyme inhibitors or angiotensin-II–receptor antagonists) were added or their doses increased to achieve the target blood pressure |
| **Outcome measures** | Reduction in albuminuria<br>Percentage reduction reported only for losartan in text and for both arms in graph<br><br>CKD progression: occurrence of end stage kidney disease<br>defined by the need for long-term dialysis or renal transplantation<br><br>Mortality: all cause<br><br>Morbidity<br>Myocardial infarction<br><br>Adverse outcome<br>First hospitalisation with heart failure |

**Study arms**

| |
|---|
| **Losartan (N = 751)** |

50 mg once daily at randomisation along with conventional antihypertensive therapy; after 4 weeks the dose was increased to 100 mg if systolic blood pressure >140 mm Hg and diastolic blood pressure >90 mm Hg

| | |
|---|---|
| Loss to follow-up | 46.5% |
| % Female | 38.5 |
| Mean age (SD) | 60 (7) |
| Condition specific characteristics | Baseline albuminuria<br>urinary albumin/creatinine ratio (mg/g): median 1237<br><br>% Diabetes<br>100 (type 2 diabetes) |

**Placebo (N = 762)**
50 mg once daily at randomisation along with conventional antihypertensive therapy; after 4 weeks placebo was increased to equivalent dose of losartan if systolic blood pressure >140 mm Hg and diastolic blood pressure >90 mm Hg

| | |
|---|---|
| Loss to follow-up | 53.5% |
| % Female | 35.2 |
| Mean age (SD) | 60 (7) |
| Condition specific characteristics | Baseline albuminuria<br>urinary albumin/creatinine ratio (mg/g): median 1261<br><br>% Diabetes<br>100 (type 2 diabetes) |

**Domain 1: Bias arising from the randomisation process**

*Risk of bias judgement for the randomisation process*

Some concerns

*(No information about randomisation method and allocation concealment)*

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

Low

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

Low

**Domain 3. Bias due to missing outcome data**

*Risk-of-bias judgement for missing outcome data*

Some concerns

*(Patients discontinued the study treatment in the placebo group (53.5%) and in the losartan group (46.5%))*

**Domain 4. Bias in measurement of the outcome**

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*Risk-of-bias judgement for selection of the reported result*

Low

**Overall bias and Directness**

*Risk of bias judgement*

Some concerns

*Overall Directness*

Directly applicable

## Ciavarella, 1985

| | |
|---|---|
| **Bibliographic Reference** | Ciavarella, A; Vannini, P; Flammini, M; Bacci, L; Forlani, G; Borgnino, L C; Effect of long-term near-normoglycemia on the progression of diabetic nephropathy.; Diabete & metabolisme; 1985; vol. 11 (no. 1); 3-8 |

**Study details**

| | |
|---|---|
| **Study type** | Randomised controlled trial (RCT) |
| **Study location** | Italy |
| **Study setting** | Outpatients |
| **Study dates** | Not reported |
| **Duration of follow-up** | 12 months |
| **Sources of funding** | Not reported |
| **Inclusion criteria** | CKD<br>Diabetic nephropathy<br><br>Proteinuria<br>Urinary protein excretion >0.5 g/24 h |

| | |
|---|---|
| | Diabetes<br>Type 1 diabetes with poor glycaemic control |
| **Interventions** | Diabetes medication<br>Subcutaneous insulin infusion vs Conventional insulin |
| **Outcome measures** | Reduction in albuminuria<br>Albumin excretion rate (mcg/min) at baseline and 12 months |

**Study arms**

**Subcutaneous insulin infusion (N = 5)**
optimised day by day by means of small adjustments of insulin dosage until a 24 h near-normal glycaemic control was reached

| | |
|---|---|
| Loss to follow-up | 2 |
| % Female | 0 |
| Mean age (SD) | 33 (8) |
| Condition specific characteristics | Baseline albuminuria<br>Albumin excretion rate (mcg/min): mean 1161 (SD 803)<br><br>% Diabetes<br>100 (type 1 diabetes) |

**Conventional insulin (N = 5)**
One, two or three injections daily

| | |
|---|---|
| Loss to follow-up | 2 |
| % Female | 0 |

| | |
|---|---|
| Mean age (SD) | 33 (9) |
| Condition specific characteristics | Baseline albuminuria<br>Albumin excretion rate (mcg/min): mean 1115 (SD 904)<br><br>% Diabetes<br>100 (type 1 diabetes) |

**Domain 1: Bias arising from the randomisation process**

*Risk of bias judgement for the randomisation process*

Some concerns

*(No information about randomisation method and allocation concealment)*

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

High

*(No information on the type of analysis (intention-to-treat or per-protocol analyses))*

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

High

*(No information about an appropriate analysis to estimate the effect of participants adherence)*

**Domain 3. Bias due to missing outcome data**

*Risk-of-bias judgement for missing outcome data*

Low

**Domain 4. Bias in measurement of the outcome**

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*Risk-of-bias judgement for selection of the reported result*

Some concerns

*(Protocol was not reported)*

**Overall bias and Directness**

*Risk of bias judgement*

High

*Overall Directness*

Directly applicable

## Fried, 2013

| | |
|---|---|
| **Bibliographic Reference** | Fried, Linda F; Emanuele, Nicholas; Zhang, Jane H; Brophy, Mary; Conner, Todd A; Duckworth, William; Leehey, David J; McCullough, Peter A; O'Connor, Theresa; Palevsky, Paul M; Reilly, Robert F; Seliger, Stephen L; Warren, Stuart R; Watnick, Suzanne; Peduzzi, Peter; Guarino, Peter; VA NEPHRON-D, Investigators; Combined angiotensin inhibition for the treatment of diabetic nephropathy.; The New England journal of medicine; 2013; vol. 369 (no. 20); 1892-903 |

**Study details**

| | |
|---|---|
| **Study type** | Randomised controlled trial (RCT) |
| **Study location** | US |
| **Study setting** | 32 Department of Veterans Affairs medical centres |
| **Study dates** | 2008 - 2012 |
| **Duration of follow-up** | median patient follow-up was 2.2 years |
| **Sources of funding** | Supported by the Cooperative Studies Program of the Department of Veterans Affairs Office of Research and Development. The Investigator-Initiated Studies Program of Merck provided the study drugs |
| **Inclusion criteria** | CKD<br>eGFR 30.0 to 89.9 ml per minute per 1.73 m²<br><br>Albuminuria<br>urinary albumin/creatinine ratio at least 300 (mg/g) in a random sample<br><br>Diabetes<br>type 2 diabetes |
| **Exclusion criteria** | Other conditions<br>non-diabetic kidney disease, a serum potassium level of more than 5.5 mmol per liter<br><br>Treatment<br>current treatment with sodium polystyrene sulfonate, or an inability to stop proscribed medications that increase the risk of hyperkalemia |
| **Sample size** | 1448 |
| **Interventions** | Blood pressure medication<br>Losartan plus Lisinopril<br><br>Placebo<br>Losartan plus Placebo |

| | |
|---|---|
| | Additional notes<br>blood-pressure medications were adjusted to target a systolic pressure of 110 to 130 mm Hg and a diastolic pressure of less than 80 mm Hg; to decrease the risk of major hyperkalemia, elevations in the potassium level (5.0 to 6.0 mmol per liter) were managed by means of dietary modification and adjustment in diuretics and other medications |
| **Outcome measures** | Reduction in albuminuria<br>urinary albumin/creatinine ratio only reported as median<br><br>CKD progression: occurrence of end stage kidney disease<br>defined by the initiation of maintenance dialysis or an eGFR of <15 ml per minute per 1.73 m² <br><br>Mortality: all cause<br><br>Morbidity<br>Myocardial infarction; Congestive heart failure; Stroke<br><br>Adverse outcome<br>Acute kidney injury |

**Study arms**

**Losartan plus Lisinopril (N = 724)**

Losartan 100 mg; lisinopril was increased every 2 weeks from 10 mg to 20 mg to 40 mg per day as long as there were no unacceptable side effects

| | |
|---|---|
| Loss to follow-up | 19 |
| % Female | 1.2 |
| Mean age (SD) | 64.5 (7.9) |
| Condition specific characteristics | Baseline proteinuria<br>urinary protein/creatinine ratio (g/g): median 2.1 (interquartile range 1.1, 3.2)<br><br>Baseline albuminuria<br>urinary albumin/creatinine ratio (mg/g): median 842 (interquartile range 495, 1698)<br><br>% Diabetes |

| | |
|---|---|
| | 100 (type 2 diabetes)<br><br>eGFR<br>mean 53.6 (SD 15.5) mL/min/1.73m²<br><br>Additional notes<br>urinary protein/creatinine ratio was measured in 86 patients at sites that did not measure the urinary albumin/creatinine ratio in patients with overt proteinuria |

**Losartan plus Placebo (N = 724)**

Losartan 100 mg; placebo was increased every 2 weeks from 10 mg to 20 mg to 40 mg per day as long as there were no unacceptable side effects

| | |
|---|---|
| Loss to follow-up | 20 |
| % Female | 0.4 |
| Mean age (SD) | 64.7 (7.7) |
| Condition specific characteristics | Baseline proteinuria<br>urinary protein/creatinine ratio (g/g): median 1.6 (interquartile range 0.9, 3.0)<br><br>Baseline albuminuria<br>urinary albumin/creatinine ratio (mg/g): median 862 (interquartile range 488, 1789)<br><br>% Diabetes<br>100 (type 2 diabetes)<br><br>eGFR<br>mean 53.7 (SD 16.2) mL/min/1.73m²<br><br>Additional notes<br>urinary protein/creatinine ratio was measured in 101 patients at sites that did not measure the urinary albumin/creatinine ratio in patients with overt proteinuria |

**Domain 1: Bias arising from the randomisation process**

*Risk of bias judgement for the randomisation process*

Some concerns

*(No information about randomisation method and allocation concealment)*

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

Low

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

Some concerns

*(No information about adherence)*

**Domain 3. Bias due to missing outcome data**

*Risk-of-bias judgement for missing outcome data*

Low

**Domain 4. Bias in measurement of the outcome**

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*Risk-of-bias judgement for selection of the reported result*

Low

**Overall bias and Directness**

*Risk of bias judgement*

Some concerns

*Overall Directness*

| |
|---|
| Directly applicable |

## Fujisaki, 2014

| | |
|---|---|
| **Bibliographic Reference** | Fujisaki, Kiichiro; Tsuruya, Kazuhiko; Nakano, Toshiaki; Taniguchi, Masatomo; Higashi, Harumichi; Katafuchi, Ritsuko; Kanai, Hidetoshi; Nakayama, Masaru; Hirakata, Hideki; Kitazono, Takanari; Impact of Combined Losartan/Hydrochlorothiazide on Proteinuria in Patients with Chronic Kidney Disease and Hypertension (ILOHA) Study, Investigators; Impact of combined losartan/hydrochlorothiazide on proteinuria in patients with chronic kidney disease and hypertension.; Hypertension research : official journal of the Japanese Society of Hypertension; 2014; vol. 37 (no. 11); 993-8 |

**Study details**

| | |
|---|---|
| **Study type** | Randomised controlled trial (RCT) |
| **Study location** | Japan |
| **Study setting** | Outpatients |
| **Study dates** | Not reported |
| **Duration of follow-up** | 12 months |
| **Sources of funding** | Not reported |
| **Inclusion criteria** | CKD<br>eGFR was 15 ml/min/1.73m² or more |

| | |
|---|---|
| | Proteinuria<br>urinary protein/creatinine ratio (mg dl-1/mg dl-1): for the 8 weeks before the study commencing exceeded 300 mg/g<br><br>Age<br>20 to 74 years<br><br>Hypertension<br>systolic blood pressure >130mm Hg and/or diastolic blood pressure <80mmHg, or taking antihypertensive drugs at the time when consent was obtained |
| **Exclusion criteria** | Other conditions<br>hepatic dysfunction (e.g., when alanine aminotransferase exceeded the normal upper limit by threefold or more); myocardial infarction or apoplexy in the previous 3 months; those who were or might be pregnant; those with the possibility of becoming pregnant within the study period and those who were breastfeeding; serious nephrotic syndrome (serum albumin <2 g dl-1); immunoglobulin A nephropathy within a year from commencing steroid therapy; hyperkalemia (5.5mEq l-1 or more)<br><br>Treatment<br>undergoing thiazide diuretics or thiazide-like diuretics administration |
| **Interventions** | Blood pressure medication<br>Losartan vs Losartan plus Hydrochlorothiazide<br><br>Additional notes<br>Antihypertensive drugs other than diuretics, ACEI and ARB, were added when blood pressure did not decline to <130/80mmHg |
| **Outcome measures** | Reduction in proteinuria<br>Urinary protein/creatinine ratio (mg/g) mean changes at 6 and 12 months |

**Study arms**

**Losartan (N = 51)**
50mg per day

| | |
|---|---|
| Loss to follow-up | 1 |
| % Female | 45.8 |
| Mean age (SD) | 58 (12) |

| | |
|---|---|
| Condition specific characteristics | Baseline proteinuria<br>urinary protein/creatinine ratio (mg/g): mean 1800 (SD 1630)<br><br>eGFR<br>mean 45.9 (SD 25.1) mL/min/1.73m² |

**Losartan plus Hydrochlorothiazide (N = 51)**
50mg losartan/12.5mg hydrochlorothiazide combination tablet was used per day

| | |
|---|---|
| Loss to follow-up | 0 |
| % Female | 41.1 |
| Mean age (SD) | 58 (11) |
| Condition specific characteristics | Baseline proteinuria<br>urinary protein/creatinine ratio (mg/g): mean 1740 (SD 1400)<br><br>eGFR<br>mean 43.8 (SD 21.9) mL/min/1.73m² |

**Domain 1: Bias arising from the randomisation process**

*Risk of bias judgement for the randomisation process*

Some concerns

*(No information about randomisation method and allocation concealment)*

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

Some concerns

*(No information about deviations because of the experimental context)*

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

Low

**Domain 3. Bias due to missing outcome data**

*Risk-of-bias judgement for missing outcome data*

Low

**Domain 4. Bias in measurement of the outcome**

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*Risk-of-bias judgement for selection of the reported result*

Low

**Overall bias and Directness**

*Risk of bias judgement*

Some concerns

*Overall Directness*

Directly applicable

## Groop, 2017

| | |
|---|---|
| **Bibliographic Reference** | Groop, P.-H.; Cooper, M.E.; Perkovic, V.; Hocher, B.; Kanasaki, K.; Haneda, M.; Schernthaner, G.; Sharma, K.; Stanton, R.C.; Toto, R.; Cescutti, J.; Gordat, M.; Meinicke, T.; Koitka-Weber, A.; Thiemann, S.; von Eynatten, M.; Linagliptin and its effects on hyperglycaemia and albuminuria in patients with type 2 diabetes and renal dysfunction: the randomized MARLINA-T2D trial; Diabetes, Obesity and Metabolism; 2017; vol. 19 (no. 11); 1610-1619 |

**Study details**

| | |
|---|---|
| **Study type** | Randomised controlled trial (RCT) |
| **Study location** | 80 clinical centres in 12 countries: Canada, Denmark, Finland, France, Germany, Japan, the Philippines, South Korea, Spain, Taiwan, the USA and Vietnam |
| **Study setting** | Not reported |
| **Study dates** | Not reported |
| **Duration of follow-up** | 6 months |
| **Sources of funding** | Boehringer Ingelheim and Eli Lilly and Company Diabetes Alliance |
| **Inclusion criteria** | CKD<br>eGFR ≥30 mL/min/1.73 m²<br><br>Albuminuria<br>urinary albumin/creatinine ratio between 30 and 3000 mg/g, or albuminuria >30 mg/L of urine or >30 mcg/min clearly documented in the previous 12 months or detected at screening; albuminuria had then to be confirmed with a geometric mean urinary albumin/creatinine ratio value between 30 and 3000 mg/g from 3 consecutive first-void morning urine samples collected 14 to 16 days before randomisation<br><br>Age |

| | |
|---|---|
| | 18 to 80 years<br><br>Diabetes<br>type 2 diabetes, HbA1c 6.5% to 10.0% (48-86 mmol/mol)<br><br>Treatment<br>required to be either treatment-naive or receiving ≤2 oral glucose-lowering drugs (metformin, sulphonylureas, meglitinides or alpha-glucosidase inhibitors) and/or basal insulin; each individual was required to be receiving a stable dose of an ACE inhibitor or an ARB but not both (dual or triple blockade of the RAAS was not permitted); additional antihypertensive agents other than RAAS inhibitors were permitted. All antihypertensive agents had to have been administered at the same dose for at least the 10 preceding weeks<br><br>Other<br>body-mass index ≤40 kg/m², |
| **Exclusion criteria** | Other conditions<br>fasting blood glucose >240 mg/ dL (>13.3 mmol/L), history of non-diabetic kidney disease, renal transplant, presence of urinary tract infection, mean arterial blood pressure >110 mm Hg and/or a cardiovascular event within the previous 3 months |
| **Sample size** | 360 |
| **Interventions** | Diabetes medication<br>Linagliptin<br><br>Placebo |
| **Outcome measures** | Reduction in albuminuria<br>urinary albumin/creatinine ratio at baseline and adjusted geometric mean for time-weighted average of percentage change from baseline with 95% confidence interval<br><br>Mortality: all cause<br><br>Adverse outcome<br>Investigator-reported hypoglycaemia was defined as an episode of documented blood glucose ≤70 mg/dL (≤3.9 mmol/L). |

**Study arms**

**Linagliptin (N = 182)**
5 mg once daily

| | |
|---|---|
| Loss to follow-up | 7 |

| | |
|---|---|
| % Female | 36.3 |
| Mean age (SD) | 61.0 (10.0) |
| Condition specific characteristics | Baseline albuminuria<br>urinary albumin/creatinine ratio (mg/g): geometric mean 120.8 (geometric coefficient of variation ±152.9)<br><br>% Diabetes<br>100 (type 2 diabetes)<br><br>eGFR<br>mean 75.4 (SD 23.9) mL/min/1.73m² |

**Placebo (N = 178)**

| | |
|---|---|
| Loss to follow-up | 8 |
| % Female | 36.5 |
| Mean age (SD) | 60.1 (9.3) |
| Condition specific characteristics | Baseline albuminuria<br>urinary albumin/creatinine ratio (mg/g): geometric mean 131.9 (geometric coefficient of variation ±166.6)<br><br>% Diabetes<br>100 (type 2 diabetes)<br><br>eGFR<br>mean 72.4 (SD 24.4) mL/min/1.73m² |

**Domain 1: Bias arising from the randomisation process**

*Risk of bias judgement for the randomisation process*

Low

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

Low

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

Low

**Domain 3. Bias due to missing outcome data**

*Risk-of-bias judgement for missing outcome data*

Low

**Domain 4. Bias in measurement of the outcome**

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*Risk-of-bias judgement for selection of the reported result*

Low

**Overall bias and Directness**

*Risk of bias judgement*

Low

*Overall Directness*

Directly applicable

## Heerspink, 2020

| | |
|---|---|
| **Bibliographic Reference** | Heerspink, Hiddo J.L.; Stefánsson, Bergur V.; Correa-Rotter, Ricardo; Chertow, Glenn M.; Greene, Tom; Hou, Fan-Fan; Mann, Johannes F.E.; McMurray, John J.V.; Lindberg, Magnus; Rossing, Peter; Sjöström, C. David; Toto, Roberto D.; Langkilde, Anna-Maria; Wheeler, David C.; Dapagliflozin in Patients with Chronic Kidney Disease; New England Journal of Medicine; 2020 |

**Study details**

| | |
|---|---|
| **Study type** | Randomised controlled trial (RCT) |
| **Study location** | Multicentre |
| **Study setting** | Not reported |
| **Study dates** | 2017 - 2020 |
| **Duration of follow-up** | Median follow-up was 2.4 years |
| **Sources of funding** | AstraZeneca |
| **Inclusion criteria** | CKD<br>eGFR 25 to 75 ml/min/1.73m²<br><br>Albuminuria<br>Urinary albumin to creatinine ratio 200 to 500 mg/g<br><br>Diabetes<br>With or without type 2 diabetes<br><br>Treatment |

| | |
|---|---|
| | All the participants were required to be receiving a stable dose of an ACE inhibitor or ARB for at least 4 weeks before screening. However, participants who were documented to be unable to take ACE inhibitors or ARBs were allowed to participate. |
| **Exclusion criteria** | Diabetes<br>Type 1 diabetes<br><br>Other conditions<br>Polycystic kidney disease, lupus nephritis, or antineutrophil cytoplasmic antibody–associated vasculitis<br><br>Treatment<br>Participants who had received immunotherapy for primary or secondary kidney disease within 6 months before enrollment |
| **Interventions** | Diabetes medication<br>Dapagliflozin<br><br>Placebo |
| **Outcome measures** | CKD progression: occurrence of end stage kidney disease<br><br>Mortality: all cause<br><br>Mortality: cardiovascular<br><br>Morbidity<br>Fracture<br><br>Adverse outcome<br>Major hypoglycaemia: symptoms of severe impairment in consciousness or behaviour, need of external assistance, intervention to treat hypoglycaemia, and prompt recovery from acute symptoms after the intervention. |

**Study arms**

**Dapagliflozin (N = 2152)**
10 mg once daily

| | |
|---|---|
| Withdrawals | 8 |

| | |
|---|---|
| Loss to follow-up | 2 |
| % Female | 32.9 |
| Mean age (SD) | 61.8 years (12.1) |
| Condition specific characteristics | Baseline albuminuria<br>Median urinary albimun to creatinine ratio 965 mg/g (interquartile range 472, 1903)<br>% Diabetes<br>Type 2 diabetes 67.6%<br>eGFR<br>Mean 43.2 (SD 12.3) |

**Placebo (N = 2152)**
Matching placebo

| | |
|---|---|
| Withdrawals | 3 |
| Loss to follow-up | 2 |
| % Female | 33.3 |
| Mean age (SD) | 61.9 years (12.1) |
| Condition specific characteristics | Baseline albuminuria<br>Median urinary albimun to creatinine ratio 934 mg/g (interquartile range 482, 1868)<br>% Diabetes<br>Type 2 diabetes 67.4%<br>eGFR<br>Mean 43.0 (SD 12.4) |

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Low |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Low |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | Low |
| | Overall Directness | Directly applicable |

## Iino, 2003

**Bibliographic Reference**

Iino, Yasuhiko; Hayashi, Matsuhiko; Kawamura, Tetsuya; Shiigai, Tatsuo; Tomino, Yasuhiko; Yamada, Kenichi; Kitajima, Takeyuki; Ideura, Terukuni; Koyama, Akio; Sugisaki, Tetsuzo; Suzuki, Hiromichi; Umemura, Satoshi; Kawaguchi, Yoshindo; Uchida, Shunya; Kuwahara, Michio; Yamazaki, Tsutomu; Japanese Lasartan Therapy Intended for the Global Renal Protection in Hypertensive Patients (JLIGHT) Study, Investigators; Interim evidence of the renoprotective effect of the angiotensin II receptor antagonist losartan versus the calcium channel blocker amlodipine in patients with chronic kidney disease and hypertension: a report of the Japanese Losartan Therapy Intended for Global Renal Protection in Hypertensive Patients (JLIGHT) Study.; Clinical and experimental nephrology; 2003; vol. 7 (no. 3); 221-30

**Study details**

| | |
|---|---|
| **Study type** | Randomised controlled trial (RCT) |
| **Study location** | Japan |
| **Study setting** | Not reported |
| **Study dates** | 1999 - 2001 |
| **Duration of follow-up** | 12 months |
| **Sources of funding** | Not reported |
| **Inclusion criteria** | CKD<br>serum creatinine (SCr) levels ≥1.5 and <3.0 mg/dl in men of body weight (BW) 60 kg or more, and SCr ≥1.3 and < 3.0 mg/dl in females or males of BW less than 60 kg<br><br>Proteinuria<br>Urinary protein excretion ≥0.5 g/day<br><br>Age<br>20 to 75 years<br><br>Hypertension<br>systolic (SBP) and diastolic (DBP) blood pressures in a sitting position measured at least two times at their visits to clinics were SBP, 140 mmHg or more or DBP, 90 mmHg or more |
| **Exclusion criteria** | Other conditions<br>Diastolic blood pressure ≥120 mmHg; renovascular hypertension and endocrine hypertension; pregnancy, possibility of pregnancy, and in a period of lactation; patients that the chief investigator judged not to be eligible<br><br>Treatment<br>Blood pressure control treatment with antihypertensive agent(s); any patients in whom anti-anxiety drugs could not be discontinued |
| **Sample size** | 93 |

| | |
|---|---|
| **Interventions** | Blood pressure medication<br>Losartan vs Amlodipine<br><br>Additional notes<br>During the first 3 months, the effects of blood pressure were targeted at systolic blood pressure (SBP) less than 130 mmHg and diastolic blood pressure (DBP) less than 85 mmHg, and patients were not allowed combination therapy with any other antihypertensive agents. However, after 3 months, if the blood pressure did not reach SBP less than 130mmHg and DBP less than 85mmHg, antihypertensive combination therapy with α- blockers, beta-blockers, α/beta-blockers, diuretics (except for potassium-sparing diuretics), and other CCBs was considered to be adopted. Guidance was given to patients to maintain their usual diet, especially for those under dietary restrictions |
| **Outcome measures** | Reduction in proteinuria<br>Urinary protein excretion (g/day) at baseline, 3 months and percentage change at 3 months<br><br>Morbidity<br>transient ischemic attack |

**Study arms**

**Losartan (N = 47)**
25 mg as a starting dose, up to 100 mg once daily

| | |
|---|---|
| Loss to follow-up | 4 |
| % Female | 46.8 |
| Mean age (SD) | 56.0 (14.3) |
| Condition specific characteristics | Baseline proteinuria<br>Urinary protein excretion (g/day): mean 2.64 (SD 2.61) |

**Amlodipine (N = 46)**
2.5 mg as a starting dose, up to 5 mg once daily

| | |
|---|---|
| Loss to follow-up | 3 |

| | |
|---|---|
| % Female | 23.9 |
| Mean age (SD) | 57.4 (11.7) |
| Condition specific characteristics | Baseline proteinuria<br>Urinary protein excretion (g/day): mean 2.79 (SD 3.72) |

**Domain 1: Bias arising from the randomisation process**

*Risk of bias judgement for the randomisation process*

Some concerns

*(No information about randomisation method and allocation concealment)*

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

High

*(No information on the type of analysis (intention-to-treat or per-protocol analyses))*

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

High

*(No information about an appropriate analysis to estimate the effect of participants adherence)*

**Domain 3. Bias due to missing outcome data**

*Risk-of-bias judgement for missing outcome data*

Low

**Domain 4. Bias in measurement of the outcome**

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*Risk-of-bias judgement for selection of the reported result*

Some concerns

*(Protocol was not reported)*

**Overall bias and Directness**

*Risk of bias judgement*

High

*Overall Directness*

Directly applicable

## Kanjanabuch, 2009

| | |
|---|---|
| **Bibliographic Reference** | Kanjanabuch, T.; Sukhato, W.; Katavetin, P.; Prakash, S.; Pongpirul, K.; Tungsanga, K.; Eiam-Ong, S.; Beneficial effect of pioglitazone in proteinuric IgA nephropathy with concomitant ACEI/ARB treatment; Asian Biomedicine; 2009; vol. 3 (no. 6); 645-652 |

**Study details**

| | |
|---|---|
| **Study type** | Randomised controlled trial (RCT) |
| **Study location** | Thailand |
| **Study setting** | Nephrology clinic |
| **Study dates** | 2007 - 2008 |
| **Duration of follow-up** | 16 weeks |
| **Sources of funding** | A grant from the Korean Foundation for Advanced Studies Asia Research Centre, Chulalongkorn University |
| **Inclusion criteria** | CKD<br>Biopsy-proven immunoglobulin A nephropathy<br><br>Proteinuria<br>Urinary protein excretion ≥0.5 g/24 h despite receiving ACEI or ARB therapy<br><br>Other<br>At least 2 risk factors for progressive disease (male gender, blood pressure >150/90 mmHg, creatinine clearance 20 to 80 mL/min/1.73 m² and chronicity index >1 point) |
| **Exclusion criteria** | Treatment<br>Receiving immunosuppressive agents or steroid (>10 mg/day of prednisolone) |
| **Sample size** | 41 |
| **Interventions** | Diabetes medication<br>Pioglitazone<br><br>Placebo<br><br>Additional notes<br>During 1 month before allocation, blood pressure was controlled by ACEI or ARB the dose could be titrated up to the maximally recommended dose for hypertension; blood pressure target <140/90 mmHg; calcium channel blocker could be added to achieve target blood pressure |
| **Outcome measures** | Reduction in proteinuria<br>Urinary protein excretion (g/day) at baseline and 16 weeks |

**Study arms**

**Pioglitazone (N = 21)**
30 mg oral daily

| | |
|---|---|
| Loss to follow-up | Not reported |
| % Female | Reported as 7 males and 17 females but sample size was 21 |
| Mean age (SD) | 42.1 (13.6) |
| Condition specific characteristics | Baseline proteinuria<br>Proteinuria (g/day): geometric mean 2.1 (95% confidence interval [CI] 1.6, 2.6) |

**Placebo (N = 20)**

| | |
|---|---|
| Loss to follow-up | Not reported |
| % Female | 50.0 |
| Mean age (SD) | 41.4 (11.4) |
| Condition specific characteristics | Baseline proteinuria<br>Proteinuria (g/day): geometric mean 2.0 (95% CI 0.9, 3.1) |

**Domain 1: Bias arising from the randomisation process**

*Risk of bias judgement for the randomisation process*

Some concerns

*(No information about randomisation method and allocation concealment)*

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

High

*(No information on the type of analysis (intention-to-treat or per-protocol analyses))*

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

High

*(No information about an appropriate analysis to estimate the effect of participants adherence)*

**Domain 3. Bias due to missing outcome data**

*Risk-of-bias judgement for missing outcome data*

Low

**Domain 4. Bias in measurement of the outcome**

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*Risk-of-bias judgement for selection of the reported result*

Some concerns

*(Protocol was not reported)*

**Overall bias and Directness**

*Risk of bias judgement*

High

*Overall Directness*

Directly applicable

## Kanno, 2006

| | |
|---|---|
| **Bibliographic Reference** | Kanno, Yoshihiko; Takenaka, Tsuneo; Nakamura, Tsukasa; Suzuki, Hiromichi; Add-on angiotensin receptor blocker in patients who have proteinuric chronic kidney diseases and are treated with angiotensin-converting enzyme inhibitors.; Clinical journal of the American Society of Nephrology : CJASN; 2006; vol. 1 (no. 4); 730-7 |

**Study details**

| | |
|---|---|
| **Study type** | Randomised controlled trial (RCT) |
| **Study location** | Japan |
| **Study setting** | Not reported |
| **Study dates** | 1999 - 2002 |
| **Duration of follow-up** | 3 years |
| **Sources of funding** | Not reported |

| | |
|---|---|
| **Inclusion criteria** | CKD<br>chronic renal insufficiency<br><br>Proteinuria<br>urinary protein excretion of >1.0 g/day<br><br>Age<br>35 to 79 years<br><br>Hypertension<br>systolic blood pressure >130 and <180 mmHg, diastolic blood pressure >80 and <120 mmHg<br><br>Other<br>serum creatinine concentration of between 1.2 and 5.0 mg/dl |
| **Exclusion criteria** | Other conditions<br>secondary hypertension, including patients who were on dialysis therapy or receiving renal transplantation; patients who had chronic renal diseases and were receiving corticosteroid hormone; patients with myocardial infarction or stroke within the previous 6 mo or angina pectoris that required treatment with beta blockers or calcium channel blocker; and patients with heart failure or left ventricular ejection fraction of 40% or less or with a disorder that in the treating physician's opinion for other types of ARB |
| **Sample size** | 90 |
| **Interventions** | Blood pressure medication<br>Candesartan plus ACE Inhibitor vs ACE Inhibitors<br><br>Additional notes<br>Calcium channel antagonist, diuretics, beta blockers, and other antihypertensive agents were used when the blood pressure level was above the predetermined limit of systolic blood pressure of <130 mmHg and diastolic blood pressure <80 mmHg |
| **Outcome measures** | Reduction in proteinuria<br>Urinary protein excretion (g/day) at baseline and 3 years |

**Study arms**

| |
|---|
| **Candesartan plus ACE Inhibitor (N = 45)**<br>Candesartan 2 to 12 mg/d; ACE inhibitors: benazepril 2.5 to 10 mg/d or trandolapril 2 to 4 mg/d |

| | |
|---|---|
| Loss to follow-up | 8% |
| % Female | 60.0 |
| Mean age (SD) | 60.3 (11.9) |
| Condition specific characteristics | Baseline proteinuria<br>Urinary protein excretion (g/day): mean 1.78 (SD 0.10) |

**ACE Inhibitors (N = 45)**

ACE inhibitors: benazepril 2.5 to 10 mg/d or trandolapril 2 to 4 mg/d

| | |
|---|---|
| Loss to follow-up | 11% |
| % Female | 60.0 |
| Mean age (SD) | 59.9 (12.0) |
| Condition specific characteristics | Baseline proteinuria<br>Urinary protein excretion (g/day): mean 1.61 (SD 0.11) |

**Domain 1: Bias arising from the randomisation process**

*Risk of bias judgement for the randomisation process*

Some concerns

*(No information about randomisation method and allocation concealment)*

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

High

*(No information on the type of analysis (intention-to-treat or per-protocol analyses))*

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

High

*(No information about an appropriate analysis to estimate the effect of participants adherence)*

**Domain 3. Bias due to missing outcome data**

*Risk-of-bias judgement for missing outcome data*

Low

**Domain 4. Bias in measurement of the outcome**

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*Risk-of-bias judgement for selection of the reported result*

Some concerns

*(Protocol was not reported)*

**Overall bias and Directness**

*Risk of bias judgement*

High

*Overall Directness*

Directly applicable

## Krairittichai, 2009

| | |
|---|---|
| **Bibliographic Reference** | Krairittichai, Udom; Chaisuvannarat, Viranya; Effects of dual blockade of renin-angiotensin system in type 2 diabetes mellitus patients with diabetic nephropathy.; Journal of the Medical Association of Thailand = Chotmaihet thangphaet; 2009; vol. 92 (no. 5); 611-7 |

**Study details**

| | |
|---|---|
| **Study type** | Randomised controlled trial (RCT) |
| **Study location** | Thailand |
| **Study setting** | Outpatient department |
| **Study dates** | Not reported |
| **Duration of follow-up** | 24 weeks |
| **Sources of funding** | Rajavithi research fund, Rajavithi Hospital |
| **Inclusion criteria** | CKD<br>Diabetic nephropathy<br><br>Proteinuria<br>Urinary protein/creatinine ratio >0.5 (g/g)<br><br>Diabetes<br>Type 2 diabetes<br><br>Hypertension |

| | |
|---|---|
| | Treatment<br>maximal recommended dose of ACE inhibitor (Enalapril 40 mg daily) over three months<br><br>Other<br>absence of any other clinical or laboratory evidence of other kidney disease |
| **Exclusion criteria** | Age<br><18 years<br><br>Other conditions<br>serum potassium more than 5.5 mEq/l, systolic blood pressure less than 100 mmHg, GFR less than 15 ml/min/1.73 m², pregnancy, breast feeding and acute systemic diseases (for example active infection, malignancy or heart failure) |
| **Sample size** | 80 |
| **Interventions** | Blood pressure medication<br>Telmisartan vs Enalapril |
| **Outcome measures** | Reduction in proteinuria<br>Urinary protein/creatinine ratio (g/g) at baseline, 8, 12, and 24 weeks |

**Study arms**

**Telmisartan (N = 40)**
80 mg daily

| | |
|---|---|
| Loss to follow-up | Not reported |
| % Female | 58.14 |
| Mean age (SD) | 54.6 (12.0) |
| Condition specific characteristics | Baseline proteinuria<br>Urinary protein/creatinine ratio (g/g): mean 2.64 (SD 1.81) |

| | |
|---|---|
| | % Diabetes<br>100 (type 2 diabetes)<br><br>eGFR<br>mean 41.7 (SD 12.1) mL/min/1.73m² |

**Enalapril (N = 40)**
40 mg daily

| | |
|---|---|
| Loss to follow-up | Not reported |
| % Female | 41.8 |
| Mean age (SD) | 56.7 (14.0) |
| Condition specific characteristics | Baseline proteinuria<br>Urinary protein/creatinine ratio (g/g): mean 1.96 (SD 1.57)<br><br>% Diabetes<br>100 (type 2 diabetes)<br><br>eGFR<br>mean 50.8 (SD 29.4) mL/min/1.73m² |

**Domain 1: Bias arising from the randomisation process**

*Risk of bias judgement for the randomisation process*

Some concerns

*(No information about randomisation method and allocation concealment)*

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

High

*(No information on the type of analysis (intention-to-treat or per-protocol analyses))*

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

High

*(No information about an appropriate analysis to estimate the effect of participants adherence)*

**Domain 3. Bias due to missing outcome data**

*Risk-of-bias judgement for missing outcome data*

Low

**Domain 4. Bias in measurement of the outcome**

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*Risk-of-bias judgement for selection of the reported result*

Some concerns

*(Protocol was not reported)*

**Overall bias and Directness**

*Risk of bias judgement*

High

*Overall Directness*

Directly applicable

## Lee, 2011

| | |
|---|---|
| **Bibliographic Reference** | Lee, Yu-Ji; Cho, Seong; Kim, Sung Rok; Jang, Hye Ryoun; Lee, Jung Eun; Huh, Wooseong; Kim, Dae Joong; Oh, Ha Young; Kim, Yoon-Goo; Effect of losartan on proteinuria and urinary angiotensinogen excretion in non-diabetic patients with chronic kidney disease.; Postgraduate medical journal; 2011; vol. 87 (no. 1032); 664-9 |

**Study details**

| | |
|---|---|
| **Study type** | Randomised controlled trial (RCT) |
| **Study location** | Korea |
| **Study setting** | Medical centre |
| **Study dates** | 2005 - 2006 |
| **Duration of follow-up** | 24 months |
| **Sources of funding** | Merck & Co. |
| **Inclusion criteria** | CKD<br>Chronic non-diabetic CKD (renal biopsy proven or clinically diagnosed by patient's history, physical examination, serum biochemistry and persistent haematuria, dysmorphic red blood cells and proteinuria over 6 months)<br><br>Proteinuria<br>Persistent proteinuria (0.045 to 0.23 g/mmol (0.4 to 2.0 g/g)) in two or more random urinary protein to creatinine ratio measurements and eGFR >60 ml/min/1.73 m2<br><br>Age<br>20 to 65 years |

| | |
|---|---|
| **Exclusion criteria** | Diabetes<br>Evidence or suspicion of diabetes mellitus<br><br>Other conditions<br>History of myocardial infarction, unstable angina, percutaneous transluminal coronary angioplasty or coronary artery bypass graft surgery within the past 6 months; congestive heart failure, valvular heart disease, history of transient ischaemic attack, or cerebral vascular accident within the past 6 months; bilateral renal artery stenosis; single kidney; collagen vascular disease; active liver disease; severe pulmonary disease; pregnancy or breast feeding<br><br>Treatment<br>Hypersensitivity or intolerance to ARBs |
| **Interventions** | Blood pressure medication<br>Losartan vs control (usual antihypertensive therapy except ACE inhibitors and ARBs) |
| **Outcome measures** | Reduction in proteinuria<br><br>Reduction in albuminuria |

**Study arms**

**Losartan (N = 17)**
Losartan 50 mg/day, and the doses were titrated up to 100 mg/day after 6 weeks unless the patient was intolerant. Additional antihypertensive agents other than ACE inhibitors and ARBs (diuretics, b-blockers, calcium-channel blockers, or a-blockers) were prescribed to achieve the blood pressure goal of 140/90 mm Hg during the active treatment period.

| | |
|---|---|
| Withdrawals | None |
| Loss to follow-up | None |
| % Female | 70.5 |
| Mean age (SD) | 41.2 years (8.0) |

| | |
|---|---|
| Condition specific characteristics | Baseline proteinuria<br>Mean urinary protein to creatinine ratio 0.13 g/mmol (SD 0.04)<br><br>Baseline albuminuria<br>Mean urinary albumin to creatinine ratio 0.10 g/mmol (SD 0.05)<br><br>eGFR<br>Mean 80.4 (SD 17.1) |

**Control (N = 15)**

The control group continued to receive their usual antihypertensive therapy except ACE inhibitors and ARBs

| | |
|---|---|
| Withdrawals | None |
| Loss to follow-up | None |
| % Female | 46.6 |
| Mean age (SD) | 38.8 years (12.0) |
| Condition specific characteristics | Baseline proteinuria<br>Mean urinary protein to creatinine ratio 0.13 g/mmol (SD 0.04)<br><br>Baseline albuminuria<br>Mean urinary albumin to creatinine ratio 0.10 g/mmol (SD 0.05)<br><br>eGFR<br>Mean 87.9 (SD 22.3) |

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | Some concerns<br>*(No information was given on whether allocation sequence was concealed until participants were enrolled and assigned to interventions)* |
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Some concerns<br>*(Both researchers and participants knew which intervention was given)* |
| Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) | Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention) | Some concerns<br>*(No information was reported about adherence to interventions or about the percentage of participants receiving additional antihypertensives)* |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | Low |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Low |
| Overall bias and Directness | Risk of bias judgement | High |
| | Overall Directness | Directly applicable |

**Leehey, 2016**

| | |
|---|---|
| **Bibliographic Reference** | Leehey, David J; Collins, Eileen; Kramer, Holly J; Cooper, Cheryl; Butler, Jolene; McBurney, Conor; Jelinek, Christine; Reda, Domenic; Edwards, Lonnie; Garabedian, Anne; O''Connell, Susan; Structured Exercise in Obese Diabetic Patients with Chronic Kidney Disease: A Randomized Controlled Trial.; American journal of nephrology; 2016; vol. 44 (no. 1); 54-62 |

**Study details**

| | |
|---|---|
| **Study type** | Randomised controlled trial (RCT) |
| **Study location** | US |
| **Study setting** | Veterans Affairs Medical Center |
| **Study dates** | Not reported |
| **Duration of follow-up** | 52 weeks |
| **Sources of funding** | Department of Veterans Affairs |
| **Inclusion criteria** | CKD<br>CKD stages 2–4 (eGFR 15 to 90 ml/min/ 1.73 m²)<br><br>Proteinuria<br>Urinary protein/creatinine ratio >200 mg/g for at least 3 months<br><br>Diabetes<br>Type 2 diabetes<br><br>Other<br>Body mass index >30 kg/m² |
| **Exclusion criteria** | Other conditions<br>cardiovascular disease precluding participation in an exercise program, moderate to severe congestive heart failure (NYHA class III–IV), moderate to severe chronic obstructive pulmonary disease, history of cerebrovascular accident with cognitive impairment, presence of a renal transplant, or inability to walk on a treadmill |

| | |
|---|---|
| **Sample size** | 36 |
| **Interventions** | Weight loss/Exercise<br>Exercise plus Diet<br><br>Dietary interventions (NaCl, protein)<br>Diet alone |
| **Outcome measures** | Reduction in proteinuria<br>Urinary protein/creatinine ratio reported as median and interquartile range<br><br>Reduction in albuminuria<br>Urinary albumin/creatinine ratio reported as median and interquartile range<br><br>Health-related quality of life<br>Center for Epidemiologic Studies Depression Scale and Medical Outcomes Study SF-36 Health Survey (physical component summary and mental component summary) reported at baseline, 12 and 52 weeks |

**Study arms**

**Exercise plus Diet (N = 18)**
In addition to nutritional counseling, patients underwent a supervised exercise program

| | |
|---|---|
| Loss to follow-up | 4 |
| % Female | 0 |
| Mean age (SD) | 65.4 (8.7) |
| Condition specific characteristics | Baseline proteinuria<br>Urinary protein/creatinine ratio (mg/g): median 625 (interquartile range 275, 1619)<br><br>Baseline albuminuria<br>Urinary albumin/creatinine ratio (mg/g): median 329 (interquartile range 94, 1307)<br><br>% Diabetes |

| | |
|---|---|
| | 100 (type 2 diabetes)<br><br>eGFR<br>mean 40.9 (SD 18.1) mL/min/1.73m² |

**Diet-Alone (N = 18)**
A nutritional counseling session at baseline with 9 follow-up telephone calls during the study

| | |
|---|---|
| Loss to follow-up | 0 |
| % Female | 0 |
| Mean age (SD) | 66.6 (7.5) |
| Condition specific characteristics | Baseline proteinuria<br>Urinary protein/creatinine ratio (mg/g): median 626 (interquartile range 414, 1563)<br><br>Baseline albuminuria<br>Urinary albumin/creatinine ratio (mg/g): median 428 (interquartile range 161, 1191)<br><br>% Diabetes<br>100 (type 2 diabetes)<br><br>eGFR<br>mean 38.9 (SD 20.3) mL/min/1.73m² |

**Domain 1: Bias arising from the randomisation process**

*Risk of bias judgement for the randomisation process*

Some concerns

*(No information about allocation concealment)*

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

High

*(No information on the type of analysis (intention-to-treat or per-protocol analyses))*

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

High

*(No information about an appropriate analysis to estimate the effect of participants adherence)*

**Domain 3. Bias due to missing outcome data**

*Risk-of-bias judgement for missing outcome data*

Low

**Domain 4. Bias in measurement of the outcome**

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*Risk-of-bias judgement for selection of the reported result*

Low

**Overall bias and Directness**

*Risk of bias judgement*

High

*Overall Directness*

Directly applicable

## Leehey, 2009

| | |
|---|---|
| **Bibliographic Reference** | Leehey, David J; Moinuddin, Irfan; Bast, Joseph P; Qureshi, Shahzad; Jelinek, Christine S; Cooper, Cheryl; Edwards, Lonnie C; Smith, Bridget M; Collins, Eileen G; Aerobic exercise in obese diabetic patients with chronic kidney disease: a randomized and controlled pilot study.; Cardiovascular diabetology; 2009; vol. 8; 62 |

**Study details**

| | |
|---|---|
| **Study type** | Randomised controlled trial (RCT) |
| **Study location** | US |
| **Study setting** | Renal outpatient clinic of VA Hospital |
| **Study dates** | Not reported |
| **Duration of follow-up** | 24 weeks |
| **Sources of funding** | Not reported |
| **Inclusion criteria** | CKD<br>stage 2-4 CKD (eGFR 15-90 mL/min/1.73 m²)<br><br>Proteinuria<br>Urinary protein/creatinine ratio (mg/g) >200 for ≥3 months<br><br>Diabetes<br>Type 2 diabetes<br><br>Treatment<br>ACE inhibitor or ARB, aspirin, and statin (if LDL >100) |

| | |
|---|---|
| | Other<br>obesity (body mass index >30 kg/m²) |
| **Exclusion criteria** | Other conditions<br>CKD stages other than 2-4; hyperparathyroidism/osteoporosis; symptomatic neuropathy/retinopathy; positive stress test due to coronary arterial disease; symptomatic cardiovascular disease; congestive heart failure (New York Heart Association Class III or IV); chronic obstructive pulmonary disease; (FEV1 < 50% predicted and/or requires supplemental oxygen support during exercise); complaints of angina during the stress test; cerebrovascular disease/cognitive impairment; renal transplant; inability to walk on the treadmill; any unforeseen illness or disability that would preclude exercise testing or training; participation in a formal exercise program within the previous 12 weeks |
| **Sample size** | 13 |
| **% Female** | 0 |
| **Mean age (SD)** | 66 (range 55 to 81) |
| **Interventions** | Weight loss/Exercise<br>Exercise<br><br>No intervention |
| **Outcome measures** | Reduction in proteinuria<br>Urinary protein/creatinine ratio (mg/g) and urinary protein excretion (mg/24 h) at baseline, 6 and 24 weeks<br><br>Reduction in albuminuria<br>Urinary albumin/creatinine ratio (mg/g) at baseline, 6 and 24 weeks |

**Study arms**

**Exercise (N = 7)**
Patients received instruction about walking and proper walking shoe selection

| | |
|---|---|
| Loss to follow-up | 0 |
| Condition specific characteristics | Baseline proteinuria<br>Urinary protein/creatinine ratio (mg/g): mean 565 (SD 600); Urinary protein excretion (mg/24 h): mean 1020 (SD 1081) |

| | |
|---|---|
| | Baseline albuminuria<br>Urinary albumin/creatinine ratio (mg/g): mean 327 (SD 385)<br><br>% Diabetes<br>100 (type 2 diabetes)<br><br>eGFR<br>mean 44 (SD 36) mL/min/1.73m² |

**Control (N = 6)**
Patients did not participate in any exercise training

| | |
|---|---|
| Loss to follow-up | 2 |
| Condition specific characteristics | Baseline proteinuria<br>Urinary protein/creatinine ratio (mg/g): mean 347 (SD 178); Urinary protein excretion (mg/24 h): mean 542 (SD 258)<br><br>Baseline albuminuria<br>Urinary albumin/creatinine ratio (mg/g): mean 156 (SD 148)<br><br>% Diabetes<br>100 (type 2 diabetes)<br><br>eGFR<br>mean 47 (SD 9.5) mL/min/1.73m² |

**Domain 1: Bias arising from the randomisation process**

*Risk of bias judgement for the randomisation process*

Some concerns

*(No information about randomisation method and allocation concealment)*

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

High

*(No information on the type of analysis (intention-to-treat or per-protocol analyses))*

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

High

*(No information about blinding, adherence or analysis to estimate adherence)*

**Domain 3. Bias due to missing outcome data**

*Risk-of-bias judgement for missing outcome data*

High

*(100% (exercise) and 66.6% (control) of available data)*

**Domain 4. Bias in measurement of the outcome**

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*Risk-of-bias judgement for selection of the reported result*

Some concerns

*(Protocol was not reported)*

**Overall bias and Directness**

*Risk of bias judgement*

High

*Overall Directness*

Directly applicable

## Lewis, 1993

| | |
|---|---|
| **Bibliographic Reference** | Lewis, Edmund J.; Hunsicker, Lawrence G.; Bain, Raymond P.; Rohde, Richard D; The Effect of Angiotensin-Converting-Enzyme Inhibition on Diabetic Nephropathy; New England Journal of Medicine; 1993; vol. 329 (no. 20); 1456-1462 |

**Study details**

| | |
|---|---|
| **Study type** | Randomised controlled trial (RCT) |
| **Study location** | US |
| **Study setting** | 30 clinical centres |
| **Study dates** | 1987 - 1990 |
| **Duration of follow-up** | 3 years |
| **Sources of funding** | Grants by the Public Health Services and by the Bristol-Myers Squibb Pharmaceutical Research Institute |
| **Inclusion criteria** | CKD<br>Diabetic nephropathy<br><br>Proteinuria<br>Urinary protein excretion ≥500 mg/24 h |

| | |
|---|---|
| | Age<br>18 to 49 years<br><br>Diabetes<br>Insulin-dependent diabetes mellitus for at least 7 years, with an onset before the age of 30 years<br><br>Other<br>Diabetic retinopathy, serum creatinine concentration ≤2.5 mg/dL (221 mmol/l) |
| **Exclusion criteria** | Other conditions<br>Pregnancy, a dietary evaluation that indicated marked departure from standard dietary recommendations, white-cell count <2500 per cubic millilitre congestive heart failure (New York Heart Association class III or worse), and a serum potassium concentration ≥6 mmol/l |
| **Sample size** | 409 |
| **Interventions** | Blood pressure medication<br>Captopril<br><br>Placebo<br><br>Additional notes<br>Therapy with an angiotensin-converting-enzyme inhibitor, other than the coded medication, and calcium antagonists was not allowed during the trial |
| **Outcome measures** | Reduction in proteinuria<br>Reduction in proteinuria was only reported for the captopril arm<br><br>CKD progression: occurrence of end stage kidney disease<br>Dialysis or transplantation<br><br>Mortality: all cause |

**Study arms**

| |
|---|
| **Captopril (N = 207)**<br>25 mg 3 times daily |

| | |
|---|---|
| Loss to follow-up | 27 |
| % Female | 38 |
| Mean age (SD) | 35 (7) |
| Condition specific characteristics | Baseline proteinuria<br>Urinary protein excretion (mg/day): mean 2500 (SD 2500)<br><br>% Diabetes<br>100 (type 1 diabetes) |

**Placebo (N = 202)**
Identical-appearing placebo tablets 3 times daily

| | |
|---|---|
| Loss to follow-up | 31 |
| % Female | 36 |
| Mean age (SD) | 34 (8) |
| Condition specific characteristics | Baseline proteinuria<br>Urinary protein excretion (mg/day): mean 3000 (SD 2600)<br><br>% Diabetes<br>100 (type 1 diabetes) |

**Domain 1: Bias arising from the randomisation process**

*Risk of bias judgement for the randomisation process*

Some concerns

*(No information about allocation concealment)*

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

High

*(No information on the type of analysis (intention-to-treat or per-protocol analyses))*

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

Low

**Domain 3. Bias due to missing outcome data**

*Risk-of-bias judgement for missing outcome data*

Low

**Domain 4. Bias in measurement of the outcome**

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*Risk-of-bias judgement for selection of the reported result*

Some concerns

*(Protocol was not reported)*

**Overall bias and Directness**

*Risk of bias judgement*

High

*Overall Directness*

Directly applicable

## Lewis, 2001

| | |
|---|---|
| **Bibliographic Reference** | Lewis, Edmund J.; Hunsicker, Lawrence G.; Clarke, William R.; Berl, Tomas; Pohl, Marc A.; Lewis, Julia B.; Ritz, Eberhard; Atkins, Robert C.; Rohde, Richard; Raz, Itamar; Renoprotective Effect of the Angiotensin-Receptor Antagonist Irbesartan in Patients with Nephropathy Due to Type 2 Diabetes; New England Journal of Medicine; 2001; vol. 345 (no. 12); 851-860 |

**Study details**

| | |
|---|---|
| **Study type** | Randomised controlled trial (RCT) |
| **Study location** | Multicentre |
| **Study setting** | 210 clinical centres |
| **Study dates** | 1996 - 1999 |
| **Duration of follow-up** | 2 years |
| **Sources of funding** | Bristol-Myers Squibb Institute for Medical Research and Sanofi–Synthelabo |
| **Inclusion criteria** | CKD<br>Diabetic nephropathy<br><br>Proteinuria |

| | |
|---|---|
| | Urinary protein excretion at least 900 mg/24 h<br><br>Age<br>30 to 70 years<br><br>Diabetes<br>Documented diagnosis of type 2 diabetes mellitus<br><br>Hypertension<br>a systolic blood pressure of more than 135 mm Hg while sitting, a diastolic blood pressure of more than 85 mm Hg while sitting, or documented treatment with antihypertensive agents<br><br>Other<br>serum creatinine concentration was required to be between 1.0 and 3.0 mg per deciliter (88 and 265 µmol per liter) in women and 1.2 and 3.0 mg per deciliter (106 and 265 µmol per liter) in men |
| **Sample size** | 1715 |
| **Interventions** | Blood pressure medication<br>Irbesartan vs amlodipine<br><br>Placebo<br><br>Additional notes<br>Antihypertensive agents other than ACE inhibitors, angiotensin-receptor blockers, and calciumchannel blockers were used as needed in each group, and the target blood pressure for all patients was the same (a systolic blood pressure of 135 mm Hg or less, or 10 mm Hg lower than the value at screening if that value was more than 145 mm Hg, and a diastolic blood pressure of 85 mm Hg or less) |
| **Outcome measures** | Reduction in proteinuria<br>Percentage reduction in proteinuria (g/24 h)<br><br>CKD progression: occurrence of end stage kidney disease<br>indicated by the initiation of dialysis, renal transplantation, or a serum creatinine concentration of at least 6.0 mg per deciliter (530 µmol per liter)<br><br>Mortality: all cause |

**Study arms**

| |
|---|
| **Irbesartan (N = 579)** |

| | |
|---|---|
| dose titrated from 75 to 300 mg per day | |
| Loss to follow-up | 5 |
| % Female | 35 |
| Mean age (SD) | 59.3 (7.1) |
| Condition specific characteristics | Baseline proteinuria<br>Urinary protein excretion (g/24 h): median 2.9 (interquartile range 1.6, 5.4)<br>Baseline albuminuria<br>Urinary albumin excretion (g/24 h): median 1.9 (interquartile range 1.0, 3.8)<br>% Diabetes<br>100 (type 2 diabetes) |
| **Amlodipine (N = 567)** | |
| dose titrated from 2.5 to 10 mg per day | |
| Loss to follow-up | 2 |
| % Female | 37 |
| Mean age (SD) | 59.1 (7.9) |
| Condition specific characteristics | Baseline proteinuria<br>Urinary protein excretion (g/24 h): median 2.9 (interquartile range 1.6, 5.2)<br>Baseline albuminuria<br>Urinary albumin excretion (g/24 h): median 1.9 (interquartile range 1.0, 3.5)<br>% Diabetes<br>100 (type 2 diabetes) |
| **Placebo (N = 569)** | |

| | |
|---|---|
| Loss to follow-up | 4 |
| % Female | 29 |
| Mean age (SD) | 58.3 (8.2) |
| Condition specific characteristics | Baseline proteinuria<br>Urinary protein excretion (g/24 h): median 2.9 (interquartile range 1.8, 5.2)<br><br>Baseline albuminuria<br>Urinary albumin excretion (g/24 h): median 1.9 (interquartile range 1.1, 3.5)<br><br>% Diabetes<br>100 (type 2 diabetes) |

**Domain 1: Bias arising from the randomisation process**

*Risk of bias judgement for the randomisation process*

Some concerns

*(No information about randomisation method and allocation concealment)*

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

Low

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

Low

**Domain 3. Bias due to missing outcome data**

*Risk-of-bias judgement for missing outcome data*

Low

**Domain 4. Bias in measurement of the outcome**

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*Risk-of-bias judgement for selection of the reported result*

Low

**Overall bias and Directness**

*Risk of bias judgement*

Some concerns

*Overall Directness*

Directly applicable

## Li, 2006

| | |
|---|---|
| **Bibliographic Reference** | Li, Philip Kam-Tao; Leung, Chi Bon; Chow, Kai Ming; Cheng, Yuk Lun; Fung, Samuel Ka-Shun; Mak, Siu Ka; Tang, Anthony Wing-Chung; Wong, Teresa Yuk-Hwa; Yung, Chun Yu; Yung, Jonathan Chee-Unn; Yu, Alex Wai-Yin; Szeto, Cheuk Chun; HKVIN Study, Group; Hong Kong study using valsartan in IgA nephropathy (HKVIN): a double-blind, randomized, placebo-controlled study.; American journal of kidney diseases : the official journal of the National Kidney Foundation; 2006; vol. 47 (no. 5); 751-60 |

**Study details**

| | |
|---|---|
| **Study type** | Randomised controlled trial (RCT) |
| **Study location** | Hong Kong |
| **Study setting** | 6 centres |
| **Study dates** | 2000 - 2003 |
| **Duration of follow-up** | 104 weeks |
| **Sources of funding** | Novartis Pharmaceuticals (Hong Kong) Ltd provided the study medication and placebo and the cost for administrative support |
| **Inclusion criteria** | CKD<br>Biopsy-confirmed immunoglobulin A nephropathy (defined using standard morphological and immunohistochemical criteria)<br><br>Proteinuria<br>Urinary protein excretion at least 1 g/day<br><br>Age<br>at least 18 years<br><br>Other<br>serum creatinine level less than 2.8 mg/dL (<250 mmol/L), or serum creatinine level between 1.4 and 2.8 mg/dL (120 and 250 mmol/L) irrespective of the magnitude of proteinuria |
| **Exclusion criteria** | Other conditions<br>accelerated or malignant hypertension; expected survival less than 2 years; secondary IgA nephropathy, including Henoch-Schönlein purpura; pregnant or lactating women; clinically significant hepatic disease; known allergy or reactions to ARBs<br><br>Treatment<br>recent treatment (within 4 weeks of enrollment) with ACE inhibitors or ARBs |
| **Sample size** | 109 |
| **Interventions** | Blood pressure medication<br>Valsartan<br><br>Placebo |

| | |
|---|---|
| | Additional notes<br>After randomization, patients' usual antihypertensive medications were continued. Target blood pressure control was set at less than 140/90 mm Hg. If target blood pressure was not achieved after a 4-week treatment period, the study medication dosage was doubled (valsartan, 160 mg/d, or equivalent placebo). Additional new antihypertensive medications (beta-blocker, calcium channel blocker, or thiazide diuretics, followed by any appropriate additional agent if blood pressure remained high) were allowed after 8 weeks at the discretion of the attending physicians |
| **Outcome measures** | Reduction in proteinuria<br>Urinary protein excretion (g/day) at baseline, 12, 24, 52, 76 and 104 weeks, absolute changes and percentage of change<br><br>Morbidity<br>Heart failure |

**Study arms**

**Valsartan (N = 54)**
80 mg/d

| | |
|---|---|
| Loss to follow-up | 5 |
| % Female | 75.9 |
| Mean age (SD) | 40 (10) |
| Condition specific characteristics | Baseline proteinuria<br>Urinary protein excretion (g/day): mean 1.8 (SD 1.2)<br><br>eGFR<br>mean 87 (SD 36) mL/min/1.73m² |

**Placebo (N = 55)**
Identical appearance, packaging, and labeling to active medication

| | |
|---|---|
| Loss to follow-up | 8 |

| | |
|---|---|
| % Female | 69.0 |
| Mean age (SD) | 41 (9) |
| Condition specific characteristics | Baseline proteinuria<br>Urinary protein excretion (g/day): mean 2.3 (SD 1.7)<br><br>eGFR<br>mean 78 (SD 38) mL/min/1.73m² |

**Domain 1: Bias arising from the randomisation process**

*Risk of bias judgement for the randomisation process*

Low

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

High

*(No information on the type of analysis (intention-to-treat or per-protocol analyses))*

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

High

*(No information on the type of analysis (intention-to-treat or per-protocol analyses))*

**Domain 3. Bias due to missing outcome data**

*Risk-of-bias judgement for missing outcome data*

Low

**Domain 4. Bias in measurement of the outcome**

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*Risk-of-bias judgement for selection of the reported result*

Some concerns

*(Protocol was not reported)*

**Overall bias and Directness**

*Risk of bias judgement*

High

*Overall Directness*

Directly applicable

## Luño, 2002

| | |
|---|---|
| **Bibliographic Reference** | Luño, José; Barrio, Vicente; Goicoechea, Maria Ángeles; González, Cesar; De Vinuesa, Soledad García; Gómez, Francisco; Bernis, Carmen; Espinosa, Mario; Ahijado, Francisco; Gómez, José; Escalada, Pedro; Effects of dual blockade of the renin-angiotensin system in primary proteinuric nephropathies; Kidney International; 2002; vol. 62; 47-s52 |

**Study details**

| | |
|---|---|
| **Study type** | Randomised controlled trial (RCT) |
| **Study location** | Spain |
| **Study setting** | 7 centres |
| **Study dates** | 2000 - 2001 |
| **Duration of follow-up** | 24 weeks |
| **Sources of funding** | Astra Zeneca Farmaceutica Espana SA |
| **Inclusion criteria** | CKD<br>eGFR >50 mL/min/1.73m²<br><br>Proteinuria<br>Urinary protein excretion >2 g/24 h in at least 2 collections<br><br>Age<br>18 to 80 years<br><br>Other<br>Women of childbearing age were included only after a negative gestation test and if they were using an effective method of birth control |
| **Exclusion criteria** | Diabetes<br><br>Other conditions<br>Nephrotic patients with serum albumin <3.0 g/dL as well as those with hypertension stage 3 (systolic blood pressure ≥180mmHg and/or diastolic blood pressure ≥110 mmHg), hyperkalemia (>5.0 mmol/L), secondary glomerular diseases, systemic diseases (amyloidosis, systemic lupus erythematosus), or those with any severe cardiovascular event in the last three months before randomisation, patients with severe cardiac, pulmonary or hepatic disease, HIV infection, and neoplasia<br><br>Treatment<br>corticosteroids and/or immunosuppressive therapy in the last six months before entry into the study |
| **Sample size** | 46 |
| **Interventions** | Blood pressure medication |

| | |
|---|---|
| | Candesartan vs Lisinopril vs Candesartan plus Lisinopril<br><br>Additional notes<br>Additional antihypertensive medication, such as beta-blockers, calcium channel blockers and/or thiazide diuretics alone or in combination were subsequently introduced from weeks 6 to 12 in order to achieve blood pressure goal, that is, blood pressure <125/75 mm Hg in all groups |
| **Outcome measures** | Reduction in proteinuria<br>Urinary protein/creatinine ratio (g/g) at baseline, 2, 3, and 6 months and percentage reduction |

**Study arms**

**Candesartan (N = 15)**
starting dose 8 mg once daily; if either systolic blood pressure was >125 mm Hg or diastolic >75mmHg dose was doubled every two weeks up to 32 mg once daily

| | |
|---|---|
| Loss to follow-up | None |
| % Female | 33.3 |
| Mean age (SD) | 45 (18) |
| Condition specific characteristics | Baseline proteinuria<br>Urinary protein/creatinine ratio (g/g): mean 4.0 (SD 2.5) |

**Lisinopril (N = 14)**
starting dose 10 mg once daily; if either systolic blood pressure was >125 mm Hg or diastolic >75mmHg dose was doubled every two weeks up to 40 mg once daily

| | |
|---|---|
| Loss to follow-up | None |
| % Female | 14.2 |
| Mean age (SD) | 50 (16) |

| | |
|---|---|
| Condition specific characteristics | Baseline proteinuria<br>Urinary protein/creatinine ratio (g/g): mean 3.6 (SD 2.9) |

**Candesartan plus Lisinopril (N = 16)**
starting dose candesartan 4 mg and lisinopril 5 mg once daily; if either systolic blood pressure was >125 mm Hg or diastolic >75mmHg dose was doubled every two weeks up to candesartan 16 mg and lisinopril 20 mg once daily

| | |
|---|---|
| Loss to follow-up | None |
| % Female | 43.7 |
| Mean age (SD) | 42 (13) |
| Condition specific characteristics | Baseline proteinuria<br>Urinary protein/creatinine ratio (g/g): mean 3.8 (SD 2.1) |

**Domain 1: Bias arising from the randomisation process**

*Risk of bias judgement for the randomisation process*

Low

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

Some concerns

*(No information about deviations because of the experimental context)*

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

Some concerns

*(No information about percentage of important co-interventions across arms)*

**Domain 3. Bias due to missing outcome data**

*Risk-of-bias judgement for missing outcome data*

Low

**Domain 4. Bias in measurement of the outcome**

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*Risk-of-bias judgement for selection of the reported result*

Some concerns

*(Protocol was not reported)*

**Overall bias and Directness**

*Risk of bias judgement*

Some concerns

*Overall Directness*

Directly applicable

## Matsuda, 2003

| | |
|---|---|
| **Bibliographic Reference** | Matsuda, H; Hayashi, K; Saruta, T; Distinct time courses of renal protective action of angiotensin receptor antagonists and ACE inhibitors in chronic renal disease.; Journal of human hypertension; 2003; vol. 17 (no. 4); 271-6 |

**Study details**

| | |
|---|---|
| **Study type** | Randomised controlled trial (RCT) |
| **Study location** | Japan |
| **Study setting** | Outpatients |
| **Study dates** | 1998 - 1999 |
| **Duration of follow-up** | 48 weeks |
| **Sources of funding** | Not reported |
| **Inclusion criteria** | CKD<br>Immunoglobulin A nephropathy (n=8); membranous nephropathy (n=5); focal segmental glomerulosclerosis (n=1); and proliferative glomerulonephritis (n=38)<br><br>Proteinuria<br>Urinary protein excretion >0.3 g/24 h<br><br>Hypertension<br>>140 and/or 90 mmHg<br><br>Other<br>Serum creatinine level <265 mmol/l or creatinine clearance >30 ml/min/1.72m². The patients had been educated on dietary therapy including low protein (0.8 g/kg/day) and low sodium intake (7 g/day) at least 3 months before the enrolment of this study |
| **Exclusion criteria** | Other conditions<br>Diabetic nephropathy, polycystic kidney disease, and chronic pyelonephritis |

| | |
|---|---|
| **Sample size** | 52 |
| **Interventions** | Blood pressure medication<br>ACE-I vs ARB<br><br>Additional notes<br>Patients were further divided into two subgroups according to the level of proteinuria; patients with mild proteinuria <1.0 g/ day were assigned to ACE-I-L and ARB-L groups, and those with moderate proteinuria >1.0 g/day were allocated to ACE-I-H and ARB-H groups |
| **Outcome measures** | Reduction in proteinuria<br>Urinary protein excretion at baseline, 12 and 48 weeks and percentage reduction |

**Study arms**

**ACE-I (N = 27)**
either perindopril (2 mg/day) or trandolapril (1 mg/day) was started, and the doses were titrated to achieve systemic blood pressure to <135/85mmHg

| | |
|---|---|
| Loss to follow-up | Not reported |
| % Female | ACE-I-L 61.5<br>ACE-I-H 35.7 |
| Mean age (SD) | ACE-I-L 50 (3)<br>ACE-I-H 50 (4) |
| Condition specific characteristics | Baseline proteinuria<br>ACE-I-L: Urinary protein excretion (g/day): mean 0.5 (SD 0.1, range 0.4, 0.9). ACE-I-H: Urinary protein excretion (g/day): mean 2.6 (SD 0.5, range 1.1, 5.9) |

**ARB (N = 25)**
either 25mg losartan or 4mg candesartan cilexetil were initially prescribed and the doses were adjusted according to the level of the blood pressure or renal haemodynamics

| | |
|---|---|
| Loss to follow-up | Not reported |
| % Female | ARB-L 53.8<br>ARB-H 33.3 |
| Mean age (SD) | ARB-L 55 (2)<br>ARB-H 53 (4) |
| Condition specific characteristics | Baseline proteinuria<br>ARB-L: Urinary protein excretion (g/day): mean 0.5 (SD 0.1, range 0.4, 0.9). ARB-H: Urinary protein excretion (g/day): mean 2.7 (SD 0.4, range 1.1, 6.9) |

**Domain 1: Bias arising from the randomisation process**

*Risk of bias judgement for the randomisation process*

Some concerns

*(No information about randomisation method and allocation concealment)*

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

High

*(No information on the type of analysis (intention-to-treat or per-protocol analyses))*

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

High

*(No information about an appropriate analysis to estimate the effect of participants adherence)*

**Domain 3. Bias due to missing outcome data**

*Risk-of-bias judgement for missing outcome data*

Low

**Domain 4. Bias in measurement of the outcome**

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*Risk-of-bias judgement for selection of the reported result*

Some concerns

*(Protocol was not reported)*

**Overall bias and Directness**

*Risk of bias judgement*

High

*Overall Directness*

Directly applicable

## Matsuda, 2003

| | |
|---|---|
| **Bibliographic Reference** | Matsuda, Hiroto; Hayashi, Koichi; Homma, Koichiro; Yoshioka, Kyoko; Kanda, Takeshi; Takamatsu, Ichiro; Tatematsu, Satoru; Wakino, Shu; Saruta, Takao; Differing anti-proteinuric action of candesartan and losartan in chronic renal disease.; Hypertension research : official journal of the Japanese Society of Hypertension; 2003; vol. 26 (no. 11); 875-80 |

**Study details**

| | |
|---|---|
| **Study type** | Randomised controlled trial (RCT) |
| **Study location** | Japan |
| **Study setting** | Not reported |
| **Study dates** | Not reported |
| **Duration of follow-up** | 96 weeks |
| **Sources of funding** | Not reported |
| **Inclusion criteria** | CKD<br>Underlying renal diseases: proliferative glomerulonephritis (n＝58), membranous nephropathy (n＝ 2), or focal segmental glomerulosclerosis (n＝2)<br><br>Proteinuria<br>Urinary protein excretion >0.5 g/day<br><br>Hypertension<br>＞140 and/or 90 mmHg<br><br>Other<br>Serum creatinine level ＜265 μmol/l or creatinine clearance ＞30 ml/min/1.72m² |
| **Exclusion criteria** | Other conditions<br>diabetic nephropathy, polycystic kidney disease, or chronic pyelonephritis |
| **Sample size** | 62 |
| **Interventions** | Blood pressure medication<br>Perindopril vs Trandolapril vs Candesartan vs Losartan<br><br>Additional notes |

| | |
|---|---|
| | Patients had been educated on dietary therapy, including the importance of low protein (0.8 g/kg/day) and low sodium intake (7 g/day) for at least 3 months before entry into this study; 14 patients had received antiplatelet therapy (dipyridamole or dilazep dihydrochloride), and these drugs were continued throughout the protocol |
| **Outcome measures** | Reduction in proteinuria<br>Urinary protein excretion (g/day) at baseline and 12 weeks and percentage change at 12 and 96 weeks |

**Study arms**

**Perindopril (N = 15)**

2 mg/day; doses were titrated to achieve systemic blood pressure of less than 135/85 mmHg

| | |
|---|---|
| Loss to follow-up | Not reported |
| % Female | 46.6 |
| Mean age (SD) | 51 (4) |
| Condition specific characteristics | Baseline proteinuria<br>Urinary protein excretion (g/day): mean 2.7 (SD 0.5) |

**Trandolapril (N = 15)**

0.5 mg/day; doses were titrated to achieve systemic blood pressure of less than 135/85 mmHg

| | |
|---|---|
| Loss to follow-up | Not reported |
| % Female | 40.0 |
| Mean age (SD) | 50 (5) |
| Condition specific characteristics | Baseline proteinuria<br>Urinary protein excretion (g/day): mean 2.7 (SD 0.5) |

**Candesartan (N = 17)**
4 mg/day; doses were titrated to achieve systemic blood pressure of less than 135/85 mmHg

| | |
|---|---|
| Loss to follow-up | Not reported |
| % Female | 47.0 |
| Mean age (SD) | 58 (5) |
| Condition specific characteristics | Baseline proteinuria<br>Urinary protein excretion (g/day): mean 3.0 (SD 0.6) |

**Losartan (N = 15)**
25 mg/day; doses were titrated to achieve systemic blood pressure of less than 135/85 mmHg

| | |
|---|---|
| Loss to follow-up | Not reported |
| % Female | 53.3 |
| Mean age (SD) | 51 (3) |
| Condition specific characteristics | Baseline proteinuria<br>Urinary protein excretion (g/day): mean 2.5 (SD 0.4) |

**Domain 1: Bias arising from the randomisation process**

*Risk of bias judgement for the randomisation process*

Some concerns

*(No information about randomisation method and allocation concealment)*

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

High

*(No information on the type of analysis (intention-to-treat or per-protocol analyses))*

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

High

*(No information about an appropriate analysis to estimate the effect of participants adherence)*

**Domain 3. Bias due to missing outcome data**

*Risk-of-bias judgement for missing outcome data*

Low

**Domain 4. Bias in measurement of the outcome**

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*Risk-of-bias judgement for selection of the reported result*

Some concerns

*(Protocol was not reported)*

**Overall bias and Directness**

*Risk of bias judgement*

High

*Overall Directness*

Directly applicable

## Mehdi, 2009

| | |
|---|---|
| **Bibliographic Reference** | Mehdi, Uzma F; Adams-Huet, Beverley; Raskin, Philip; Vega, Gloria L; Toto, Robert D; Addition of angiotensin receptor blockade or mineralocorticoid antagonism to maximal angiotensin-converting enzyme inhibition in diabetic nephropathy.; Journal of the American Society of Nephrology : JASN; 2009; vol. 20 (no. 12); 2641-50 |

**Study details**

| | |
|---|---|
| **Study type** | Randomised controlled trial (RCT) |
| **Study location** | US |
| **Study setting** | Not reported |
| **Study dates** | 2003 - 2007 |
| **Duration of follow-up** | 48 weeks |
| **Sources of funding** | The National Institute of Diabetes Digestive and Kidney Diseases and the National Center for Research Resources General Clinical Research Center |

| | |
|---|---|
| **Inclusion criteria** | Proteinuria<br>24 h urinary albumin/creatinine ratio ≥300 mg/g despite treatment with an ACEi or an ARB for at least 3 months<br><br>Age<br>20 to 65 years<br><br>Diabetes<br>type 1 or type 2 diabetes mellitus<br><br>Hypertension<br>seated systolic blood pressure >130 mmHg |
| **Exclusion criteria** | Other conditions<br>body mass index >45 kg/m², serum creatinine >3.0 mg/dl in females and >4.0 mg/dl in males, known non-diabetic kidney disease, serum potassium concentration >5.5 mEq/L, hemoglobin A1c >11%, stroke or myocardial infarction within the preceding 12 months, heart failure, known adverse reaction to losartan or spironolactone, or anticipated need for dialysis within 12 months |
| **Sample size** | 81 |
| **Interventions** | Blood pressure medication<br>Losartan vs Spironolactone<br><br>Placebo<br><br>Additional notes<br>A research dietitian counseled each study subject on the recommended daily dietary restrictions, including 4 g of sodium, 0.8 g/kg protein, and 0.8 mEq/kg potassium |
| **Outcome measures** | Reduction in albuminuria<br>Urinary albumin/creatinine ratio reported as percentage change at 48 weeks<br><br>Mortality: cardiovascular<br>stroke, heart failure, myocardial infarction<br><br>Adverse outcome<br>Hospitalisation for cardiovascular events |

**Study arms**

**Losartan (N = 27)**
starting dose 50 mg once daily for the first week; thereafter, dose was doubled by administering 2 capsules once daily (100 mg)

| | |
|---|---|
| Loss to follow-up | 6 |
| % Female | 50.0 |
| Mean age (SD) | 52.3 (9.1) |
| Condition specific characteristics | Baseline albuminuria<br>Urinary albumin/creatinine ratio (mg/g): geometric mean 897 (95% confidence interval [CI] 611, 1316)<br><br>% Diabetes<br>84.6 |

**Spironolactone (N = 27)**
starting dose 12.5 mg once daily for the first week; thereafter, dose was doubled by administering 2 capsules once daily (25 mg)

| | |
|---|---|
| Loss to follow-up | 10 |
| % Female | 51.8 |
| Mean age (SD) | 51.7 (9.3) |
| Condition specific characteristics | Baseline albuminuria<br>Urinary albumin/creatinine ratio (mg/g): geometric mean 1094 (95% CI 758, 1579)<br><br>% Diabetes<br>85.1 |

**Placebo (N = 27)**
starting dose a single capsule once daily for the first week; thereafter, dose was doubled by administering 2 capsules once daily

| | |
|---|---|
| Loss to follow-up | 6 |

| | |
|---|---|
| % Female | 55.5 |
| Mean age (SD) | 49.3 (8.8) |
| Condition specific characteristics | Baseline albuminuria<br>Urinary albumin/creatinine ratio (mg/g): geometric mean 917 (95% CI 633, 1329)<br><br>% Diabetes<br>85.1 |

**Domain 1: Bias arising from the randomisation process**

*Risk of bias judgement for the randomisation process*

Low

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

Low

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

Low

**Domain 3. Bias due to missing outcome data**

*Risk-of-bias judgement for missing outcome data*

Some concerns

*(77.7% (losartan), 62.9% (spirinolactone), 77.7% (placebo) of available data)*

**Domain 4. Bias in measurement of the outcome**

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*Risk-of-bias judgement for selection of the reported result*

Low

**Overall bias and Directness**

*Risk of bias judgement*

Some concerns

*Overall Directness*

Directly applicable

## Neuen, 2019

| | |
|---|---|
| **Bibliographic Reference** | Neuen, B.L.; Ohkuma, T.; Neal, B.; Matthews, D.R.; De Zeeuw, D.; Mahaffey, K.W.; Fulcher, G.; Li, Q.; Jardine, M.; Oh, R.; Heerspink, H.L.; Perkovic, V.; Effect of canagliflozin on renal and cardiovascular outcomes across different levels of albuminuria: Data from the CANVAS program; Journal of the American Society of Nephrology; 2019; vol. 30 (no. 11); 2229-2242 |

**Study details**

| | |
|---|---|
| **Study type** | Randomised controlled trial (RCT) |
| **Study location** | 30 countries |

| | |
|---|---|
| **Study setting** | 667 centres |
| **Study dates** | Not reported |
| **Duration of follow-up** | 312 weeks |
| **Sources of funding** | Janssen Research & Development, LLC |
| **Inclusion criteria** | CKD<br>mean eGFR mL/min/1.73m² at baseline: 74.4 (SD 21.3) for people with microalbuminuria and 66.4 (SD 22.3) for people with macroalbuminuria<br><br>Albuminuria<br>Subgroups with microalbuminuria (urinary albumin/creatinine ratio 30 to <300 mg/g) and macroalbuminuria (urinary albumin/creatinine ratio ≥300 mg/g)<br><br>Age<br>30 years or older with established atherosclerotic vascular disease, or 50 years or older with 2 or more cardiovascular risk factors (duration of diabetes of at least 10 years, systolic blood pressure higher than 140 mmHg while receiving one or more antihypertensive agents, microalbuminuria or macroalbuminuria, current smoking, or high-density lipoprotein cholesterol level of less than 1 mmol/L)<br><br>Diabetes<br>Type 2 diabetes<br><br>Other<br>HbA1c levels ≥7.0% and ≤10.5% |
| **Exclusion criteria** | Other conditions<br>eGFR <30 mL/min/1.73 m² |
| **Sample size** | 3026 |
| **Interventions** | Diabetes medication<br>Canagliflozin<br><br>Placebo |
| **Outcome measures** | Mortality: all cause |

**Study arms**

**Canagliflozin (N = 1728)**
100 to 300 mg daily

| | |
|---|---|
| Loss to follow-up | 3.9% |
| % Female | Microalbuminuria: 29.2<br>Macroalbuminuria: 30.0 |
| Mean age (SD) | Microalbuminuria: 63.8 (8.3)<br>Macroalbuminuria: 63.4 (8.3) |
| Condition specific characteristics | Baseline albuminuria<br>Microalbuminuria: urinary albumin/creatinine ratio (mg/g) median 67.1 (interquartile range 42.6, 127.2); Macroalbuminuria: urinary albumin/creatinine ratio (mg/g) median 691.9 (interquartile range 433.2, 1255.4)<br><br>% Diabetes<br>100 (type 2 diabetes)<br><br>eGFR<br>Microalbuminuria: mean 74.8 (SD 20.9) mL/min/1.73m²; Macroalbuminuria: mean 65.9 (SD 22.2) mL/min/1.73m² |

**Placebo (N = 1298)**
Matching placebo

| | |
|---|---|
| Loss to follow-up | 4.2% |
| % Female | Microalbuminuria: 32.4<br>Macroalbuminuria: 29.9 |
| Mean age (SD) | Microalbuminuria: 64.2 (8.3)<br>Macroalbuminuria: 64.0 (8.2) |
| Condition specific characteristics | Baseline albuminuria<br>Microalbuminuria: urinary albumin/creatinine ratio (mg/g) median 69.4 (interquartile range 44.6, 120.5); Macroalbuminuria: urinary albumin/creatinine ratio (mg/g) median 763.2 (interquartile range 451.5, 1394.1)<br><br>% Diabetes |

| | |
|---|---|
| | 100 (type 2 diabetes)<br><br>eGFR<br>Microalbuminuria: mean 73.9 (SD 21.9) mL/min/1.73m²; Macroalbuminuria: mean 66.9 (SD 22.5) mL/min/1.73m² |

**Domain 1: Bias arising from the randomisation process**

*Risk of bias judgement for the randomisation process*

Low

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

Low

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

Low

**Domain 3. Bias due to missing outcome data**

*Risk-of-bias judgement for missing outcome data*

Some concerns

*(Lost to follow-up was reported by arm (3.9% for canagliflozin and 4.2% for placebo); lost to follow-up was not report for subgroups of microalbuminuria and macroalbuminuria)*

**Domain 4. Bias in measurement of the outcome**

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*Risk-of-bias judgement for selection of the reported result*

Low

**Overall bias and Directness**

*Risk of bias judgement*

Low

*Overall Directness*

Directly applicable

## Perkovic, 2019

| | |
|---|---|
| **Bibliographic Reference** | Perkovic, Vlado; Jardine, Meg J; Neal, Bruce; Bompoint, Severine; Heerspink, Hiddo J L; Charytan, David M; Edwards, Robert; Agarwal, Rajiv; Bakris, George; Bull, Scott; Cannon, Christopher P; Capuano, George; Chu, Pei-Ling; de Zeeuw, Dick; Greene, Tom; Levin, Adeera; Pollock, Carol; Wheeler, David C; Yavin, Yshai; Zhang, Hong; Zinman, Bernard; Meininger, Gary; Brenner, Barry M; Mahaffey, Kenneth W; CREDENCE Trial, Investigators; Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy.; The New England journal of medicine; 2019; vol. 380 (no. 24); 2295-2306 |

**Study details**

| | |
|---|---|
| **Study type** | Randomised controlled trial (RCT) |
| **Study location** | 34 countries |
| **Study setting** | 690 centres |

| | |
|---|---|
| **Study dates** | 2014 - 2017 |
| **Duration of follow-up** | 26 weeks |
| **Sources of funding** | Janssen Research and Development |
| **Inclusion criteria** | CKD<br>defined as an eGFR 30 to <90 ml per minute per 1.73 m²<br><br>Albuminuria<br>Urinary albumin/creatinine ratio >300 to 5000 mg/g<br><br>Age<br>≥30 years<br><br>Diabetes<br>Type 2 diabetes<br><br>Treatment<br>stable dose of an angiotensin-converting–enzyme inhibitor or angiotensin-receptor blocker for at least 4 weeks before randomization; a stable dose was considered to be either the maximum labeled dose or a dose not associated with unacceptable side effects<br><br>Other<br>glycated hemoglobin level of 6.5 to 12.0% (6.5 to 10.5% in Germany, according to a country amendment) |
| **Exclusion criteria** | Other conditions<br>suspected nondiabetic kidney disease or type 1 diabetes, had been treated with immunosuppression for kidney disease, or had a history of dialysis or kidney transplantation<br><br>Treatment<br>Dual-agent treatment with an angiotensin- converting–enzyme inhibitor and an angiotensin- receptor blocker, a direct renin inhibitor, or a mineralocorticoid-receptor antagonist |
| **Sample size** | 4401 |
| **Interventions** | Diabetes medication<br>Canagliflozin<br><br>Placebo<br><br>Additional notes<br>The use of other background therapy for glycemic management and control of cardiovascular risk factors was recommended in accordance with local guidelines |

| | |
|---|---|
| **Outcome measures** | CKD progression: occurrence of end stage kidney disease<br>eGFR <15 ml/min/1.73 m² or dialysis initiated/kidney transplantation<br><br>Mortality: all cause<br><br>Mortality: cardiovascular<br><br>Adverse outcome<br>Hospitalisation for heart failure; acute kidney injury |

**Study arms**

**Canagliflozin (N = 2202)**
100 mg orally once daily

| | |
|---|---|
| Loss to follow-up | 15 |
| % Female | 34.6 |
| Mean age (SD) | 62.9 (9.2) |
| Condition specific characteristics | Baseline albuminuria<br>Urinary albumin/creatinine ratio (mg/g): median 923 (interquartile range 459, 1794)<br><br>% Diabetes<br>100 (type 2 diabetes)<br><br>eGFR<br>mean 56.3 (SD 18.2) mL/min/1.73m² |

**Placebo (N = 2199)**
Matching placebo

| | |
|---|---|
| Loss to follow-up | 25 |

| | |
|---|---|
| % Female | 33.3 |
| Mean age (SD) | 63.2 (9.2) |
| Condition specific characteristics | Baseline albuminuria<br>Urinary albumin/creatinine ratio (mg/g): median 931 (interquartile range 473, 1868)<br><br>% Diabetes<br>100 (type 2 diabetes)<br><br>eGFR<br>mean 56.0 (SD 18.3) mL/min/1.73m² |

**Domain 1: Bias arising from the randomisation process**

*Risk of bias judgement for the randomisation process*

Low

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

Low

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

Low

**Domain 3. Bias due to missing outcome data**

*Risk-of-bias judgement for missing outcome data*

Low

**Domain 4. Bias in measurement of the outcome**

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*Risk-of-bias judgement for selection of the reported result*

Low

**Overall bias and Directness**

*Risk of bias judgement*

Low

*Overall Directness*

Directly applicable

## Pollock, 2019

| | |
|---|---|
| **Bibliographic Reference** | Pollock, C.; Stefansson, B.; Reyner, D.; Rossing, P.; Sjostrom, C.D.; Wheeler, D.C.; Langkilde, A.M.; Heerspink, H.J.L.; Albuminuria-lowering effect of dapagliflozin alone and in combination with saxagliptin and effect of dapagliflozin and saxagliptin on glycaemic control in patients with type 2 diabetes and chronic kidney disease (DELIGHT): a randomised, double-blind, placebo-controlled trial; The Lancet Diabetes and Endocrinology; 2019; vol. 7 (no. 6); 429-441 |

**Study details**

| | |
|---|---|
| **Study type** | Randomised controlled trial (RCT)<br>double-blind and double-dummy design, with each patient receiving two pills per dose. Patients receiving dapagliflozin received placebo for saxagliptin and vice versa. Patients on placebo received dapagliflozin and saxagliptin placebos |

| | |
|---|---|
| **Study location** | Australia, Canada, Japan, South Korea, Mexico, South Africa, Spain, Taiwan, and US |
| **Study setting** | 116 research centres |
| **Study dates** | 2015 - 2018 |
| **Duration of follow-up** | 24 weeks |
| **Sources of funding** | AstraZeneca |
| **Inclusion criteria** | CKD<br>eGFR 20 to 80 mL/min per 1.73 m² to enter the lead-in period (25 to 75 mL/min per 1.73 m² for randomisation)<br><br>Albuminuria<br>Urinary albumin/creatinine ratio 30 to 3500 mg/g<br><br>Age<br>18 years or older<br><br>Diabetes<br>type 2 diabetes for more than 12 months<br><br>Treatment<br>stable glucose-lowering and antihypertensive treatments, including angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, at a clinically appropriate dose for at least 12 weeks before randomisation<br><br>Other<br>HbA1c of 7.0 to 11.0% (53 to 97 mmol/mol) at screening |
| **Exclusion criteria** | Other conditions<br>type 1 diabetes, known non-diabetic kidney disease, severe cardiovascular disease, two or more major hypoglycaemia events within 12 weeks before screening, haemoglobin less than 9 g/dL (or 5.6 mmol/L), or evidence of hepatic disease, poorly controlled blood pressure (systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥110 mm Hg)<br><br>Treatment<br>current use of SGLT2 inhibitors, GLP-1 receptor agonists, or DPP-4 inhibitors, and long-term treatment with glucocorticoids |
| **Sample size** | 461 |

| | |
|---|---|
| **Interventions** | Diabetes medication<br>Dapagliflozin plus Saxagliptin vs Dapagliflozin<br><br>Placebo<br><br>Additional notes<br>Antihypertensive treatments were to be kept stable throughout the entire study, from the start of the run-in period until the end of follow-up |
| **Outcome measures** | Reduction in albuminuria<br>24-h urinary albumin excretion (g/day) reported as median at baseline and 24 weeks and adjusted mean change from baseline<br><br>Mortality: all cause<br><br>Adverse outcome<br>Minor hypoglycaemia was defined as symptomatic episodes with capillary or plasma glucose <3.5 mmol/L [63 mg/dL], regardless of need for external assistance; or asymptomatic capillary or plasma glucose <3.5 mmol/L [63 mg/dL] not qualifying as a major episode. Major hypoglycaemia was defined as symptomatic episodes requiring external [third party] assistance because of severe impairment in consciousness or behaviour [capillary or plasma glucose <3 mmol/L or <54 mg/dL] and prompt recovery after glucose or glucagon administration. |

**Study arms**

**Dapagliflozin plus Saxagliptin (N = 157)**
once-daily dapagliflozin (10 mg) and saxagliptin (2·5 mg)

| | |
|---|---|
| Loss to follow-up | 7 |
| % Female | 29 |
| Mean age (SD) | 64.0 (9.2) |
| Condition specific characteristics | Baseline albuminuria<br>Urinary albumin/creatinine ratio (mg/g): median 218.4 (interquartile range 74, 936)<br><br>% Diabetes<br>100 (type 2 diabetes) |

| | |
|---|---|
| | eGFR<br>mean 49.0 (SD 13.0) mL/min/1.73m² |

**Dapagliflozin (N = 151)**
once-daily dapagliflozin (10 mg)

| | |
|---|---|
| Loss to follow-up | 14 |
| % Female | 30 |
| Mean age (SD) | 64.7 (8.6) |
| Condition specific characteristics | Baseline albuminuria<br>Urinary albumin/creatinine ratio (mg/g): median 270.0 (interquartile range 69, 751)<br><br>% Diabetes<br>100 (type 2 diabetes)<br><br>eGFR<br>mean 50.2 (SD 13.0) mL/min/1.73m² |

**Placebo (N = 153)**
once-daily matched placebo

| | |
|---|---|
| Loss to follow-up | 10 |
| % Female | 29 |
| Mean age (SD) | 64.7 (8.5) |
| Condition specific characteristics | Baseline albuminuria<br>Urinary albumin/creatinine ratio (mg/g): median 257.5 (interquartile range 80, 949)<br><br>% Diabetes<br>100 (type 2 diabetes) |

| | |
|---|---|
| | eGFR<br>mean 47.7 (SD 13.5) mL/min/1.73m² |

**Domain 1: Bias arising from the randomisation process**

*Risk of bias judgement for the randomisation process*

Low

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

Low

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

Low

**Domain 3. Bias due to missing outcome data**

*Risk-of-bias judgement for missing outcome data*

Low

**Domain 4. Bias in measurement of the outcome**

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*Risk-of-bias judgement for selection of the reported result*

Low

**Overall bias and Directness**

*Risk of bias judgement*

Low

*Overall Directness*

Directly applicable

## Praga, 2003

| | |
|---|---|
| **Bibliographic Reference** | Praga, Manuel; Andrade, Carlos Fernandez; Luno, Jose; Arias, Manuel; Poveda, Rafael; Mora, Jose; Prat, Marti Valles; Rivera, Francisco; Galceran, Jose Maria; Ara, Jorge Martinez; Aguirre, Roman; Bernis, Carmen; Marin, Rafael; Campistol, Jose Maria; Antiproteinuric efficacy of losartan in comparison with amlodipine in non-diabetic proteinuric renal diseases: a double-blind, randomized clinical trial.; Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association; 2003; vol. 18 (no. 9); 1806-13 |

**Study details**

| | |
|---|---|
| **Study type** | Randomised controlled trial (RCT) |
| **Study location** | Spain |
| **Study setting** | 14 centres |
| **Study dates** | Not reported |
| **Duration of follow-up** | 20 weeks |

| | |
|---|---|
| **Sources of funding** | Merck Sharp & Dohme, Spain |
| **Inclusion criteria** | CKD<br>chronic proteinuric nephropathy of non-diabetic cause<br><br>Proteinuria<br>Urinary protein excretion >1.5 g/24 h<br><br>Age<br>>18 years<br><br>Hypertension<br>systolic blood pressure >140 mm Hg while sitting and/or a diastolic blood pressure >90 mm Hg while sitting<br><br>Other<br>Serum creatinine ≤2.5 mg/dl |
| **Exclusion criteria** | Diabetes<br>type 1 or type 2 diabetes<br><br>Other conditions<br>severe hypertension (systolic blood pressure >170 mm Hg and/or diastolic blood pressure >105 mm Hg despite treatment with antihypertensive agents, or patients requiring more than one antihypertensive drug), secondary types of hypertension (renal artery stenosis, primary aldosteronism, pheochromocytoma or other reversible forms of hypertension), rapidly deteriorating renal function (defined by an increase of >50% in the level of serum creatinine during the last 6 months) or severe obesity (body mass index >35 kg/m²), myocardial infarction within the previous 6 months or any history of heart failure<br><br>Treatment<br>patients who required diuretics because of oedema, |
| **Sample size** | 97 |
| **Interventions** | Blood pressure medication<br>Losartan vs Amlodipine |
| **Outcome measures** | Reduction in proteinuria<br>Urinary protein excretion (g/24 h) at baseline and 4, 8 and 20 weeks with percentage change |

**Study arms**

**Losartan (N = 50)**
starting dose 50 mg once daily; at week 4, hydrochlorothiazide (12.5 mg once daily) was added if blood pressure was above target (systolic blood pressure >140 mm Hg and diastolic blood pressure >90 mm Hg); at week 8, losartan was increased to 100 mg if blood pressure was still above the target level; at week 12, hydrochlorothiazide was increased to 25 mg once daily if blood pressure was still above the target level

| | |
|---|---|
| Loss to follow-up | 3 |
| % Female | 26 |
| Mean age (SD) | 48 (13) |
| Condition specific characteristics | Baseline proteinuria<br>Urinary protein excretion (g/24 h): geometric mean 3.1 (95% confidence interval (CI) 2.5, 3.8) |

**Amlodipine (N = 47)**
starting dose 5 mg once daily; at week 4, hydrochlorothiazide (12.5 mg once daily) was added if blood pressure was above target (systolic blood pressure >140 mm Hg and diastolic blood pressure >90 mm Hg); at week 8, amlodipine was increased to 10 mg if blood pressure was still above the target level; at week 12, hydrochlorothiazide was increased to 25 mg once daily if blood pressure was still above the target level

| | |
|---|---|
| Loss to follow-up | 6 |
| % Female | 27 |
| Mean age (SD) | 47 (14) |
| Condition specific characteristics | Baseline proteinuria<br>Urinary protein excretion (g/24 h): geometric mean 2.5 (95% CI 2, 3.2) |

**Domain 1: Bias arising from the randomisation process**

*Risk of bias judgement for the randomisation process*

Some concerns

*(No information about randomisation method and allocation concealment)*

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

Low

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

Low

**Domain 3. Bias due to missing outcome data**

*Risk-of-bias judgement for missing outcome data*

Low

**Domain 4. Bias in measurement of the outcome**

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*Risk-of-bias judgement for selection of the reported result*

Some concerns

*(Protocol was not reported)*

**Overall bias and Directness**

*Risk of bias judgement*

Some concerns

*Overall Directness*

Directly applicable

## Ruggenenti, 1999

| | |
|---|---|
| **Bibliographic Reference** | Ruggenenti, P; Perna, A; Gherardi, G; Garini, G; Zoccali, C; Salvadori, M; Scolari, F; Schena, F P; Remuzzi, G; Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria.; Lancet (London, England); 1999; vol. 354 (no. 9176); 359-64 |

**Study details**

| | |
|---|---|
| **Study type** | Randomised controlled trial (RCT)<br>This paper reports stratum 1 of this RCT which contains participants with proteinuria 1 to 2.9 g/24 h. Stratum 2 is reported by GISEN group 1997 |
| **Study location** | Italy |
| **Study setting** | Not reported |
| **Study dates** | Not reported |
| **Duration of follow-up** | 72 months |
| **Sources of funding** | Grant from Hoechst Mario Roussel Clinical Research Institute, Frankfurt am Main, Germany |
| **Inclusion criteria** | CKD<br>chronic nephropathy defined as creatinine clearance in the range 20 to 70 mL/min/1.73m² with variation <30% in the 3 months before screening evaluation<br><br>Proteinuria |

| | |
|---|---|
| | Urinary protein excretion ≥1 g/24 h for at least 3 months without evidence of urinary tract infection or overt heart failure (class III or IV)<br><br>Age<br>18 to 70 years<br><br>Hypertension<br>normotensive (defined as systolic <140 and diastolic <90 mm Hg without antihypertensive therapy) or hypertensive<br><br>Treatment<br>without ACE inhibition therapy for at least 2 months or corticosteroids, non-steroidal anti-inflammatory drugs, or immunosuppressive drugs for at least 6 months |
| **Exclusion criteria** | Other conditions<br>acute myocardial infarction or cerebrovascular accident in the previous 6 months; severe uncontrolled hypertension (diastolic blood pressure ≥115 and/or systolic blood pressure ≥220 mm Hg); evidence or suspicion of renovascular disease, obstructive uropathy, insulin-dependent diabetes mellitus, collagen disease, cancer, higher serum aminotransferase concentrations, or chronic cough; drug or alcohol abuse; pregnancy breast feeding; and ineffective contraception<br><br>Treatment<br>corticosteroids, non-steroidal anti-inflammatory drugs, or immunosuppressive drugs |
| **Sample size** | 186 |
| **Condition specific characteristics** | Additional notes<br>This paper reports stratum 2 which contains participants with proteinuria >1 to 2.9 g/24 h |
| **Interventions** | Blood pressure medication<br>Ramipril<br><br>Placebo<br><br>Additional notes<br>Antihypertensive agents other than ACE or angiotensin II antagonists were introduced as appropriate to achieve and maintain diastolic blood pressure <90 mg Hg. In patients already on antihypertensive agents the dose of study drug was titrated upward and the doses of other antihypertensive agents were progressively reduced, to avoid symptomatic hypotension. The general goal was to achieve and maintain the target blood pressure within the minimum dose of concomitant antihypertensive agents. All patients were recommended to limit sodium intake and to eat 0.6 to 0.8 g protein per kg body weight per day. No change in diet was introduced during the study |
| **Outcome measures** | CKD progression: occurrence of end stage kidney disease<br><br>Mortality: cardiovascular<br>Atrial fibrillation, heart failure, stroke |

**Study arms**

**Ramipril (N = 99)**
starting dose 1.25 mg; dose was titrated every 2 weeks until diastolic blood pressure was below 90 mg Hg; incremental dose was 2.5 or 5 mg

| | |
|---|---|
| Loss to follow-up | 7 |
| % Female | 24.2 |
| Mean age (SD) | 49.1 (SE 1.3) |
| Condition specific characteristics | Baseline proteinuria<br>Urinary protein excretion (g/day): mean 1.7 (SE 0.1)<br><br>eGFR<br>mean 49.5 (SD 2.0) mL/min/1.73m² |

**Placebo (N = 87)**
starting dose 1.25 mg; dose was titrated every 2 weeks until diastolic blood pressure was below 90 mg Hg; incremental dose was 2.5 or 5 mg

| | |
|---|---|
| Loss to follow-up | 4 |
| % Female | 26.4 |
| Mean age (SD) | 50.3 (SE 1.5) |
| Condition specific characteristics | Baseline proteinuria<br>Urinary protein excretion (g/day): mean 1.7 (SE 0.1)<br><br>eGFR<br>mean 43.4 (SD 1.8) mL/min/1.73m² |

**Domain 1: Bias arising from the randomisation process**

*Risk of bias judgement for the randomisation process*

Some concerns

*(No information about randomisation method and allocation concealment)*

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

Low

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

Low

**Domain 3. Bias due to missing outcome data**

*Risk-of-bias judgement for missing outcome data*

Low

**Domain 4. Bias in measurement of the outcome**

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*Risk-of-bias judgement for selection of the reported result*

Low

**Overall bias and Directness**

*Risk of bias judgement*

Some concerns

*Overall Directness*

Directly applicable

## Saglimbene, 2018

| | |
|---|---|
| **Bibliographic Reference** | Saglimbene, Valeria; Palmer, Suetonia C; Ruospo, Marinella; Natale, Patrizia; Maione, Ausilia; Nicolucci, Antonio; Vecchio, Mariacristina; Tognoni, Gianni; Craig, Jonathan C; Pellegrini, Fabio; Lucisano, Giuseppe; Hegbrant, Jorgen; Ariano, Rosario; Lamacchia, Olga; Sasso, Antonio; Morano, Susanna; Filardi, Tiziana; De Cosmo, Salvatore; Pugliese, Giuseppe; Procaccini, Deni A; Gesualdo, Loreto; Palasciano, Giuseppe; Johnson, David W; Tonelli, Marcello; Strippoli, Giovanni F M; Long-Term Impact of RAS Inhibition on Cardiorenal Outcomes (LIRICO), Investigators; The Long-Term Impact of Renin-Angiotensin System (RAS) Inhibition on Cardiorenal Outcomes (LIRICO): A Randomized, Controlled Trial.; Journal of the American Society of Nephrology : JASN; 2018; vol. 29 (no. 12); 2890-2899 |

**Study details**

| | |
|---|---|
| **Study type** | Randomised controlled trial (RCT) |
| **Study location** | Italy |
| **Study setting** | 47 internal medicine clinics and nephrology units |
| **Study dates** | 2007 - 2013 |
| **Duration of follow-up** | median follow-up 2.7 years |
| **Sources of funding** | Agenzia Italiana del Farmaco (Italian Medicines Agency) project grant |
| **Inclusion criteria** | Albuminuria<br>moderate albuminuria (urinary albumin/creatinine ratio 30–299 mg/g) or severe albuminuria (urinary albumin/creatinine ratio ≥300 mg/g)<br><br>Age<br>≥18 years |

| | |
|---|---|
| | Diabetes<br>Type 1 or type 2 diabetes<br><br>Hypertension<br>systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or antihypertensive treatment<br><br>Other<br>one or more cardiovascular risk factors: current or recent smoking, hypertension, abdominal obesity, dyslipidemia, or family history of premature cardiovascular events |
| **Exclusion criteria** | Other conditions<br>pregnant, intended to become pregnant, had active malignancy (except basal cell carcinoma), r had substantially reduced life expectancy<br><br>Treatment<br>contraindication to ACE inhibitor or ARB |
| **Sample size** | 1287 |
| **Interventions** | Blood pressure medication<br>ACE inhibitor vs ARB vs ACE inhibitor plus ARB |
| **Outcome measures** | CKD progression: occurrence of end stage kidney disease<br><br>Mortality: all cause<br><br>Mortality: cardiovascular<br><br>Morbidity<br>Non-fatal myocardial infarction, non-fatal stroke,<br><br>Adverse outcome<br>Hospitalisation for cardiovascular cause, hypotension |

**Study arms**

**ACE inhibitor (N = 413)**
Initial dosing was at the investigator's discretion. Treatment doses were titrated to the full tolerated dose by the usual attending physician

| | |
|---|---|
| Loss to follow-up | 56 |
| % Female | 71.3 |
| Mean age (SD) | 62.2 (11.2) |
| Condition specific characteristics | Baseline albuminuria<br>Urinary albumin/creatinine ratio (mg/g): median 108 (interquartile range 55, 302)<br>% Diabetes<br>Type 2 diabetes 96.8<br>eGFR<br>mean 70.2 (SD 28.0) mL/min/1.73m² |

**ARB (N = 414)**
Initial dosing was at the investigator's discretion. Treatment doses were titrated to the full tolerated dose by the usual attending physician

| | |
|---|---|
| Loss to follow-up | 44 |
| % Female | 71.5 |
| Mean age (SD) | 62.7 (10.7) |
| Condition specific characteristics | Baseline albuminuria<br>Urinary albumin/creatinine ratio (mg/g): median 110 (interquartile range 52, 316)<br>% Diabetes<br>Type 2 diabetes 96.8<br>eGFR<br>mean 68.0 (SD 27.7) mL/min/1.73m² |

**ACE inhibitor plus ARB (N = 416)**
Initial dosing was at the investigator's discretion. Treatment doses were titrated to the full tolerated dose by the usual attending physician

| | |
|---|---|
| Loss to follow-up | 39 |
| % Female | 72.5 |
| Mean age (SD) | 63.4 (10.0) |
| Condition specific characteristics | Baseline albuminuria<br>Urinary albumin/creatinine ratio (mg/g): median 128 (interquartile range 57, 325)<br><br>% Diabetes<br>Type 2 diabetes 97.1<br><br>eGFR<br>mean 65.5 (SD 27.8) mL/min/1.73m² |

**Domain 1: Bias arising from the randomisation process**

*Risk of bias judgement for the randomisation process*

Low

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

High

*(No information on the type of analysis (intention-to-treat or per-protocol analyses))*

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

High

*(No information about an appropriate analysis to estimate the effect of participants adherence)*

**Domain 3. Bias due to missing outcome data**

*Risk-of-bias judgement for missing outcome data*

Low

**Domain 4. Bias in measurement of the outcome**

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*Risk-of-bias judgement for selection of the reported result*

Low

**Overall bias and Directness**

*Risk of bias judgement*

High

*Overall Directness*

Directly applicable

## van den Meiracker, 2006

| | |
|---|---|
| **Bibliographic Reference** | van den Meiracker, Anton H; Baggen, Rini Ga; Pauli, Sacha; Lindemans, Anouk; Vulto, Arnold G; Poldermans, Don; Boomsma, Frans; Spironolactone in type 2 diabetic nephropathy: Effects on proteinuria, blood pressure and renal function.; Journal of hypertension; 2006; vol. 24 (no. 11); 2285-92 |

**Study details**

| | |
|---|---|
| **Study type** | Randomised controlled trial (RCT) |
| **Study location** | The Netherlands |
| **Study setting** | Outpatient departments of internal medicine |
| **Study dates** | Not reported |
| **Duration of follow-up** | 12 months |
| **Sources of funding** | Not reported |
| **Inclusion criteria** | CKD<br>Diabetic nephropathy was diagnosed clinically with albuminuria persistently greater than 300 mg/24 h, absence of any clinical or laboratory evidence of other kidney or renal tract disease and presence of retinopathy<br><br>Albuminuria<br>Urinary albumin excretion >300 mg/24 h or urinary albumin/creatinine ratio >20 mg/mmol despite use of an ACE inhibitor or ARB in recommended dosages for at least 1 year<br><br>Age<br>20 to 80 years<br><br>Diabetes<br>Type 2 diabetes |
| **Exclusion criteria** | Other conditions<br>serum creatinine concentration >265 µmol/l, serum potassium >5.0 mmol/l, renal disease other than diabetic nephropathy, nephrotic syndrome, underlying malignant, hepatic or gastrointestinal disease, myocardial infarction or stroke within the past 3 months, unstable angina pectoris, alcohol or drug abuse or psychological illness |
| **Withdrawals** | If serum potassium concentration had increased to >5.5 mmol/l after randomisation, study medication was reduced to one tablet once daily and serum potassium concentration was measured again after a 2-week interval. Patients were withdrawn from the<br>study if their serum potassium concentration remained >5.5 mmol/l with one tablet of study medication |

| | |
|---|---|
| **Sample size** | 59 |
| **Interventions** | Blood pressure medication<br>Spironolactone<br><br>Placebo<br><br>Additional notes<br>Apart from antidiabetic medication, antihypertensive medications were kept constant throughout the course of the study |
| **Outcome measures** | Reduction in proteinuria<br>Urinary protein/creatinine ratio reported as percentage reduction with 95% confidence interval<br><br>Reduction in albuminuria<br>Urinary albumin/creatinine ratio reported as percentage reduction with 95% confidence interval |

**Study arms**

**Spironolactone (N = 29)**
2 tablets of 25 mg daily added to the antihypertensive medication already used by the patients

| | |
|---|---|
| Loss to follow-up | 5 |
| % Female | 29.1 |
| Mean age (SD) | 55.2 (range 38, 78) |
| Condition specific characteristics | Baseline proteinuria<br>Urinary protein/creatinine ratio (mg/mmol): geometric mean 111 (interquartile range 69, 173)<br><br>Baseline albuminuria<br>Urinary albumin/creatinine ratio (mg/mmol): geometric mean 64.6 (interquartile range 33.1, 107.7)<br><br>% Diabetes<br>100 (type 2 diabetes) |

| | |
|---|---|
| | eGFR<br>geometric mean 87 (interquartile range 67, 109) mL/min/1.73m² |

**Placebo (N = 30)**
2 matched placebo tablets added to the antihypertensive medication already used by the patients

| | |
|---|---|
| Loss to follow-up | 2 |
| % Female | 41.3 |
| Mean age (SD) | 55.2 (range 29, 75) |
| Condition specific characteristics | Baseline proteinuria<br>Urinary protein/creatinine ratio (mg/mmol): geometric mean 145 (interquartile range 63, 262)<br><br>Baseline albuminuria<br>Urinary albumin/creatinine ratio (mg/mmol): geometric mean 101.6 (interquartile range 43.7, 285)<br><br>% Diabetes<br>100 (type 2 diabetes)<br><br>eGFR<br>geometric mean 64 (interquartile range 47, 87) mL/min/1.73m² |

**Domain 1: Bias arising from the randomisation process**

*Risk of bias judgement for the randomisation process*

Low

**Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

*Risk of bias for deviations from the intended interventions (effect of assignment to intervention)*

High

*(No information on the type of analysis (intention-to-treat or per-protocol analyses))*

**Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

*Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)*

High

*(No information about an appropriate analysis to estimate the effect of participants adherence)*

**Domain 3. Bias due to missing outcome data**

*Risk-of-bias judgement for missing outcome data*

Low

**Domain 4. Bias in measurement of the outcome**

*Risk-of-bias judgement for measurement of the outcome*

Low

**Domain 5. Bias in selection of the reported result**

*Risk-of-bias judgement for selection of the reported result*

Some concerns

*(Protocol was not reported)*

**Overall bias and Directness**

*Risk of bias judgement*

High

*Overall Directness*

Directly applicable

# Appendix F – Forest plots

**Scales for forest plot outcomes**

Mean difference – higher value (above zero) favours comparator; apart from health-related quality of life (lower value (below zero) favours comparator)

Relative Risk - higher value (above 1) favours comparator

# Adults with type 2 diabetes

**Figure 1 Aldosterone antagonist vs Placebo; outcome: Urinary albumin/creatinine ratio (mean percentage change)**

**Figure 2 ARB vs Placebo; outcome: End stage kidney disease**

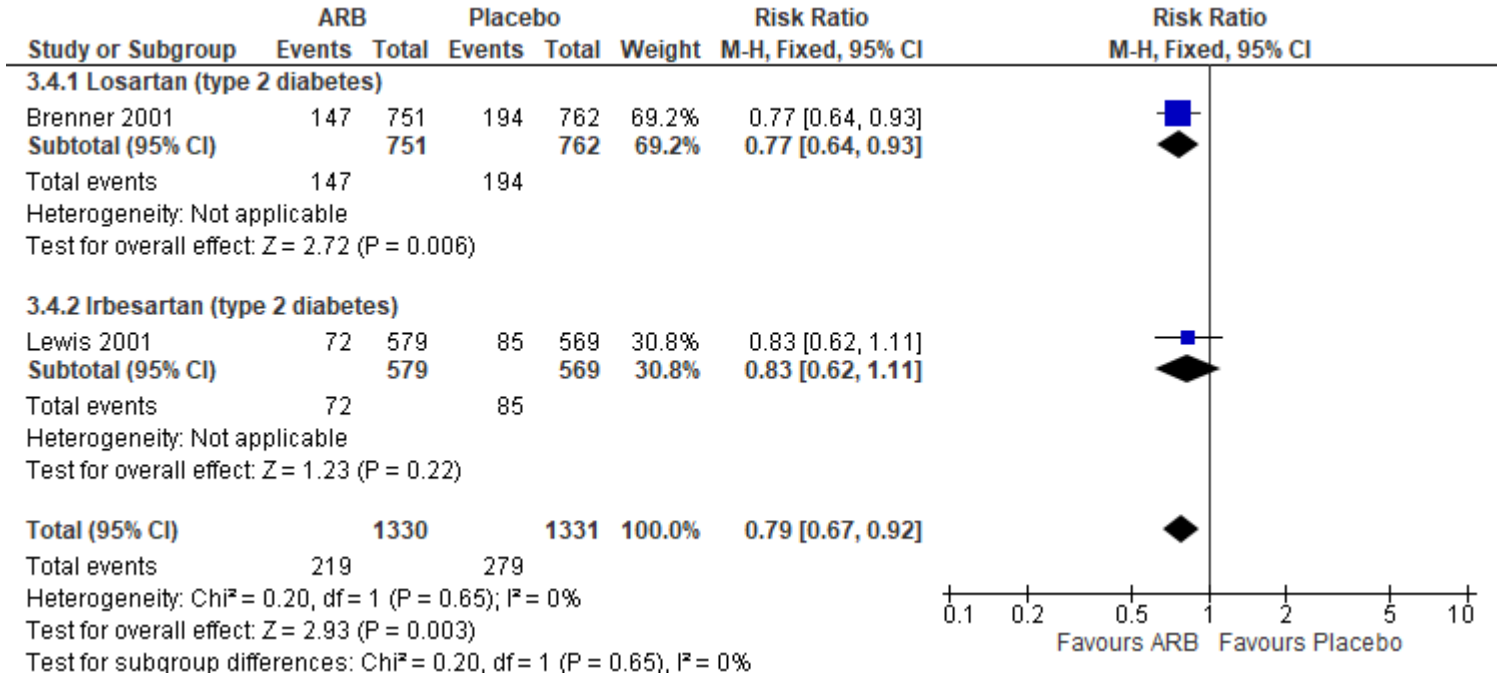


**Figure 3 ARB vs Placebo; outcome: All-cause mortality**

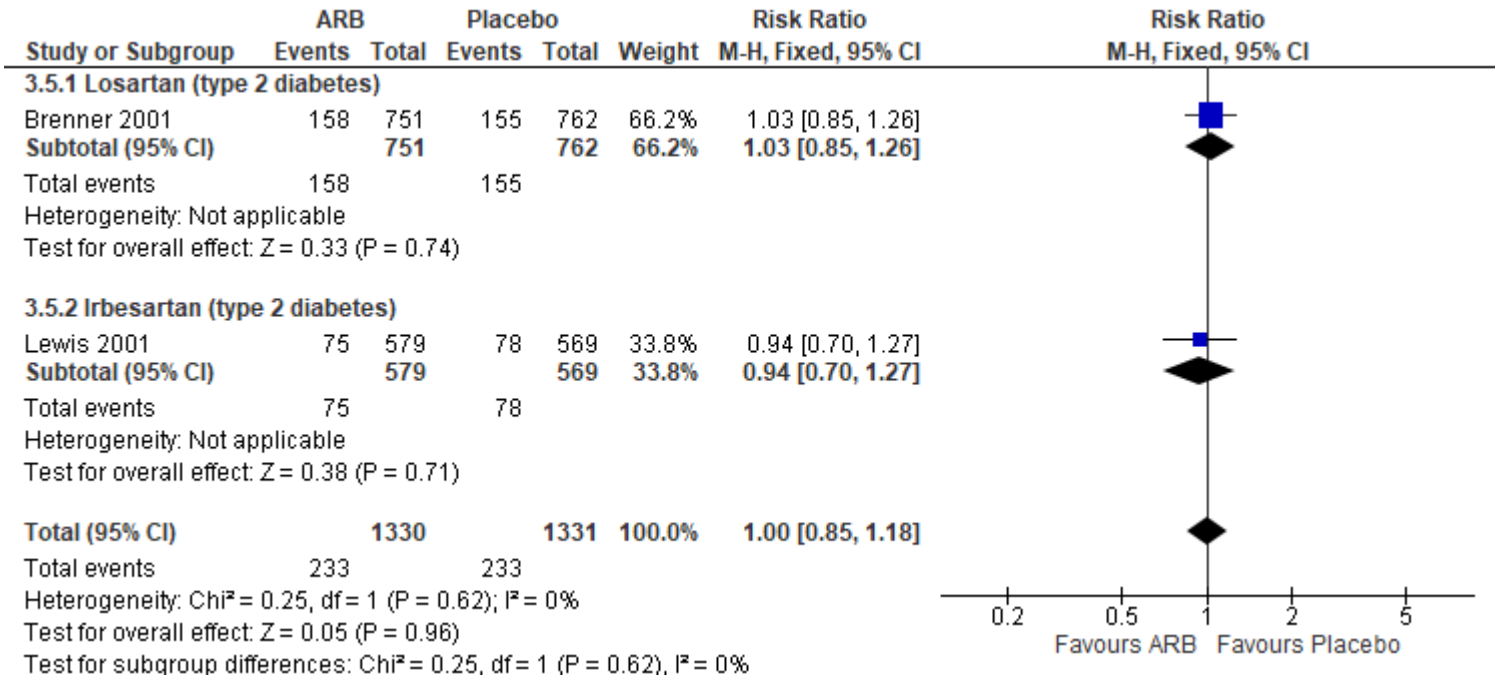


**Figure 4 ARB vs Placebo; outcome: Non-fatal CV events**

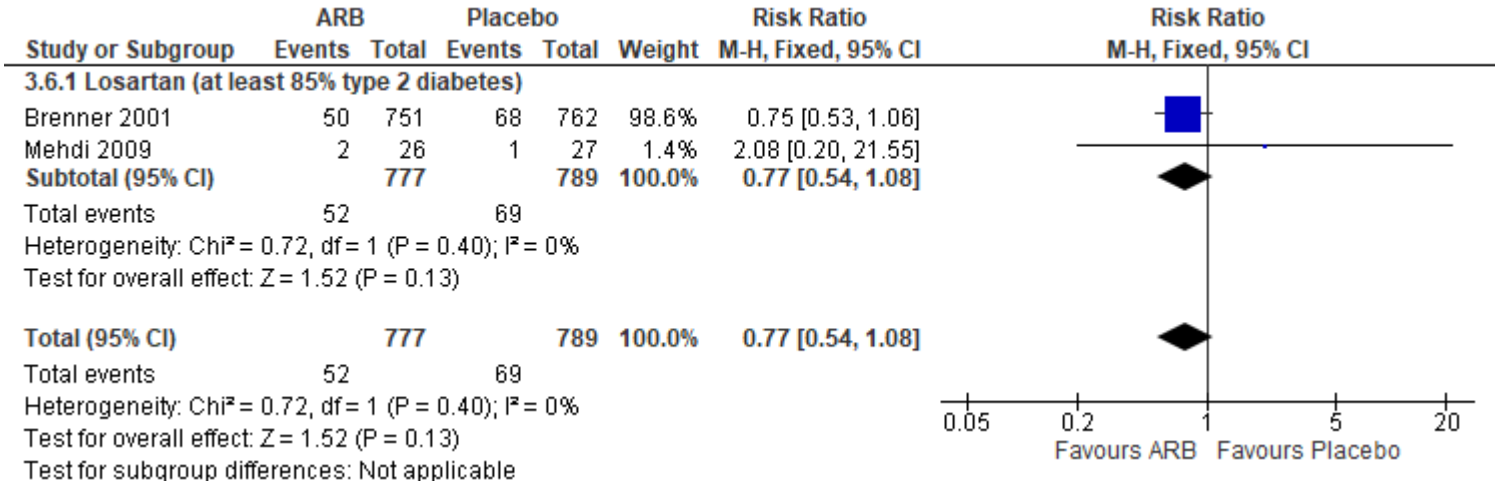



**Figure 5 ARB vs Placebo; outcome: Hospitalisation**

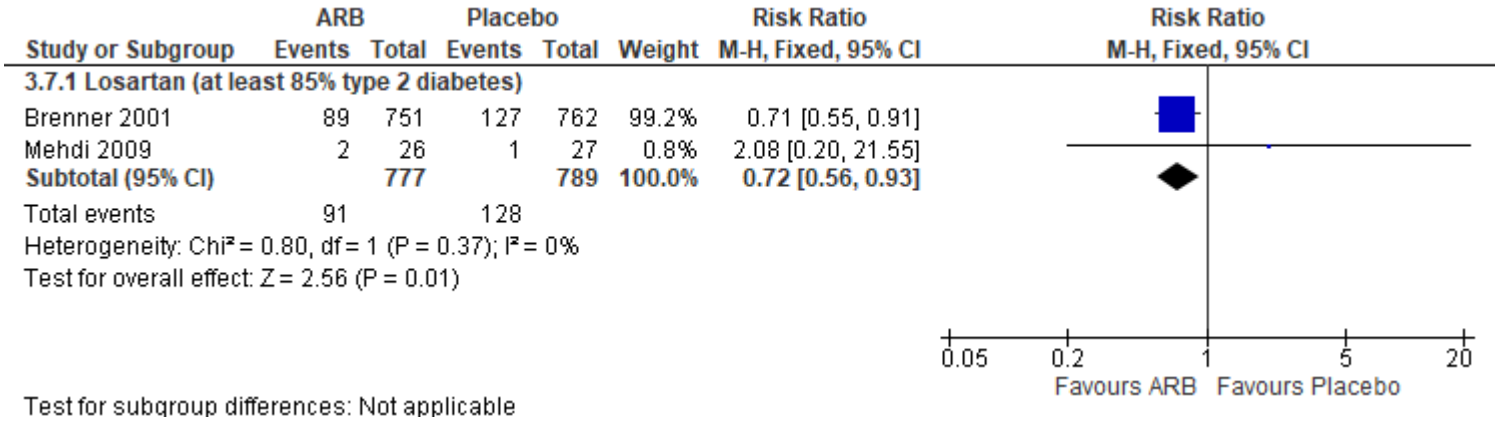
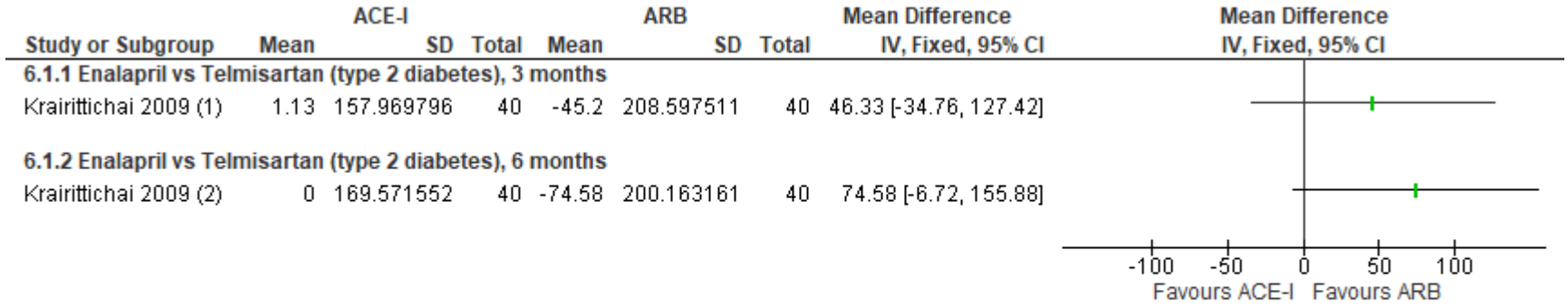


**Figure 6 ACE-I vs ARB; outcome: Urinary protein/creatinine ratio (mg/mmol)**




Footnotes

(1) Mean change from baseline, g/g converted to mg/g (g/g multiplied by 1000), mg/g converted to mg/mmol multiplying mg/g by 0.113

(2) Mean change from baseline, g/g converted to mg/g (g/g multiplied by 1000), mg/g converted to mg/mmol multiplying mg/g by 0.113

**Figure 7 SGLT2 inhibitor vs Placebo; outcome: End stage kidney disease**

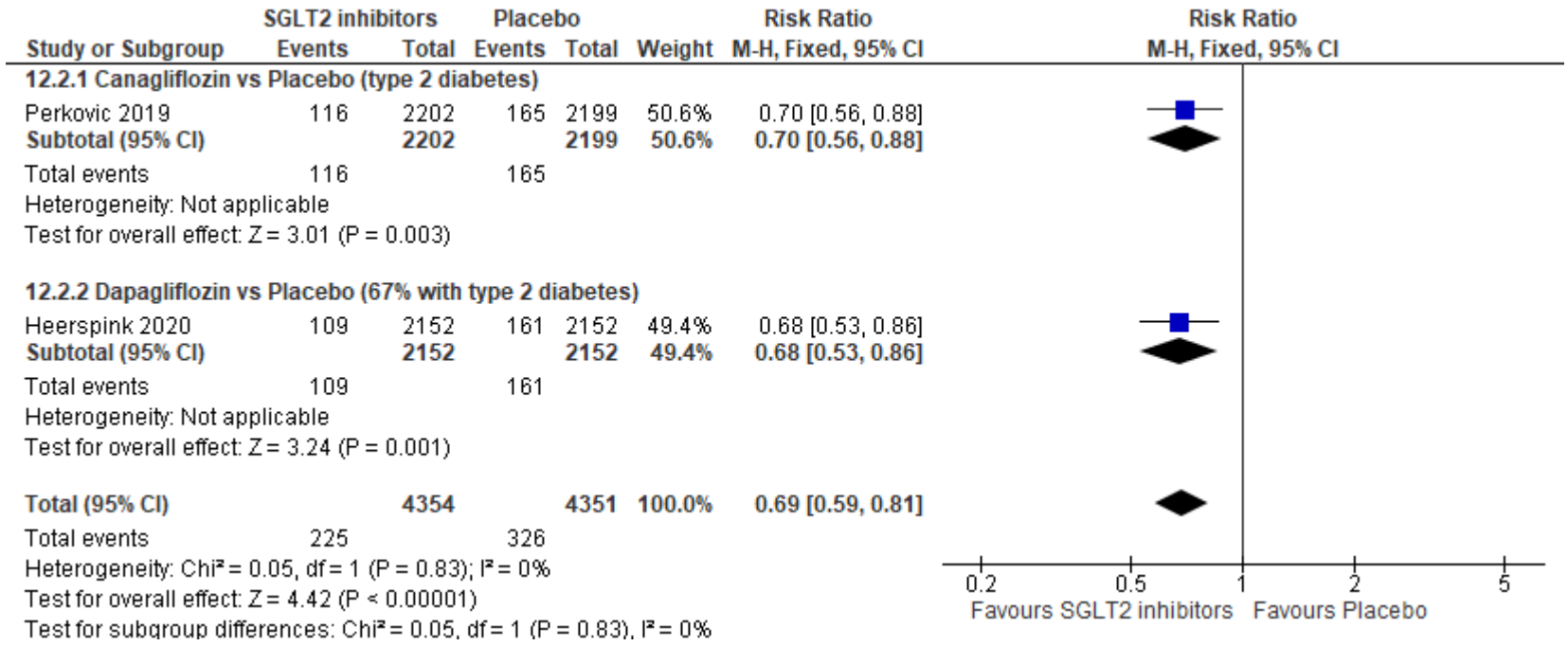


**Figure 8 SGLT2 inhibitor vs Placebo; outcome: All-cause mortality**

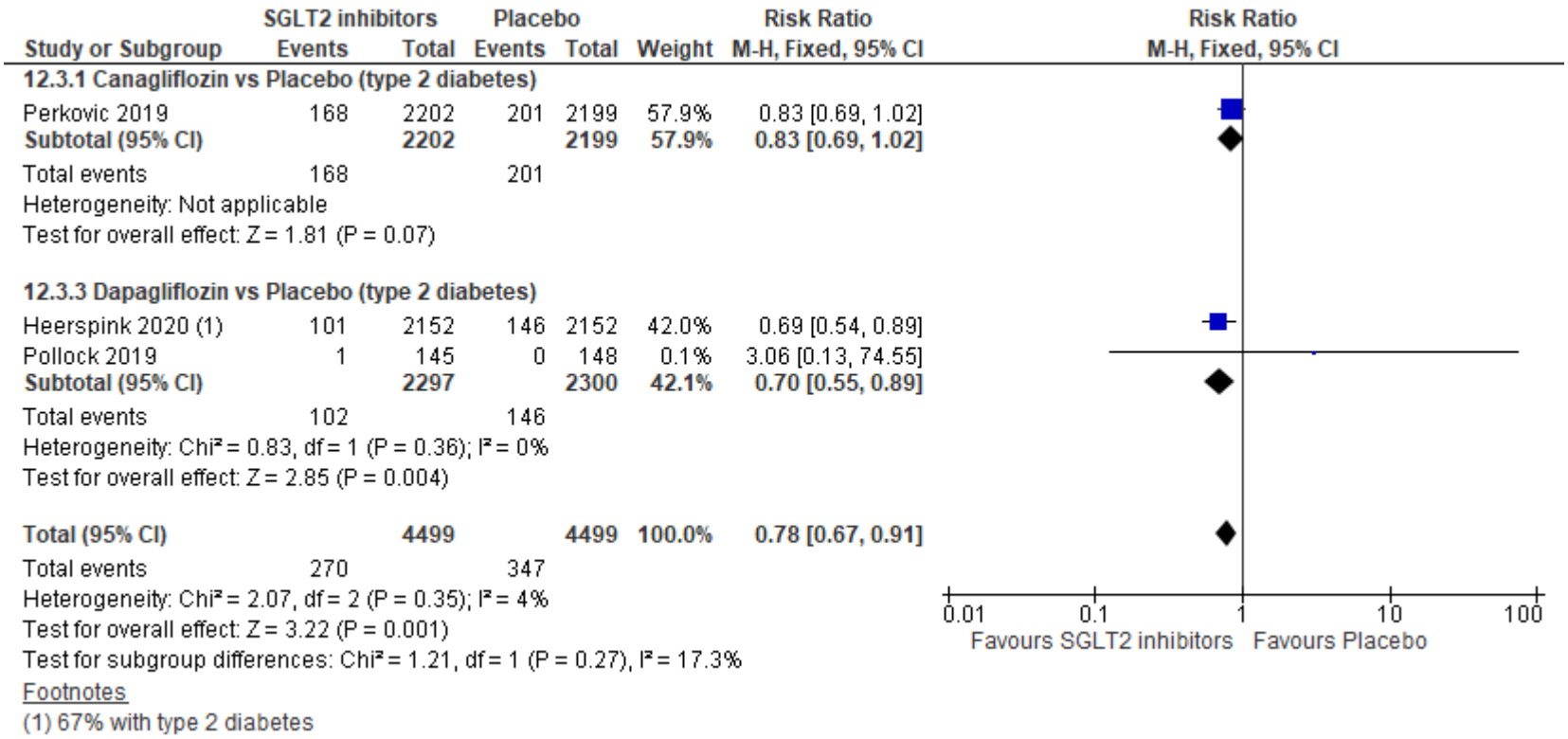
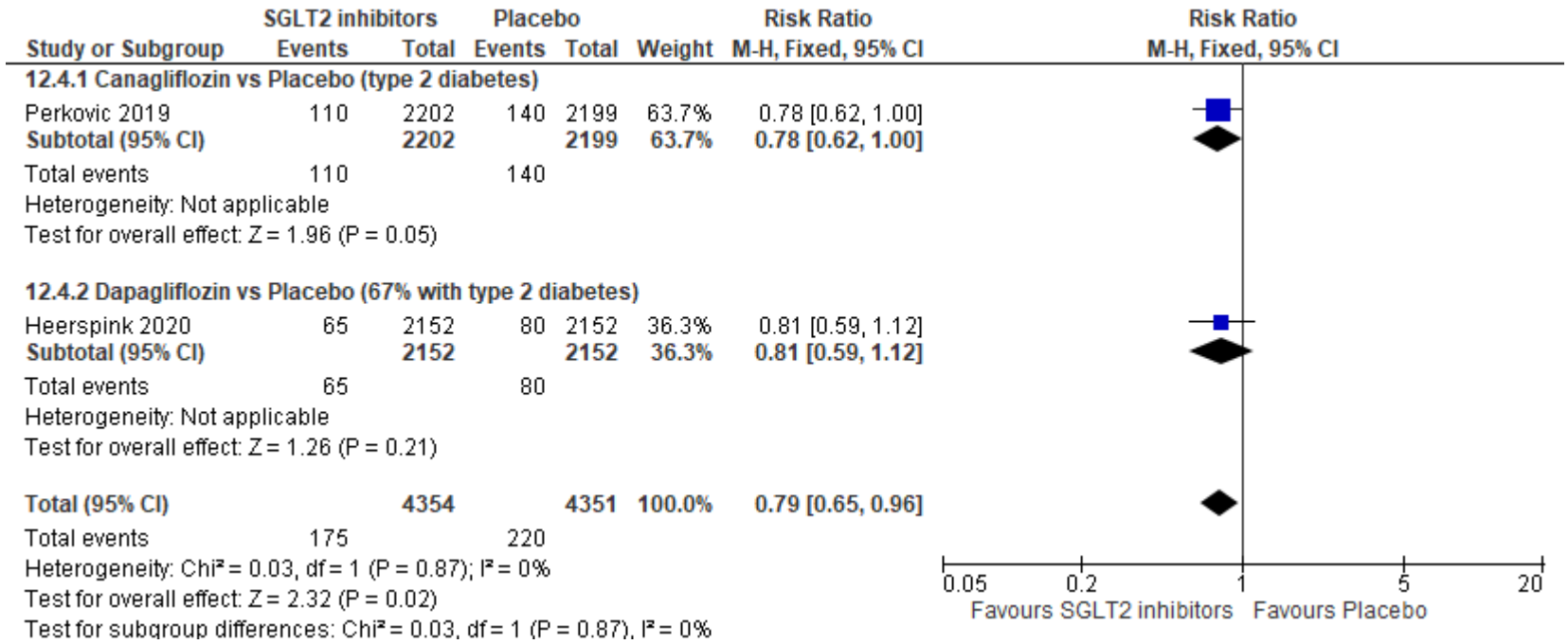


**Figure 9 SGLT2 inhibitor vs Placebo; outcome: Cardiovascular mortality**




Exercise vs Diet; outcome: Health-related quality of life

**Figure 10 ACE-I + ARB vs ARB; outcome: End stage kidney disease**

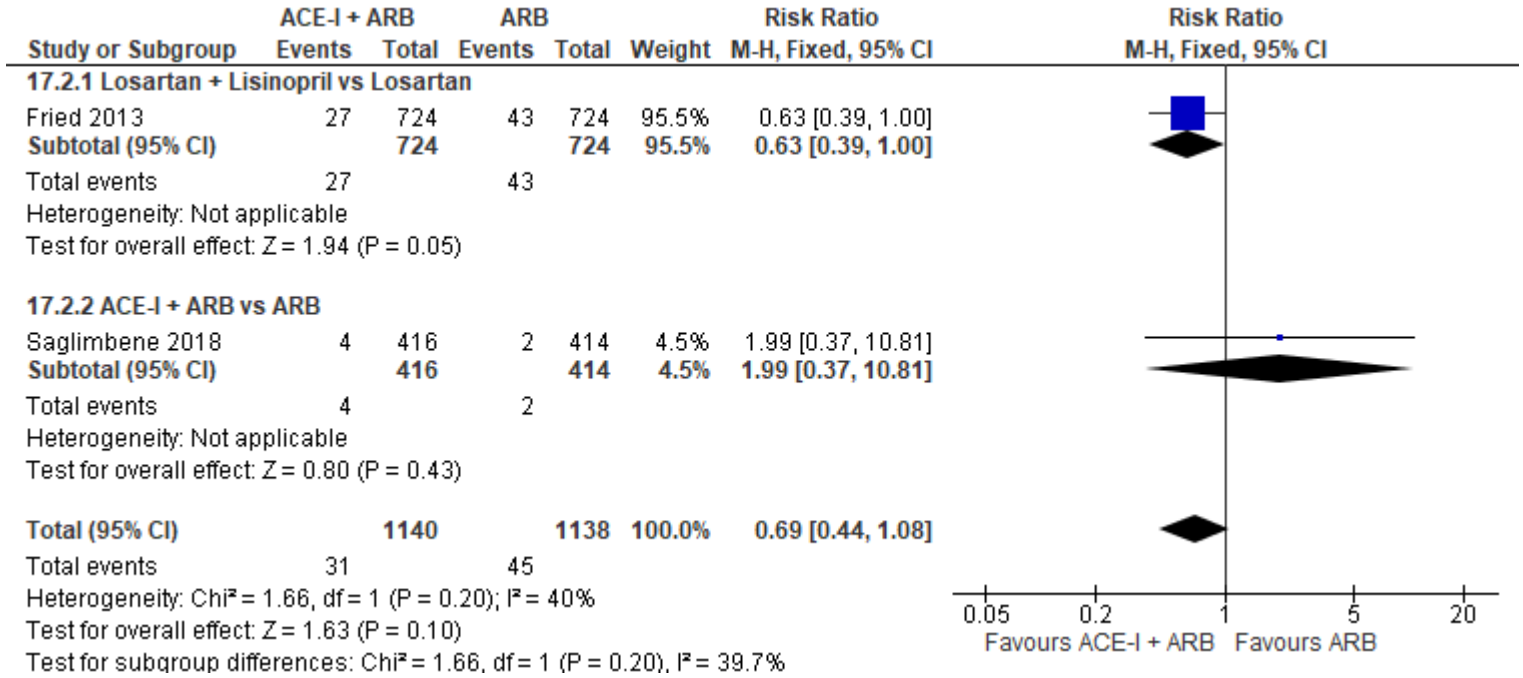


**Figure 11 ACE-I + ARB vs ARB; outcome: All-cause mortality**

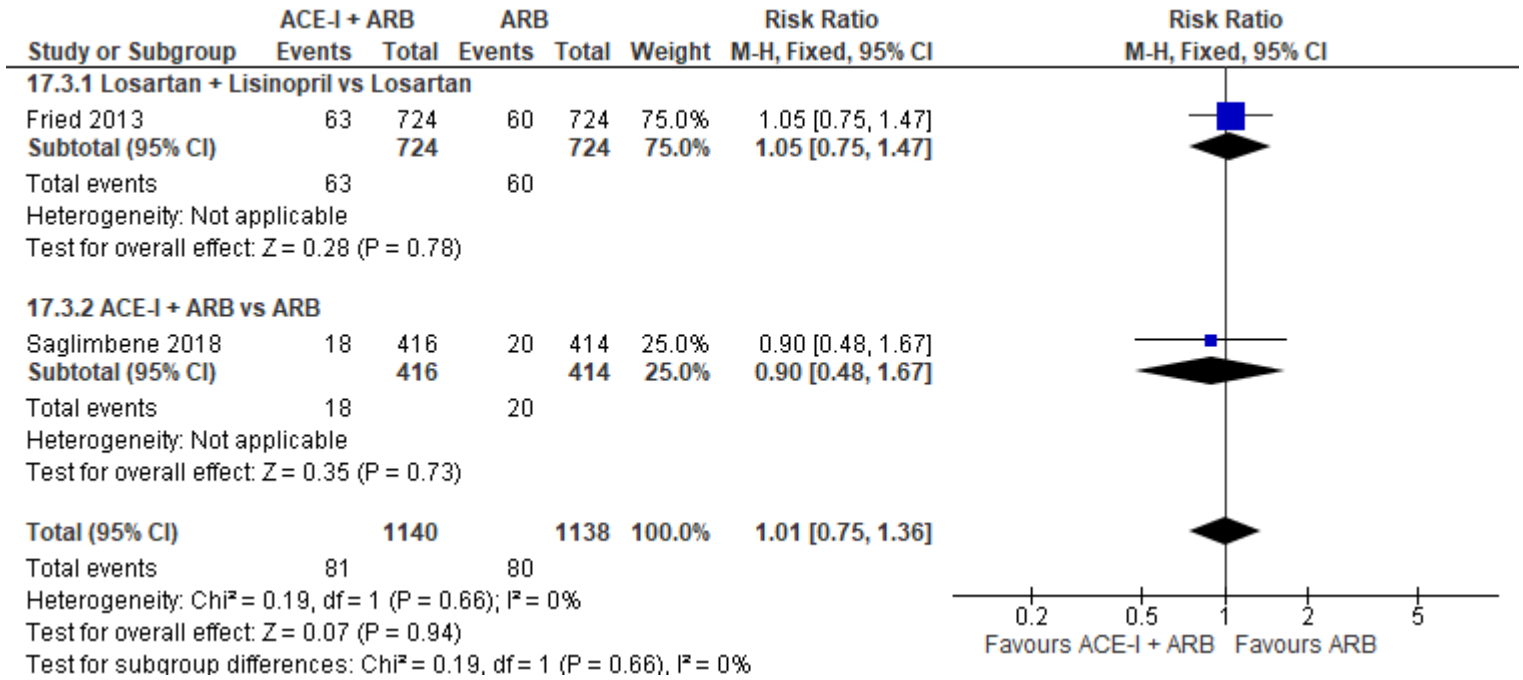
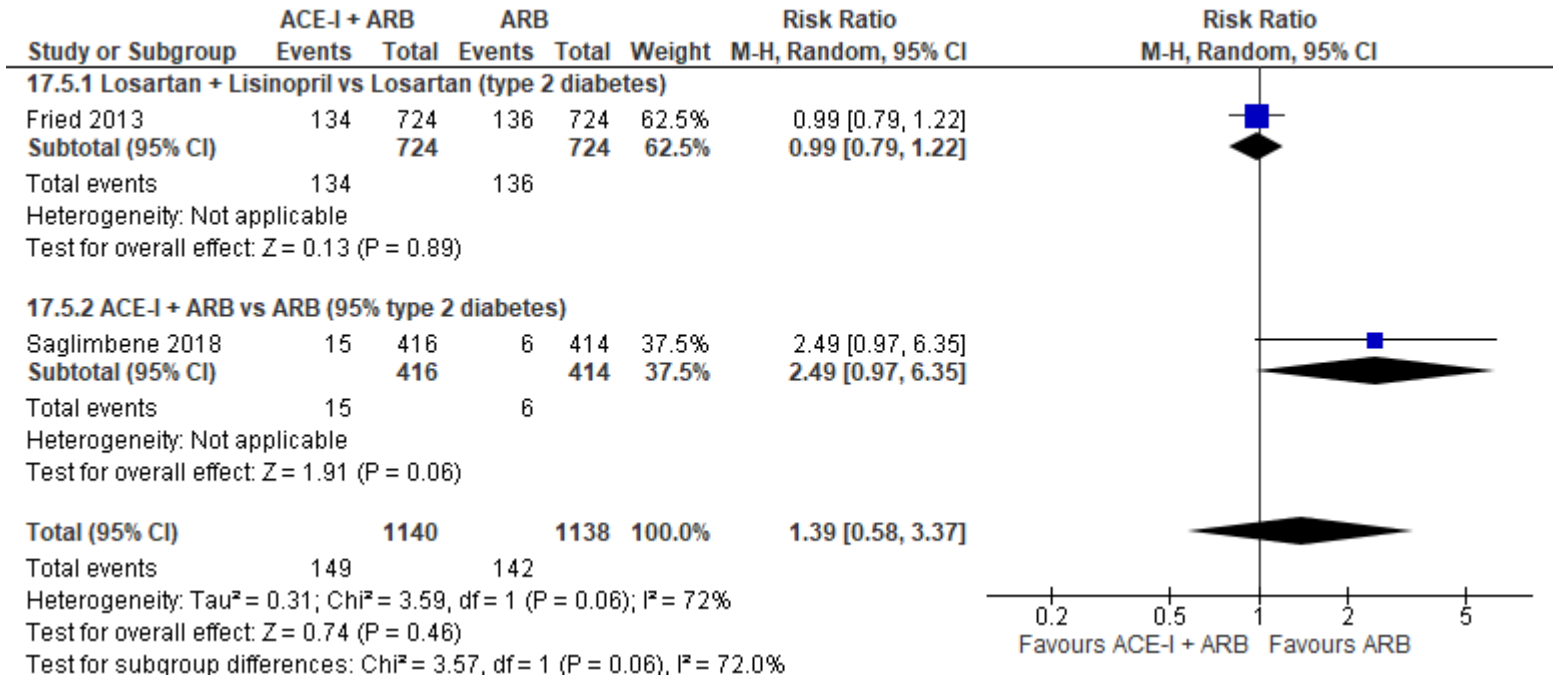


**Figure 12 ACE-I + ARB vs ARB; outcome: Non-fatal CV events**



# Adults without type 2 diabetes

**Figure 13 ACE-I vs Placebo; outcome: End stage kidney disease**

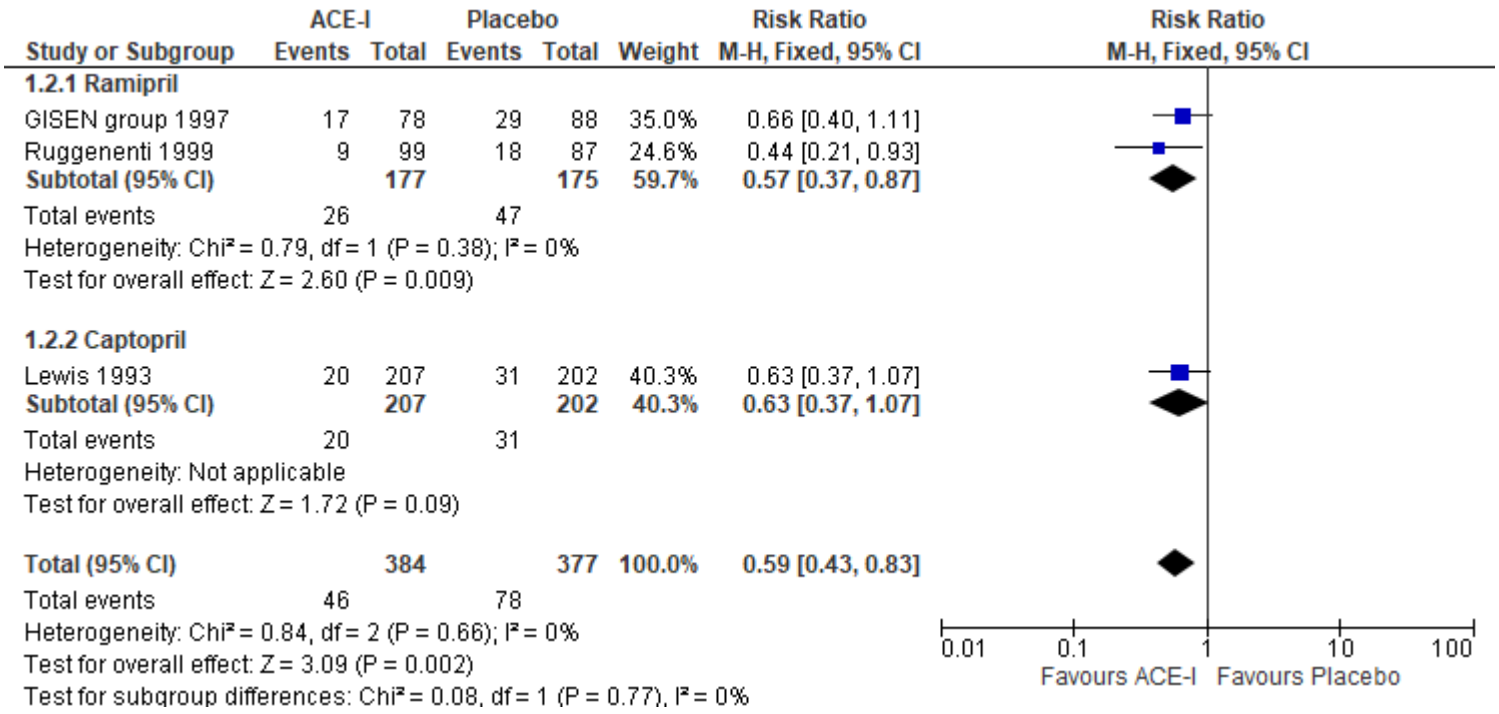


**Figure 14 ACE-I vs Placebo; outcome: All-cause mortality**

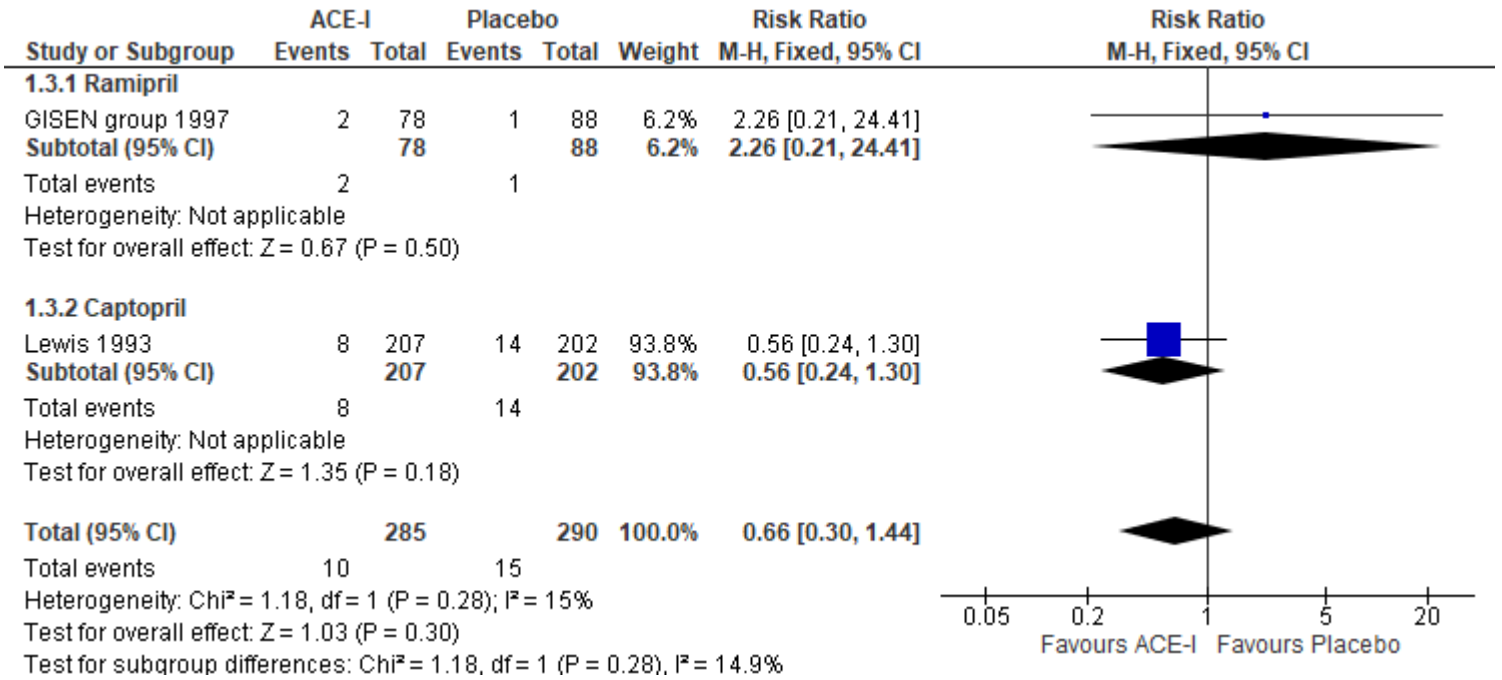


**Figure 15 ACE-I vs Placebo; outcome: CV mortality**

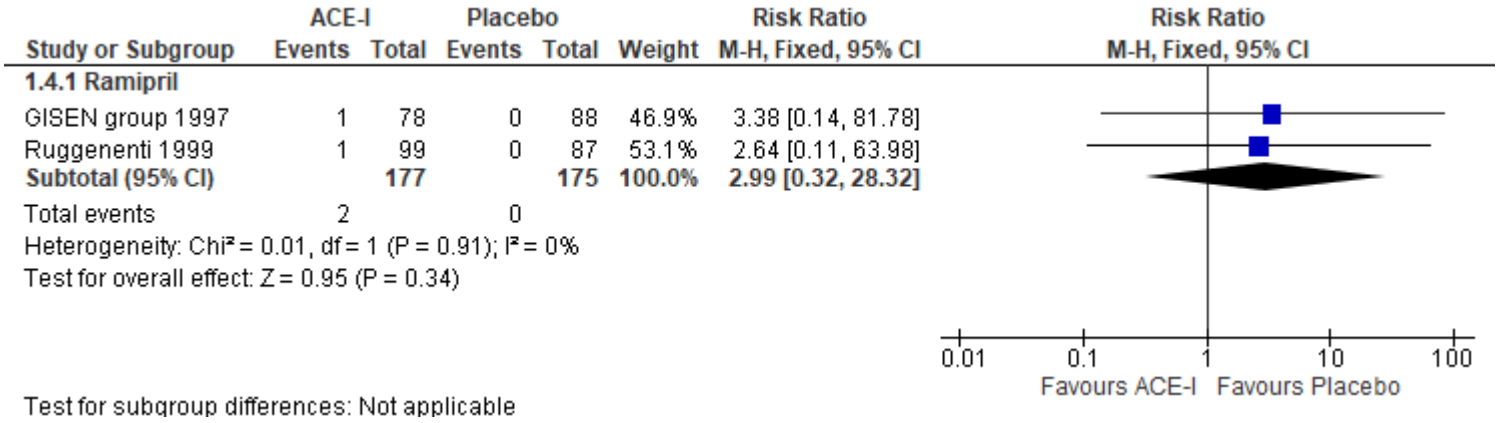



**Figure 16 ACE-I vs Placebo; outcome: Non-fatal CV events**

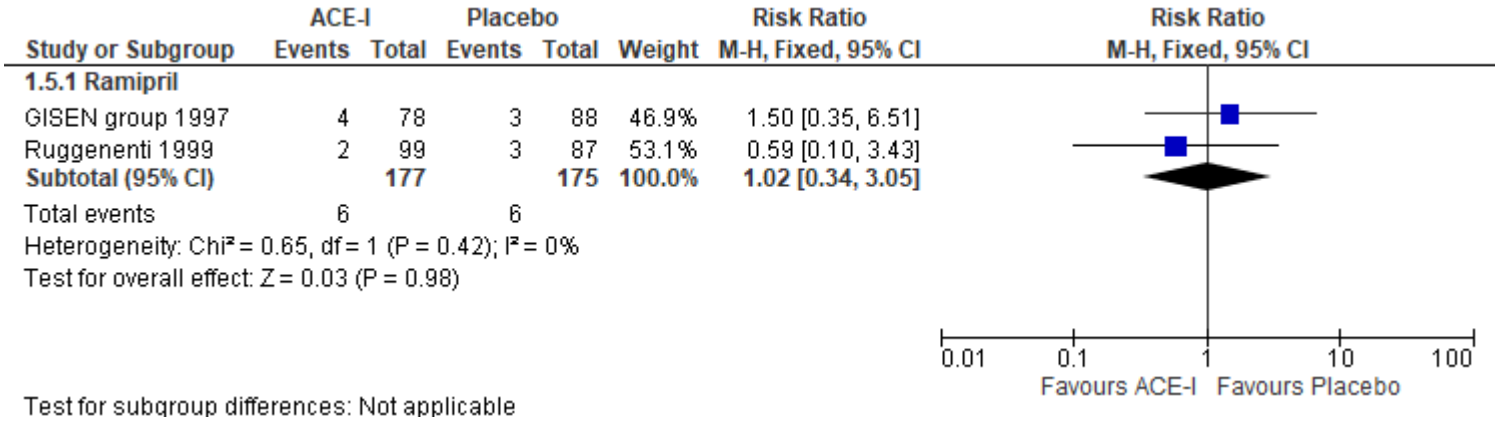


**Figure 17 ARB vs Placebo; outcome: Urinary albumin excretion (g/24 h)**

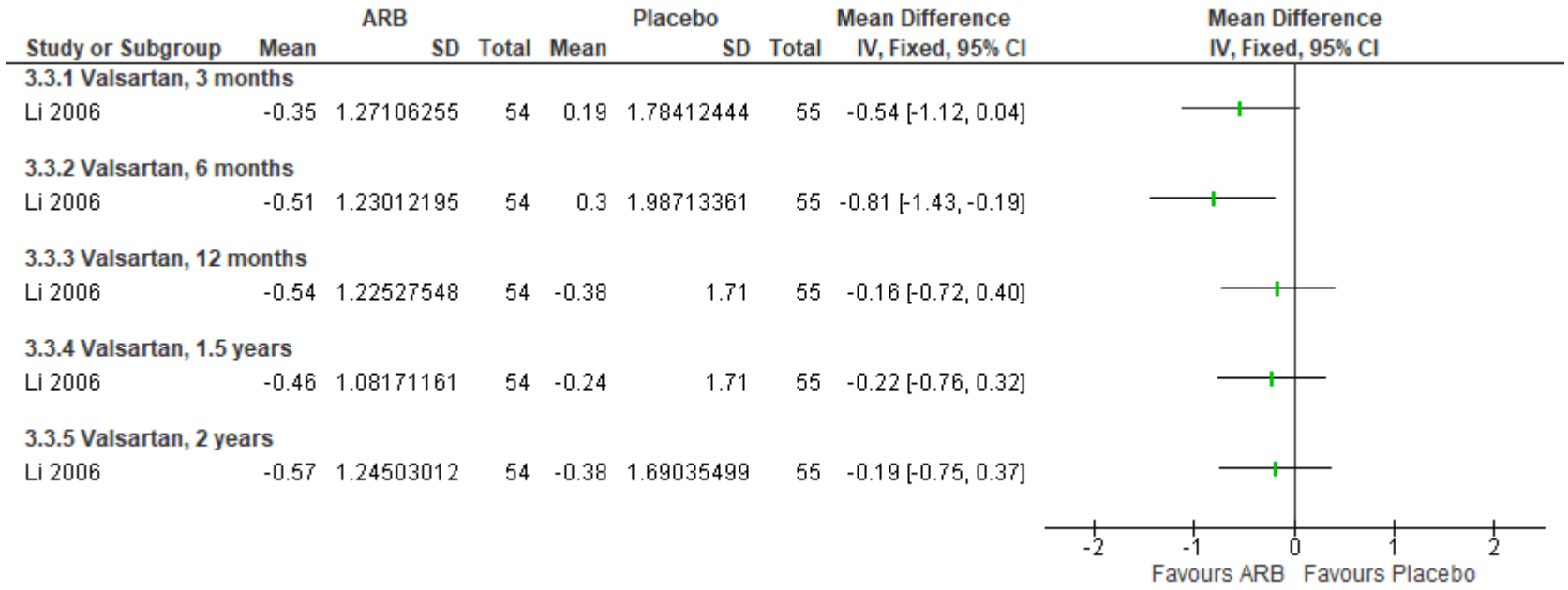
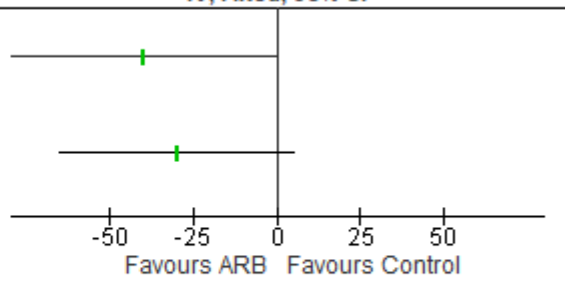


**Figure 18 ARB vs Control (usual antihypertensive therapy except ACE inhibitors and ARBs); outcome: Urinary protein creatinine ratio (mg/mmol)**

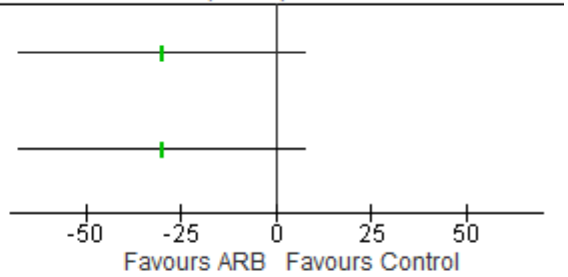
| | ARB | | | Control | | | Mean Difference | Mean Difference |
|---|---|---|---|---|---|---|---|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | IV, Fixed, 95% CI | IV, Fixed, 95% CI |
| **4.1.1 Losartan, 12 months** | | | | | | | | |
| Lee 2011 (1) | -60 | 60.827625 | 17 | -20 | 52.915026 | 15 | -40.00 [-79.41, -0.59] | |
| **4.1.2 Losartan, 24 months** | | | | | | | | |
| Lee 2011 (2) | -60 | 36.055513 | 17 | -30 | 60.827625 | 15 | -30.00 [-65.23, 5.23] | |




Footnotes
(1) g/mmol converted to mg/mmol multiplying g/mmol by 1000
(2) g/mmol converted to mg/mmol multiplying g/mmol by 1000

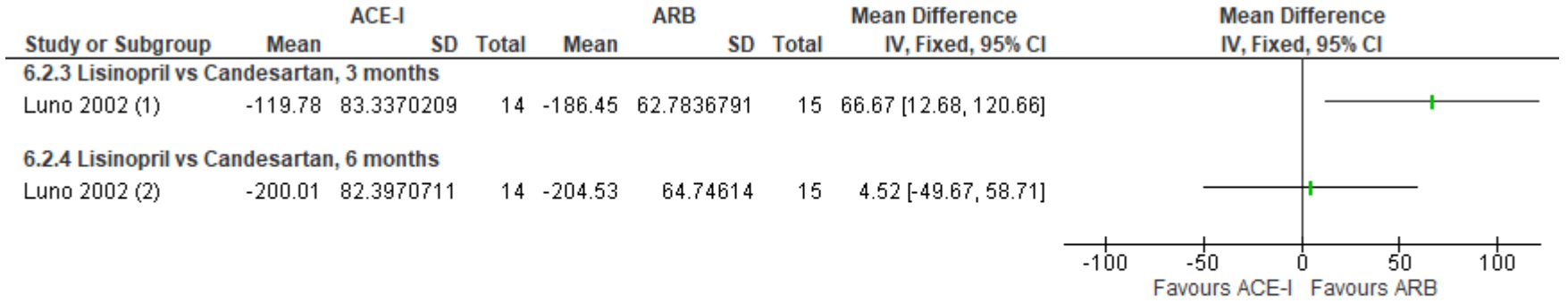
**Figure 19 ARB vs Control (usual antihypertensive therapy except ACE inhibitors and ARBs); outcome: Urinary albumin creatinine ratio (mg/mmol)**

| | ARB | | | Control | | | Mean Difference | Mean Difference |
|---|---|---|---|---|---|---|---|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | IV, Fixed, 95% CI | IV, Fixed, 95% CI |
| **4.2.1 Losartan, 12 months** | | | | | | | | |
| Lee 2011 (1) | -40 | 62.44998 | 17 | -10 | 45.825757 | 15 | -30.00 [-67.67, 7.67] | |
| **4.2.2 Losartan, 24 months** | | | | | | | | |
| Lee 2011 (2) | -50 | 43.588989 | 17 | -20 | 62.44998 | 15 | -30.00 [-67.79, 7.79] | |




Footnotes
(1) g/mmol converted to mg/mmol multiplying g/mmol by 1000
(2) g/mmol converted to mg/mmol multiplying g/mmol by 1000

**Figure 20 ACE-I vs ARB; outcome: Urinary protein/creatinine ratio (mg/mmol)**




Footnotes
(1) Mean change from baseline, g/g converted to mg/g (g/g multiplied by 1000), mg/g converted to mg/mmol multiplying mg/g by 0.113
(2) Mean change from baseline, g/g converted to mg/g (g/g multiplied by 1000), mg/g converted to mg/mmol multiplying mg/g by 0.113

**Figure 21 ACE-I vs ARB; outcome: Urinary protein excretion (g/24h), Mean percentage reduction from baseline in adults with moderate proteinuria**

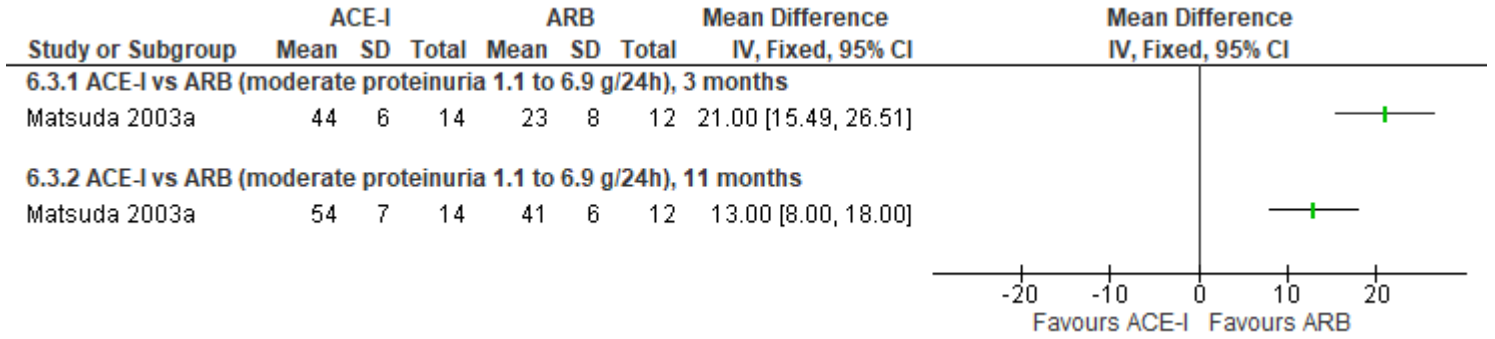


**Figure 22 ACE-I vs ARB; outcome: Urinary protein excretion (g/24h), Mean percentage reduction from baseline to 3 months**

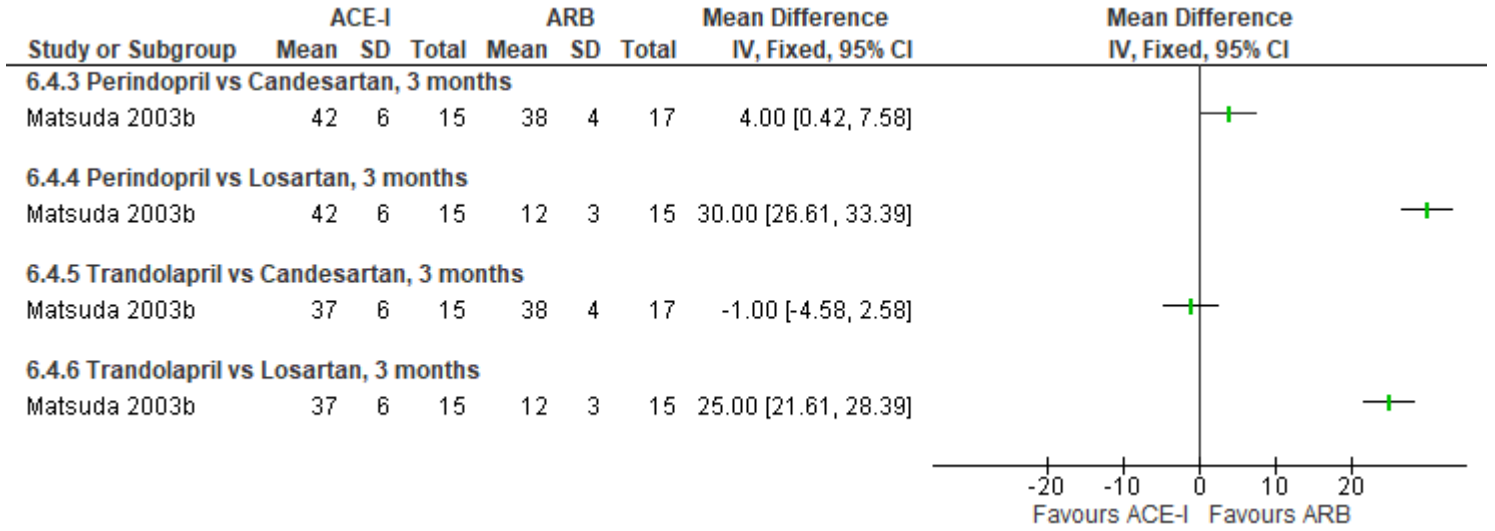


**Figure 23 ACE-I vs ARB; outcome: Urinary protein excretion (g/24h), Mean percentage reduction from baseline to 22 months**

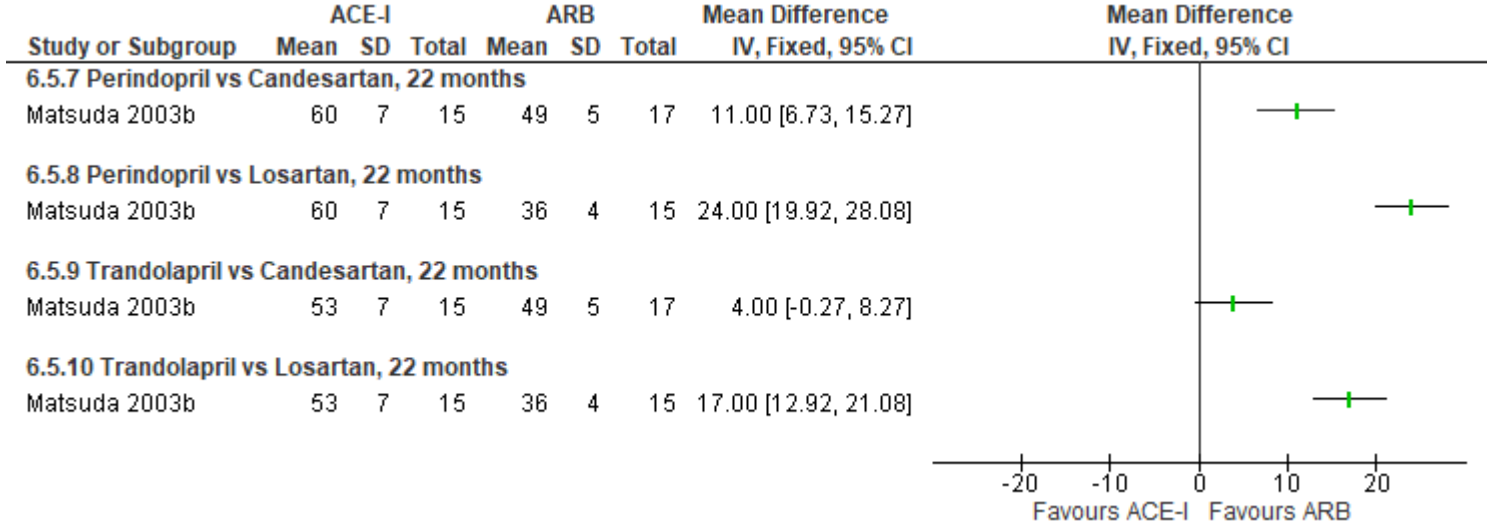
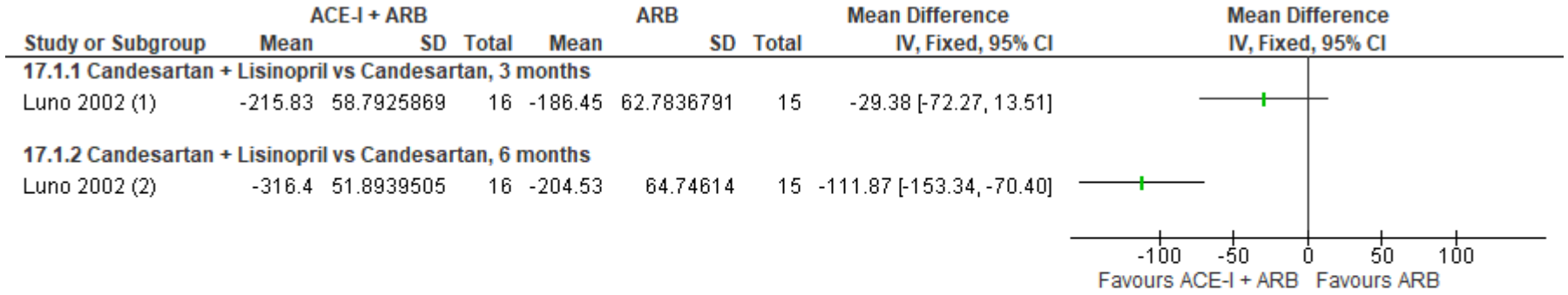


**Figure 24 ACE-I + ARB vs ARB; outcome: Urinary protein/creatinine ratio (mg/mmol)**

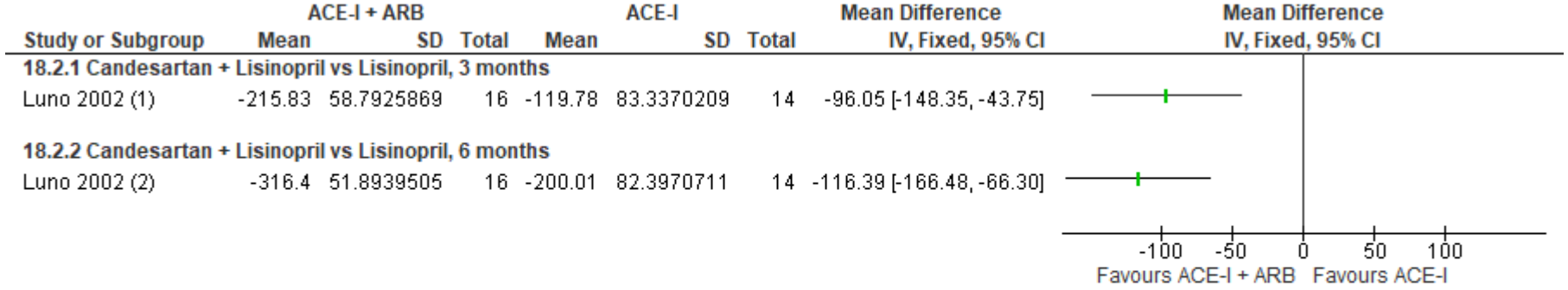



Footnotes

(1) Mean change from baseline, g/g converted to mg/g (g/g multiplied by 1000), mg/g converted to mg/mmol multiplying mg/g by 0.113

(2) Mean change from baseline, g/g converted to mg/g (g/g multiplied by 1000), mg/g converted to mg/mmol multiplying mg/g by 0.113

**Figure 25 ACE-I + ARB vs ACE-I; outcome: Urinary protein/creatinine ratio (mg/mmolg/g)**

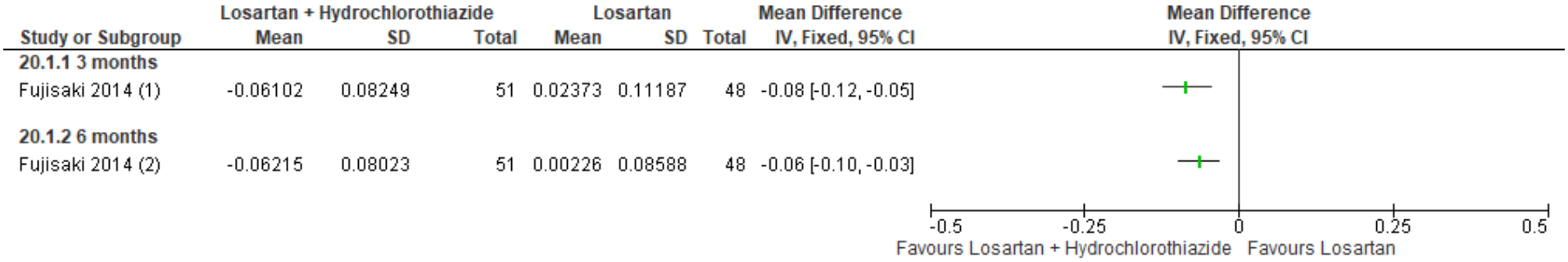



Footnotes

(1) Mean change from baseline, g/g converted to mg/g (g/g multiplied by 1000), mg/g converted to mg/mmol multiplying mg/g by 0.113

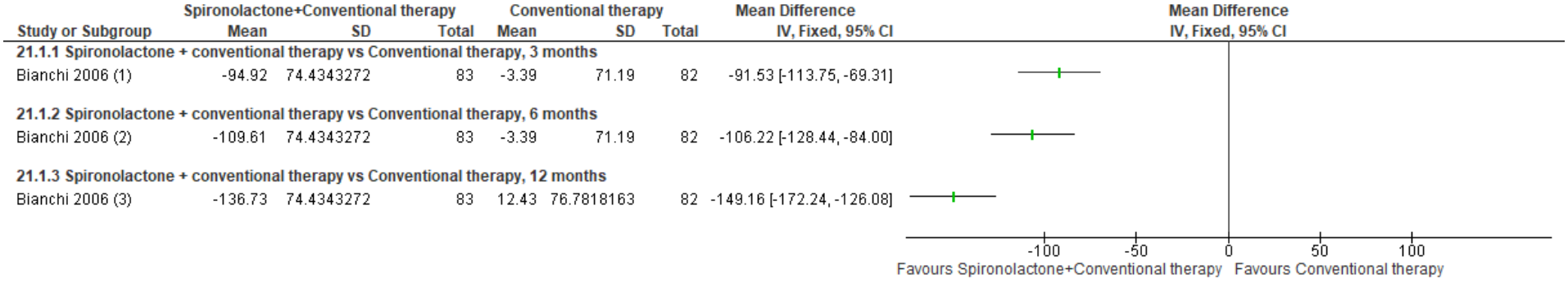
(2) Mean change from baseline, g/g converted to mg/g (g/g multiplied by 1000), mg/g converted to mg/mmol multiplying mg/g by 0.113

**Figure 26 ARB + Diuretic vs ARB; outcome: Urinary protein/creatinine ratio (mg/mmol)**




Footnotes
(1) Mean change from baseline, mg/g converted to mg/mmol multiplying mg/g by 0.113
(2) Mean change from baseline, mg/g converted to mg/mmol multiplying mg/g by 0.113

**Figure 27 Spironolactone vs placebo; outcome: Urinary protein/creatinine ratio (mg/mmol)**




Footnotes
(1) Mean change from baseline, g/g converted to mg/g (g/g multiplied by 1000), mg/g converted to mg/mmol multiplying mg/g by 0.113
(2) Mean change from baseline, g/g converted to mg/g (g/g multiplied by 1000), mg/g converted to mg/mmol multiplying mg/g by 0.113
(3) Mean change from baseline, g/g converted to mg/g (g/g multiplied by 1000), mg/g converted to mg/mmol multiplying mg/g by 0.113

# Appendix G – GRADE

# Adults with type 2 diabetes

### Aldosterone antagonist vs placebo

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Aldosterone antagonist | Placebo | Relative (95% CI) | Absolute | |
| **Urinary protein/creatinine ratio (mean percentage change) - Spironolactone (type 2 diabetes) (Better indicated by lower values [MID 36.6])** | | | | | | | | | | | |
| 1 | randomised trials[1] | very serious[2] | no serious inconsistency | no serious indirectness | serious[3] | none | 24 | 28 | - | MD 27.1 lower (58.75 lower to 4.55 higher) | VERY LOW |
| **Urinary albumin/creatinine ratio (mean percentage change) - Spironolactone (at least 85% type 2 diabetes) (Better indicated by lower values [MID 50.7])** | | | | | | | | | | | |
| 2 | randomised trials | very serious[2] | serious[4] | no serious indirectness | serious[3] | none | 51 | 55 | - | MD 29.13 higher (58.10 to 0.16 lower) | VERY LOW |
| **Non-fatal CV events - Spironolactone (85% type 2 diabetes)** | | | | | | | | | | | |
| 1 | randomised trials[5] | serious[6] | no serious inconsistency | no serious indirectness | very serious[7] | none | 6/27 (22.2%) | 1/27 (3.7%) | RR 6 (0.77 to 46.55) | 19 more per 100 (from 1 fewer to 100 more) | VERY LOW |
| **Hospitalisation - Spironolactone (85% type 2 diabetes)** | | | | | | | | | | | |
| 1 | randomised trials[5] | serious[6] | no serious inconsistency | no serious indirectness | very serious[7] | none | 6/27 (22.2%) | 1/27 (3.7%) | RR 6 (0.77 to 46.55) | 19 more per 100 (from 1 fewer to 100 more) | VERY LOW |

[1] van den Meiracker 2006
[2] >33.3% of weighted data from studies at high risk of bias
[3] 95% confidence interval crosses one end of a defined MID interval
[4] i-squared >33.3%
[5] Mehdi 2009
[6] >33.3% of weighted data from studies at moderate or high risk of bias
[7] 95% confidence interval crosses both ends of a defined MID interval

## ARB vs placebo

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | ARB | Placebo | Relative (95% CI) | Absolute | |
| **Urinary protein excretion (g/24 h) - Irbesartan (type 2 diabetes) (Better indicated by lower values [MID 2.15])** | | | | | | | | | | | |
| 1 | randomised trials[1] | serious[2] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 579 | 569 | - | MD 0.8 lower (1.18 to 0.42 lower) | MODERATE |
| **Urinary albumin/creatinine ratio (mean percentage change) - Losartan (85% type 2 diabetes) (Better indicated by lower values [MID 63.82])** | | | | | | | | | | | |
| 1 | randomised trials[3] | serious[2] | no serious inconsistency | no serious indirectness | serious[4] | none | 26 | 27 | - | MD 13.6 lower (70.73 lower to 43.53 higher) | LOW |
| **End stage kidney disease** | | | | | | | | | | | |
| 2 | randomised trials[5] | serious[2] | no serious inconsistency | no serious indirectness | serious[4] | none | 219/1330 (16.5%) | 279/1331 (21%) | RR 0.79 (0.67 to 0.92) | 4 fewer per 100 (from 2 fewer to 7 fewer) | LOW |
| **End stage kidney disease - Losartan (type 2 diabetes)** | | | | | | | | | | | |
| 1 | randomised trials[6] | serious[2] | no serious inconsistency | no serious indirectness | serious[4] | none | 147/751 (19.6%) | 194/762 (25.5%) | RR 0.77 (0.64 to 0.93) | 6 fewer per 100 (from 2 fewer to 9 fewer) | LOW |
| **End stage kidney disease - Irbesartan (type 2 diabetes)** | | | | | | | | | | | |
| 1 | randomised trials[7] | serious[2] | no serious inconsistency | no serious indirectness | serious[4] | none | 72/579 (12.4%) | 85/569 (14.9%) | RR 0.83 (0.62 to 1.11) | 3 fewer per 100 (from 6 fewer to 2 more) | LOW |
| **All-cause mortality** | | | | | | | | | | | |
| 2 | randomised trials[5] | serious[2] | no serious inconsistency | no serious indirectness | serious[8] | none | 233/1330 (17.5%) | 233/1331 (17.5%) | RR 1 (0.85 to 1.18) | 0 fewer per 100 (from 3 fewer to 3 more) | LOW |
| **All-cause mortality - Losartan (type 2 diabetes)** | | | | | | | | | | | |
| 1 | randomised trials[6] | serious[2] | no serious inconsistency | no serious indirectness | serious[8] | none | 158/751 (21%) | 155/762 (20.3%) | RR 1.03 (0.85 to 1.26) | 1 more per 100 (from 3 fewer to 5 more) | LOW |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **All-cause mortality - Irbesartan (type 2 diabetes)** | | | | | | | | | | | |
| 1 | randomised trials[7] | serious[2] | no serious inconsistency | no serious indirectness | serious[8] | none | 75/579 (13%) | 78/569 (13.7%) | RR 0.94 (0.7 to 1.27) | 1 fewer per 100 (from 4 fewer to 4 more) | LOW |
| **Non-fatal CV events - Losartan (at least 85% type 2 diabetes)** | | | | | | | | | | | |
| 2 | randomised trials[9] | serious[2] | no serious inconsistency | no serious indirectness | serious[4] | none | 52/777 (6.7%) | 69/789 (8.7%) | RR 0.77 (0.54 to 1.08) | 2 fewer per 100 (from 4 fewer to 1 more) | LOW |
| **Hospitalisation - Losartan (at least 85% type 2 diabetes)** | | | | | | | | | | | |
| 2 | randomised trials[9] | serious[2] | no serious inconsistency | no serious indirectness | serious[4] | none | 91/777 (11.7%) | 128/789 (16.2%) | RR 0.72 (0.56 to 0.93) | 5 fewer per 100 (from 1 fewer to 7 fewer) | LOW |

[1] Lewis 2001
[2] >33.3% of weighted data from studies at moderate or high risk of bias
[3] Mehdi 2009
[4] 95% confidence interval crosses one end of a defined MID interval
[5] Brenner 2001; Lewis 2001
[6] Brenner 2001
[7] Lewis 2001
[8] 95% confidence interval crosses line of no effect
[9] Brenner 2001; Mehdi 2009

## CCB vs Placebo

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **CCB** | **Placebo** | **Relative (95% CI)** | **Absolute** | |
| **Urinary protein excretion (g/24 h) - Amlodipine vs Placebo (type 2 diabetes) (Better indicated by lower values [MID 2.15])** | | | | | | | | | | | |
| 1 | randomised trials[1] | serious[2] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 567 | 569 | - | MD 0.2 higher (0.23 lower to 0.63 higher) | MODERATE |
| **End stage kidney disease - Amlodipine vs Placebo (type 2 diabetes)** | | | | | | | | | | | |
| 1 | randomised trials[1] | serious[2] | no serious inconsistency | no serious indirectness | serious[3] | none | 85/567 (15%) | 78/569 (13.7%) | RR 1.09 (0.82 to 1.45) | 1 more per 100 (from 2 fewer to 6 more) | LOW |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **All-cause mortality - Amlodipine vs Placebo (type 2 diabetes)** | | | | | | | | | | | |
| 1 | randomised trials[1] | serious[4] | no serious inconsistency | no serious indirectness | serious[3] | none | 66/567 (11.6%) | 74/569 (13%) | RR 0.9 (0.66 to 1.22) | 1 fewer per 100 (from 4 fewer to 3 more) | LOW |

[1] Lewis 2001
[2] Study at moderate risk of bias
[3] 95% confidence interval crosses one end of a defined MID interval
[4] 95% confidence interval crosses line of no effect

## ACE-I vs ARB

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **ACE-I** | **ARB** | **Relative (95% CI)** | **Absolute** | |
| **Urinary protein/creatinine ratio (mg/mmol) - Enalapril vs Telmisartan (type 2 diabetes), 3 months (Better indicated by lower values [MID 104.2])** | | | | | | | | | | | |
| 1 | randomised trials[1] | very serious[2] | no serious inconsistency | no serious indirectness | serious[3] | none | 40 | 40 | - | MD 46.33 higher (34.76 lower to 127.42 higher) | VERY LOW |
| **Urinary protein/creatinine ratio (mg/mmol) - Enalapril vs Telmisartan (type 2 diabetes), 6 months (Better indicated by lower values [MID 100.0])** | | | | | | | | | | | |
| 1 | randomised trials[1] | very serious[2] | no serious inconsistency | no serious indirectness | serious[3] | none | 40 | 40 | - | MD 74.58 higher (6.72 lower to 155.88 higher) | VERY LOW |
| **End stage kidney disease - 95% type 2 diabetes** | | | | | | | | | | | |
| 1 | randomised trials[4] | very serious[2] | no serious inconsistency | no serious indirectness | very serious[5] | none | 6/413 (1.5%) | 2/414 (0.48%) | RR 3.01 (0.61 to 14.81) | 1 more per 100 (from 0 fewer to 7 more) | VERY LOW |
| **All-cause mortality - 95% type 2 diabetes** | | | | | | | | | | | |
| 1 | randomised trials[4] | very serious[2] | no serious inconsistency | no serious indirectness | serious[6] | none | 15/413 (3.6%) | 20/414 (4.8%) | RR 0.75 (0.39 to 1.45) | 1 fewer per 100 (from 3 fewer to 2 more) | VERY LOW |
| **CV mortality - 95% type 2 diabetes** | | | | | | | | | | | |
| 1 | randomised trials[4] | very serious[2] | no serious inconsistency | no serious indirectness | serious[6] | none | 6/413 (1.5%) | 7/414 (1.7%) | RR 0.86 (0.29 to 2.53) | 0 fewer per 100 (from 1 fewer to 3 more) | VERY LOW |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Non-fatal CV events - 95% type 2 diabetes** | | | | | | | | | | | |
| 1 | randomised trials[4] | very serious[2] | no serious inconsistency | no serious indirectness | very serious[5] | none | 8/413 (1.9%) | 6/414 (1.4%) | RR 1.34 (0.47 to 3.82) | 0 more per 100 (from 1 fewer to 4 more) | VERY LOW |
| **Adverse events (hypotension) - 95% type 2 diabetes** | | | | | | | | | | | |
| 1 | randomised trials[4] | very serious[2] | no serious inconsistency | no serious indirectness | very serious[5] | none | 3/413 (0.73%) | 2/414 (0.48%) | RR 1.5 (0.25 to 8.95) | 0 more per 100 (from 0 fewer to 4 more) | VERY LOW |
| **Hospitalisation - 95% type 2 diabetes** | | | | | | | | | | | |
| 1 | randomised trials[4] | very serious[2] | no serious inconsistency | no serious indirectness | very serious[5] | none | 25/413 (6.1%) | 20/414 (4.8%) | RR 1.25 (0.71 to 2.22) | 1 more per 100 (from 1 fewer to 6 more) | VERY LOW |

[1] Krairittichai 2009
[2] Study at high risk of bias
[3] 95% confidence interval crosses one end of a defined MID interval
[4] Saglimbene 2018
[5] 95% confidence interval crosses both ends of a defined MID interval
[6] 95% confidence interval crosses line of no effect

## ARB vs Aldosterone antagonist

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **ARB** | **Aldosterone antagonist** | **Relative (95% CI)** | **Absolute** | |
| **Urinary albumin/creatinine ratio (mean percentage change) - Losartan vs Spironolactone (85% type 2 diabetes) (Better indicated by lower values [MID 38.17])** | | | | | | | | | | | |
| 1 | randomised trials[1] | serious[2] | no serious inconsistency | no serious indirectness | serious[3] | none | 26 | 27 | - | MD 13.4 higher (28.72 lower to 55.52 higher) | LOW |
| **Non-fatal CV events - Losartan vs Spironolactone (85% type 2 diabetes)** | | | | | | | | | | | |
| 1 | randomised trials[1] | serious[2] | no serious inconsistency | no serious indirectness | very serious[4] | none | 2/26 (7.7%) | 6/27 (22.2%) | RR 0.35 (0.08 to 1.56) | 14 fewer per 100 (from 20 fewer to 12 more) | VERY LOW |
| **Hospitalisation - Losartan vs Spironolactone (85% type 2 diabetes)** | | | | | | | | | | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials[1] | serious[2] | no serious inconsistency | no serious indirectness | very serious[4] | none | 2/26 (7.7%) | 6/27 (22.2%) | RR 0.35 (0.08 to 1.56) | 14 fewer per 100 (from 20 fewer to 12 more) | VERY LOW |

[1] Mehdi 2009
[2] Study at moderate risk of bias
[3] 95% confidence interval crosses one end of a defined MID interval
[4] 95% confidence interval crosses both ends of a defined MID interval

## ARB vs CCB

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **ARB** | **CCB** | **Relative (95% CI)** | **Absolute** | |
| **Urinary protein excretion (g/24 h) - Irbesartan vs Amlodipine (type 2 diabetes) (Better indicated by lower values [MID 1.45])** | | | | | | | | | | | |
| 1 | randomised trials[1] | serious[2] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 579 | 567 | - | MD 1 lower (1.28 to 0.72 lower) | MODERATE |
| **End stage kidney disease - Irbesartan vs Amlodipine (type 2 diabetes)** | | | | | | | | | | | |
| 1 | randomised trials[1] | serious[2] | no serious inconsistency | no serious indirectness | serious[3] | none | 71/579 (12.3%) | 91/567 (16%) | RR 0.76 (0.57 to 1.02) | 4 fewer per 100 (from 7 fewer to 0 more) | LOW |
| **All-cause mortality - Irbesartan vs Amlodipine (type 2 diabetes)** | | | | | | | | | | | |
| 1 | randomised trials[1] | serious[2] | no serious inconsistency | no serious indirectness | serious[4] | none | 78/579 (13.5%) | 73/567 (12.9%) | RR 1.05 (0.78 to 1.41) | 1 more per 100 (from 3 fewer to 5 more) | LOW |

[1] Lewis 2001
[2] Study at moderate risk of bias
[3] 95% confidence interval crosses one end of a defined MID interval
[4] 95% confidence interval crosses line of no effect

## Gliptin vs placebo

| Quality assessment | No of patients | Effect | Quality |
|---|---|---|---|

| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Gliptin | Placebo | Relative (95% CI) | Absolute | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Urinary albumin/creatinine ratio (mean percentage change) - Linagliptin vs Placebo (type 2 diabetes) (Better indicated by lower values [MID 22.64])** | | | | | | | | | | | |
| 1 | randomised trials[1] | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 182 | 178 | - | MD 5.9 lower (15.03 lower to 3.23 higher) | HIGH |
| **Hypoglycaemia - Linagliptin vs Placebo (type 2 diabetes)** | | | | | | | | | | | |
| 1 | randomised trials[1] | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[2] | none | 24/182 (13.2%) | 10/178 (5.6%) | RR 2.35 (1.16 to 4.77) | 8 more per 100 (from 1 more to 21 more) | MODERATE |

[1] Groop 2017
[2] 95% confidence interval crosses one end of a defined MID interval

## Thiazolidinedione vs placebo

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Thiazolidinedione | Placebo (type 2 diabetes) | Relative (95% CI) | Absolute | |
| **Urinary protein excretion (g/24 h) - Pioglitazone vs Placebo (Better indicated by lower values [MID 1.05])** | | | | | | | | | | | |
| 1 | randomised trials[1] | very serious[2] | no serious inconsistency | no serious indirectness | serious[3] | none | 21 | 20 | - | MD 1 lower (2.04 lower to 0.04 higher) | VERY LOW |

[1] Kanjanabuch 2009
[2] Study at high risk of bias
[3] 95% confidence interval crosses one end of a defined MID interval

## SGLT2 inhibitor vs placebo

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | SGLT2 inhibitor | Placebo | Relative (95% CI) | Absolute | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Urinary albumin excretion (g/24 h) - Dapagliflozin vs Placebo (type 2 diabetes) (Better indicated by lower values [MID 71.44])** | | | | | | | | | | | |
| 1 | randomised trials[1] | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 108 | 99 | - | MD 19.7 lower (56.39 lower to 16.99 higher) | HIGH |
| **End stage kidney disease** | | | | | | | | | | | |
| 2 | randomised trials[2] | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[3] | none | 225/4354 (5.2%) | 326/4351 (7.5%) | RR 0.69 (0.59 to 0.81) | 2 fewer per 100 (from 1 fewer to 3 fewer) | MODERATE |
| **End stage kidney disease - Canagliflozin vs Placebo (type 2 diabetes)** | | | | | | | | | | | |
| 1 | randomised trials[4] | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[3] | none | 116/2202 (5.3%) | 165/2199 (7.5%) | RR 0.7 (0.56 to 0.88) | 2 fewer per 100 (from 1 fewer to 3 fewer) | MODERATE |
| **End stage kidney disease - Dapagliflozin vs Placebo (67% with type 2 diabetes)** | | | | | | | | | | | |
| 1 | randomised trials[5] | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[3] | none | 109/2152 (5.1%) | 161/2152 (7.5%) | RR 0.68 (0.53 to 0.86) | 2 fewer per 100 (from 1 fewer to 4 fewer) | MODERATE |
| **All-cause mortality** | | | | | | | | | | | |
| 3 | randomised trials[6] | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 270/4499 (6%) | 347/4499 (7.7%) | RR 0.78 (0.67 to 0.91) | 2 fewer per 100 (from 1 fewer to 3 fewer) | HIGH |
| **All-cause mortality - Dapagliflozin vs Placebo (type 2 diabetes)** | | | | | | | | | | | |
| 2 | randomised trials[7] | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 102/2297 (4.4%) | 146/2300 (6.3%) | RR 0.70 (0.55 to 0.89) | 2 fewer per 100 (from 1 fewer to 3 fewer) | HIGH |
| **All-cause mortality - Canagliflozin vs Placebo (type 2 diabetes)** | | | | | | | | | | | |
| 1 | randomised trials[4] | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[8] | none | 168/2202 (7.6%) | 201/2199 (9.1%) | RR 0.83 (0.69 to 1.02) | 2 fewer per 100 (from 3 fewer to 0 more) | MODERATE |
| **All-cause mortality - Canagliflozin vs Placebo, microalbuminuria: urinary albumin/creatinine ratio 3 to 30 mg/mmol** | | | | | | | | | | | |
| 1 | randomised trials[9] | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[8] | none | 23.5 patients with an event per 1000 patient-years | 22.9 patients with an event per 1000 patient-years | HR 1.00 (0.74 to 1.34) | -[10] | MODERATE |
| **All-cause mortality - Canagliflozin vs Placebo, macroalbuminuria: urinary albumin/creatinine ratio >30 mg/mmol** | | | | | | | | | | | |
| 1 | randomised trials[9] | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 37.3 patients with an event per 1000 patient-years | 57.5 patients with an event per 1000 patient-years | HR 0.63 (0.43, 0.92) | -[10] | HIGH |
| **CV mortality** | | | | | | | | | | | |
| 2 | randomised trials[2] | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 175/4354 (4%) | 220/4351 (5.1%) | RR 0.79 (0.65 to 0.96) | 1 fewer per 100 (from 0 fewer to 2 fewer) | HIGH |
| **CV mortality - Canagliflozin vs Placebo (type 2 diabetes)** | | | | | | | | | | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials[4] | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[8] | none | 110/2202 (5%) | 140/2199 (6.4%) | RR 0.78 (0.62 to 1) | 1 fewer per 100 (from 2 fewer to 0 more) | MODERATE |
| **CV mortality - Dapagliflozin vs Placebo (67% with type 2 diabetes)** | | | | | | | | | | | |
| 1 | randomised trials[5] | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[8] | none | 65/2152 (3%) | 80/2152 (3.7%) | RR 0.81 (0.59 to 1.12) | 1 fewer per 100 (from 2 fewer to 0 more) | MODERATE |
| **CV mortality - Canagliflozin vs Placebo, microalbuminuria: urinary albumin/creatinine ratio 3 to 30 mg/mmol** | | | | | | | | | | | |
| 1 | randomised trials[9] | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[8] | none | 16.0 patients with an event per 1000 patient-years | 15.8 patients with an event per 1000 patient-years | HR 0.98 (0.69 to 1.41) | -[10] | MODERATE |
| **CV mortality - Canagliflozin vs Placebo, macroalbuminuria: urinary albumin/creatinine ratio >30 mg/mmol** | | | | | | | | | | | |
| 1 | randomised trials[9] | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[8] | none | 31.3 patients with an event per 1000 patient-years | 42.6 patients with an event per 1000 patient-years | HR 0.70 (0.45 to 1.07) | -[10] | MODERATE |
| **Acute kidney injury - Canagliflozin vs Placebo (type 2 diabetes)** | | | | | | | | | | | |
| 1 | randomised trials[4] | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[3] | none | 86/2200 (3.9%) | 98/2197 (4.5%) | RR 0.88 (0.66 to 1.16) | 1 fewer per 100 (from 2 fewer to 1 more) | MODERATE |
| **Minor hypoglycaemia - Dapagliflozin vs Placebo (type 2 diabetes)** | | | | | | | | | | | |
| 1 | randomised trials[1] | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[11] | none | 35/145 (24.1%) | 29/148 (19.6%) | RR 1.23 (0.8 to 1.9) | 5 more per 100 (from 4 fewer to 18 more) | LOW |
| **Major hypoglycaemia - Dapagliflozin vs Placebo (67% with type 2 diabetes)** | | | | | | | | | | | |
| 1 | randomised trials[5] | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[3] | none | 14/2149 (0.65%) | 28/2149 (1.3%) | RR 0.50 (0.26 to 0.95) | 1 fewer per 100 (from 0 fewer to 1 fewer) | MODERATE |
| **Hospitalisation - Canagliflozin vs Placebo (type 2 diabetes)** | | | | | | | | | | | |
| 1 | randomised trials[4] | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[3] | none | 89/2202 (4%) | 141/2199 (6.4%) | RR 0.63 (0.49 to 0.82) | 2 fewer per 100 (from 1 fewer to 3 fewer) | MODERATE |
| **Fractures - Dapagliflozin vs Placebo (67% with type 2 diabetes)** | | | | | | | | | | | |
| 1 | randomised trials[5] | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[3] | none | 85/2149 (4%) | 69/2149 (3.2%) | RR 1.23 (0.9 to 1.68) | 1 more per 100 (from 0 fewer to 2 more) | MODERATE |

[1] Pollock 2019
[2] Heerspink 2020; Perkovic 2019
[3] 95% confidence interval crosses one end of a defined MID interval
[4] Perkovic 2019
[5] Heerspink 2020
[6] Heerspink 2020; Perkovic 2019; Pollock 2019
[7] Heerspink 2020; Pollock 2019
[8] 95% confidence interval crosses line of no effect
[9] Neuen 2019

[10] Outcome reported as patients with an event per 1000 patient-years
[11] 95% confidence interval crosses both ends of a defined MID interval

## SGLT2 inhibitor + gliptin vs SGLT2 inhibitor

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | SGLT2 inhibitor + gliptin | SGLT2 inhibitor | Relative (95% CI) | Absolute | |
| **Urinary albumin excretion (mcg/min) - Dapagliflozin + Saxagliptin vs Dapagliflozin (type 2 diabetes) (Better indicated by lower values [MID 62.38])** | | | | | | | | | | | |
| 1 | randomised trials[1] | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 107 | 108 | - | MD 19.6 lower (48.4 lower to 9.2 higher) | HIGH |
| **All-cause mortality - Dapagliflozin + Saxagliptin vs Dapagliflozin (type 2 diabetes)** | | | | | | | | | | | |
| 1 | randomised trials[1] | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[2] | none | 1/152 (0.66%) | 1/145 (0.69%) | RR 0.95 (0.06 to 15.11) | 0 fewer per 100 (from 1 fewer to 10 more) | MODERATE |
| **Minor hypoglycaemia - Dapagliflozin + Saxagliptin vs Dapagliflozin (type 2 diabetes))** | | | | | | | | | | | |
| 1 | randomised trials[1] | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[3] | none | 50/152 (32.9%) | 35/145 (24.1%) | RR 1.36 (0.94 to 1.97) | 9 more per 100 (from 1 fewer to 23 more) | MODERATE |
| **Any serious adverse events of hypoglycaemia - Dapagliflozin + Saxagliptin vs Dapagliflozin (type 2 diabetes)** | | | | | | | | | | | |
| 1 | randomised trials[1] | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[4] | none | 2/152 (1.3%) | 0/145 (0%) | RR 4.77 (0.23 to 98.54) | - | LOW |

[1] Pollock 2019
[2] 95% confidence interval crosses line of no effect
[3] 95% confidence interval crosses one end of a defined MID interval
[4] 95% confidence interval crosses both ends of a defined MID interval

## Exercise vs No intervention

| Quality assessment | No of patients | Effect | Quality |
|---|---|---|---|

| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Exercise | No intervention | Relative (95% CI) | Absolute | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Urinary protein/creatinine ratio (mg/mmol) - Type 2 diabetes (Better indicated by lower values [MID 18.3])** | | | | | | | | | | | |
| 1 | randomised trials[1] | very serious[2] | no serious inconsistency | no serious indirectness | very serious[3] | none | 7 | 6 | - | MD 12.66 lower (68.94 lower to 43.62 higher) | VERY LOW |
| **Urinary albumin/creatinine ratio (mg/mmol) - Type 2 diabetes (Better indicated by lower values [MID 14.8])** | | | | | | | | | | | |
| 1 | randomised trials[1] | very serious[2] | no serious inconsistency | no serious indirectness | very serious[3] | none | 7 | 6 | - | MD 9.83 lower (52.64 lower to 32.97 higher) | VERY LOW |

[1] Leehey 2009
[2] Study at high risk of bias
[3] 95% confidence interval crosses both ends of a defined MID interval

## Exercise vs Diet

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Exercise | Diet | Relative (95% CI) | Absolute | |
| **Health-related quality of life (type 2 diabetes) - SF-36 PCS (type 2 diabetes), 3 months (Better indicated by higher values [MID 4])** | | | | | | | | | | | |
| 1 | randomised trials[1] | very serious[2] | no serious inconsistency | no serious indirectness | very serious[3] | none | 14 | 18 | - | MD 0.5 higher (6.66 lower to 7.66 higher) | VERY LOW |
| **Health-related quality of life (type 2 diabetes) - SF-36 PCS (type 2 diabetes), 12 months (Better indicated by higher values [MID 4])** | | | | | | | | | | | |
| 1 | randomised trials[1] | very serious[2] | no serious inconsistency | no serious indirectness | very serious[3] | none | 14 | 18 | - | MD 1.9 higher (4.62 lower to 8.42 higher) | VERY LOW |
| **Health-related quality of life (type 2 diabetes) - SF-36 MCS (type 2 diabetes), 3 months (Better indicated by higher values [MID 4])** | | | | | | | | | | | |
| 1 | randomised trials[1] | very serious[2] | no serious inconsistency | no serious indirectness | serious[4] | none | 14 | 18 | - | MD 6.1 higher (0.94 lower to 13.14 higher) | VERY LOW |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Health-related quality of life (type 2 diabetes) - SF-36 MCS (type 2 diabetes), 12 months (Better indicated by higher values [MID 4])** | | | | | | | | | | | |
| 1 | randomised trials[1] | very serious[2] | no serious inconsistency | no serious indirectness | serious[4] | none | 14 | 18 | - | MD 3.8 higher (3.66 lower to 11.26 higher) | VERY LOW |

[1] Leehey 2016
[2] Study at high risk of bias
[3] 95% confidence interval crosses both ends of a defined MID interval
[4] 95% confidence interval crosses one end of a defined MID interval

## ACE-I + ARB vs ARB

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **ACE-I + ARB** | **ARB** | **Relative (95% CI)** | **Absolute** | |
| **End stage kidney disease (at least 95% type 2 diabetes)** | | | | | | | | | | | |
| 2 | randomised trials[1] | serious[2] | no serious inconsistency | no serious indirectness | serious[3] | none | 31/1140 (2.7%) | 45/1138 (4%) | RR 0.69 (0.44 to 1.08) | 1 fewer per 100 (from 2 fewer to 0 more) | LOW |
| **End stage kidney disease (at least 95% type 2 diabetes) - Losartan + Lisinopril vs Losartan (type 2 diabetes)** | | | | | | | | | | | |
| 1 | randomised trials[4] | serious[5] | no serious inconsistency | no serious indirectness | serious[3] | none | 27/724 (3.7%) | 43/724 (5.9%) | RR 0.63 (0.39 to 1) | 2 fewer per 100 (from 4 fewer to 0 more) | LOW |
| **End stage kidney disease (at least 95% type 2 diabetes) - ACE-I + ARB vs ARB (95% type 2 diabetes)** | | | | | | | | | | | |
| 1 | randomised trials[6] | very serious[7] | no serious inconsistency | no serious indirectness | very serious[8] | none | 4/416 (0.96%) | 2/414 (0.48%) | RR 1.99 (0.37 to 10.81) | 0 more per 100 (from 0 fewer to 5 more) | VERY LOW |
| **All-cause mortality (at least 95% type 2 diabetes)** | | | | | | | | | | | |
| 2 | randomised trials[1] | serious[2] | no serious inconsistency | no serious indirectness | serious[9] | none | 81/1140 (7.1%) | 80/1138 (7%) | RR 1.01 (0.75 to 1.36) | 0 more per 100 (from 2 fewer to 3 more) | LOW |
| **All-cause mortality (at least 95% type 2 diabetes) - Losartan + Lisinopril vs Losartan (type 2 diabetes)** | | | | | | | | | | | |
| 1 | randomised trials[4] | serious[5] | no serious inconsistency | no serious indirectness | serious[9] | none | 63/724 (8.7%) | 60/724 (8.3%) | RR 1.05 (0.75 to 1.47) | 0 more per 100 (from 2 fewer to 4 more) | LOW |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **All-cause mortality (at least 95% type 2 diabetes) - ACE-I + ARB vs ARB (95% type 2 diabetes)** | | | | | | | | | | | |
| 1 | randomised trials[6] | very serious[7] | no serious inconsistency | no serious indirectness | serious[9] | none | 18/416 (4.3%) | 20/414 (4.8%) | RR 0.9 (0.48 to 1.67) | 0 fewer per 100 (from 3 fewer to 3 more) | VERY LOW |
| **CV mortality - ACE-I + ARB vs ARB (95% type 2 diabetes)** | | | | | | | | | | | |
| 1 | randomised trials[6] | very serious[7] | no serious inconsistency | no serious indirectness | serious[9] | none | 4/416 (0.96%) | 7/414 (1.7%) | RR 0.57 (0.17 to 1.93) | 1 fewer per 100 (from 1 fewer to 2 more) | VERY LOW |
| **Non-fatal CV events (at least 95% type 2 diabetes)** | | | | | | | | | | | |
| 2 | randomised trials[1] | very serious[10] | very serious[11] | no serious indirectness | very serious[8] | none | 149/1140 (13.1%) | 142/1138 (12.5%) | RR 1.39 (0.58 to 3.37) | 5 more per 100 (from 5 fewer to 30 more) | VERY LOW |
| **Non-fatal CV events (at least 95% type 2 diabetes) - Losartan + Lisinopril vs Losartan (type 2 diabetes)** | | | | | | | | | | | |
| 1 | randomised trials[4] | serious[5] | no serious inconsistency | no serious indirectness | serious[3] | none | 134/724 (18.5%) | 136/724 (18.8%) | RR 0.99 (0.79 to 1.22) | 0 fewer per 100 (from 4 fewer to 4 more) | LOW |
| **Non-fatal CV events (at least 95% type 2 diabetes) - ACE-I + ARB vs ARB (95% type 2 diabetes)** | | | | | | | | | | | |
| 1 | randomised trials[6] | very serious[7] | no serious inconsistency | no serious indirectness | serious[3] | none | 15/416 (3.6%) | 6/414 (1.4%) | RR 2.49 (0.97 to 6.35) | 2 more per 100 (from 0 fewer to 8 more) | VERY LOW |
| **Acute kidney injury - Losartan + Lisinopril vs Losartan (type 2 diabetes)** | | | | | | | | | | | |
| 1 | randomised trials[4] | serious[5] | no serious inconsistency | no serious indirectness | serious[3] | none | 130/724 (18%) | 80/724 (11%) | RR 1.62 (1.25 to 2.1) | 7 more per 100 (from 3 more to 12 more) | LOW |
| **Hypotension - ACE-I + ARB vs ARB (95% type 2 diabetes)** | | | | | | | | | | | |
| 1 | randomised trials[6] | very serious[7] | no serious inconsistency | no serious indirectness | very serious[8] | none | 2/416 (0.48%) | 2/414 (0.48%) | RR 1 (0.14 to 7.03) | 0 fewer per 100 (from 0 fewer to 3 more) | VERY LOW |
| **Hospitalisation - ACE-I + ARB vs ARB (95% type 2 diabetes)** | | | | | | | | | | | |
| 1 | randomised trials[6] | very serious[7] | no serious inconsistency | no serious indirectness | serious[3] | none | 34/416 (8.2%) | 20/414 (4.8%) | RR 1.69 (0.99 to 2.89) | 3 more per 100 (from 0 fewer to 9 more) | VERY LOW |

[1] Fried 2013; Saglimbene 2018
[2] >33.3% of weighted data from studies at moderate or high risk of bias
[3] 95% confidence interval crosses one end of a defined MID interval
[4] Fried 2013

[5] Study at moderate risk of bias
[6] Saglimbene 2018
[7] Study at high risk of bias
[8] 95% confidence interval crosses both ends of a defined MID interval
[9] 95% confidence interval crosses line of no effect
[10] >33.3% of weighted data from studies at high risk of bias
[11] i-squared >66. 7%; random-effects model was used

## ACE-I + ARB vs ACE-I

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | ACE-I + ARB | ACE-I | Relative (95% CI) | Absolute | |
| **End stage kidney disease - ACE-I + ARB vs ACE-I (95% type 2 diabetes)** | | | | | | | | | | | |
| 1 | randomised trials[1] | very serious[2] | no serious inconsistency | no serious indirectness | very serious[3] | none | 4/416 (0.96%) | 6/413 (1.5%) | RR 0.66 (0.19 to 2.33) | 0 fewer per 100 (from 1 fewer to 2 more) | VERY LOW |
| **All-cause mortality - ACE-I + ARB vs ACE-I (95% type 2 diabetes)** | | | | | | | | | | | |
| 1 | randomised trials[1] | very serious[2] | no serious inconsistency | no serious indirectness | serious[4] | none | 18/416 (4.3%) | 15/413 (3.6%) | RR 1.19 (0.61 to 2.33) | 1 more per 100 (from 1 fewer to 5 more) | VERY LOW |
| **CV mortality - ACE-I + ARB vs ACE-I (95% type 2 diabetes)** | | | | | | | | | | | |
| 1 | randomised trials[1] | very serious[2] | no serious inconsistency | no serious indirectness | serious[4] | none | 4/416 (0.96%) | 6/413 (1.5%) | RR 0.66 (0.19 to 2.33) | 0 fewer per 100 (from 1 fewer to 2 more) | VERY LOW |
| **Non-fatal CV events - ACE-I + ARB vs ACE-I (95% type 2 diabetes)** | | | | | | | | | | | |
| 1 | randomised trials[1] | very serious[2] | no serious inconsistency | no serious indirectness | very serious[3] | none | 15/416 (3.6%) | 8/413 (1.9%) | RR 1.86 (0.8 to 4.34) | 2 more per 100 (from 0 fewer to 6 more) | VERY LOW |
| **Hypotension - ACE-I + ARB vs ACE-I (95% type 2 diabetes)** | | | | | | | | | | | |
| 1 | randomised trials[1] | very serious[2] | no serious inconsistency | no serious indirectness | very serious[3] | none | 2/416 (0.48%) | 3/413 (0.73%) | RR 0.66 (0.11 to 3.94) | 0 fewer per 100 (from 1 fewer to 2 more) | VERY LOW |
| **Hospitalisation - ACE-I + ARB vs ACE-I (95% type 2 diabetes)** | | | | | | | | | | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials[1] | very serious[2] | no serious inconsistency | no serious indirectness | serious[5] | none | 34/416 (8.2%) | 25/413 (6.1%) | RR 1.35 (0.82 to 2.22) | 2 more per 100 (from 1 fewer to 7 more) | VERY LOW |

[1] Saglimbene 2018
[2] Study at high risk of bias
[3] 95% confidence interval crosses both ends of a defined MID interval
[4] 95% confidence interval crosses line of no effect
[5] 95% confidence interval crosses one end of a defined MID interval

# Adults without type 2 diabetes

## ACE-I vs placebo

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **ACE-I** | **Placebo** | **Relative (95% CI)** | **Absolute** | |
| **End stage kidney disease** | | | | | | | | | | | |
| 3 | randomised trials[1] | very serious[2] | no serious inconsistency | no serious indirectness | serious[3] | none | 46/384 (12%) | 78/377 (20.7%) | RR 0.59 (0.43 to 0.83) | 8 fewer per 100 (from 4 fewer to 12 fewer) | VERY LOW |
| **End stage kidney disease - Ramipril** | | | | | | | | | | | |
| 2 | randomised trials[4] | serious[5] | no serious inconsistency | no serious indirectness | serious[3] | none | 26/177 (14.7%) | 47/175 (26.9%) | RR 0.57 (0.37 to 0.87) | 12 fewer per 100 (from 3 fewer to 17 fewer) | LOW |
| **End stage kidney disease - Captopril** | | | | | | | | | | | |
| 1 | randomised trials[6] | very serious[2] | no serious inconsistency | no serious indirectness | serious[3] | none | 20/207 (9.7%) | 31/202 (15.3%) | RR 0.63 (0.37 to 1.07) | 6 fewer per 100 (from 10 fewer to 1 more) | VERY LOW |
| **All-cause mortality** | | | | | | | | | | | |
| 2 | randomised trials[7] | very serious[2] | no serious inconsistency | no serious indirectness | serious[8] | none | 10/285 (3.5%) | 15/290 (5.2%) | RR 0.66 (0.3 to 1.44) | 2 fewer per 100 (from 4 fewer to 2 more) | VERY LOW |
| **All-cause mortality - Ramipril** | | | | | | | | | | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials[9] | serious[5] | no serious inconsistency | no serious indirectness | serious[8] | none | 2/78 (2.6%) | 1/88 (1.1%) | RR 2.26 (0.21 to 24.41) | 1 more per 100 (from 1 fewer to 27 more) | LOW |
| **All-cause mortality - Captopril** | | | | | | | | | | | |
| 1 | randomised trials[6] | very serious[2] | no serious inconsistency | no serious indirectness | serious[8] | none | 8/207 (3.9%) | 14/202 (6.9%) | RR 0.56 (0.24 to 1.3) | 3 fewer per 100 (from 5 fewer to 2 more) | VERY LOW |
| **CV mortality - Ramipril** | | | | | | | | | | | |
| 2 | randomised trials[4] | serious[5] | no serious inconsistency | no serious indirectness | serious[8] | none | 2/177 (1.1%) | 0/175 (0%) | RR 2.99 (0.32 to 28.32) | - | LOW |
| **Non-fatal CV events - Ramipril** | | | | | | | | | | | |
| 2 | randomised trials[4] | serious[5] | no serious inconsistency | no serious indirectness | very serious[10] | none | 6/177 (3.4%) | 6/175 (3.4%) | RR 1.02 (0.34 to 3.05) | 0 more per 100 (from 2 fewer to 7 more) | VERY LOW |

[1] GISEN group 1997; Ruggenenti 1999; Lewis 1993
[2] >33.3% of weighted data from studies at high risk of bias
[3] 95% confidence interval crosses one end of a defined MID interval
[4] GISEN group 1997; Ruggenenti 1999
[5] >33.3% of weighted data from studies at moderate or high risk of bias
[6] Lewis 1993
[7] GISEN group 1997; Lewis 1993
[8] 95% confidence interval crosses line of no effect
[9] GISEN group 1997
[10] 95% confidence interval crosses both ends of a defined MID interval

## Aldosterone antagonist vs placebo

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Aldosterone antagonist** | **Placebo** | **Relative (95% CI)** | **Absolute** | |
| **Urinary albumin/creatinine ratio (mean percentage change) - Eplerenone (Better indicated by lower values [MID 36.68])** | | | | | | | | | | | |
| 1 | randomised trials[1] | very serious[2] | no serious inconsistency | no serious indirectness | serious[3] | none | 158 | 146 | - | MD 27.6 lower (47.72 to 7.48 lower) | VERY LOW |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **All-cause mortality - Eplerenone** | | | | | | | | | | | |
| 1 | randomised trials[1] | very serious[2] | no serious inconsistency | no serious indirectness | serious[4] | none | 1/169 (0.59%) | 0/163 (0%) | RR 2.89 (0.12 to 70.53) | - | VERY LOW |
| **Non-fatal CV events - Eplerenone** | | | | | | | | | | | |
| 1 | randomised trials[1] | very serious[2] | no serious inconsistency | no serious indirectness | very serious[5] | none | 1/169 (0.59%) | 1/163 (0.61%) | RR 0.96 (0.06 to 15.29) | 0 fewer per 100 (from 1 fewer to 9 more) | VERY LOW |

[1] Ando 2014b
[2] Study at high risk of bias
[3] 95% confidence interval crosses one end of a defined MID interval
[4] 95% confidence interval crosses line of no effect
[5] 95% confidence interval crosses both ends of a defined MID interval

## ARB vs placebo

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **ARB** | **Placebo** | **Relative (95% CI)** | **Absolute** | |
| **Urinary albumin excretion (g/24 h) - Valsartan, 3 months (Better indicated by lower values [MID 0.89])** | | | | | | | | | | | |
| 1 | randomised trials[1] | very serious[2] | no serious inconsistency | no serious indirectness | serious[3] | none | 54 | 55 | - | MD 0.54 lower (1.12 lower to 0.04 higher) | VERY LOW |
| **Urinary albumin excretion (g/24 h) - Valsartan, 6 months (Better indicated by lower values [MID 0.99])** | | | | | | | | | | | |
| 1 | randomised trials[1] | very serious[2] | no serious inconsistency | no serious indirectness | serious[3] | none | 54 | 55 | - | MD 0.81 lower (1.43 to 0.19 lower) | VERY LOW |
| **Urinary albumin excretion (g/24 h) - Valsartan, 12 months (Better indicated by lower values [MID 0.86])** | | | | | | | | | | | |
| 1 | randomised trials[1] | very serious[2] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 54 | 55 | - | MD 0.16 lower (0.72 lower to 0.4 higher) | LOW |
| **Urinary albumin excretion (g/24 h) - Valsartan, 1.5 years (Better indicated by lower values [MID 0.86])** | | | | | | | | | | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials[1] | very serious[2] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 54 | 55 | - | MD 0.22 lower (0.76 lower to 0.32 higher) | LOW |
| **Urinary albumin excretion (g/24 h) - Valsartan, 2 years (Better indicated by lower values [MID 0.85])** | | | | | | | | | | | |
| 1 | randomised trials[1] | very serious[2] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 54 | 55 | - | MD 0.19 lower (0.75 lower to 0.37 higher) | LOW |
| **Non-fatal CV events - Valsartan** | | | | | | | | | | | |
| 1 | randomised trials[1] | very serious[2] | no serious inconsistency | no serious indirectness | very serious[4] | none | 0/54 (0%) | 1/55 (1.8%) | RR 0.34 (0.01 to 8.15) | 1 fewer per 100 (from 2 fewer to 13 more) | VERY LOW |

[1] Li 2006
[2] Study at high risk of bias
[3] 95% confidence interval crosses one end of a defined MID interval
[4] 95% confidence interval crosses both ends of a defined MID interval

## ARB vs control (usual antihypertensive therapy except ACE inhibitors and ARBs)

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **ARB** | **Control** | **Relative (95% CI)** | **Absolute** | |
| **Urinary protein creatinine ratio (mg/mmol) - Losartan, 12 months [MID 0.02] (Better indicated by lower values [MID 26.4])** | | | | | | | | | | | |
| 1 | randomised trials[1] | very serious[2] | no serious inconsistency | no serious indirectness | serious[3] | none | 17 | 15 | - | MD 40.00 lower (79.41 to 0.59 lower) | VERY LOW |
| **Urinary protein creatinine ratio (mg/mmol) - Losartan, 24 months [MID 0.03] (Better indicated by lower values [MID 30.4])** | | | | | | | | | | | |
| 1 | randomised trials[1] | very serious[2] | no serious inconsistency | no serious indirectness | serious[3] | none | 17 | 15 | - | MD 30.00 lower (65.23 lower to 5.23 higher) | VERY LOW |
| **Urinary albumin creatinine ratio (mg/mmol) - Losartan, 12 months [MID 0.02] (Better indicated by lower values [MID 22.9])** | | | | | | | | | | | |
| 1 | randomised trials[1] | very serious[2] | no serious inconsistency | no serious indirectness | serious[3] | none | 17 | 15 | - | MD 30.00 lower (67.67 lower to 7.67 higher) | VERY LOW |

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|---|---|---|---|---|---|---|---|---|---|---|---|
| **Urinary albumin creatinine ratio (mg/mmol) - Losartan, 24 months [MID 0.03] (Better indicated by lower values [MID 31.2])** | | | | | | | | | | | |
| 1 | randomised trials[1] | very serious[2] | no serious inconsistency | no serious indirectness | serious[3] | none | 17 | 15 | - | MD 30.00 lower (67.79 lower to 7.79 higher) | VERY LOW |

[1] Lee 2011
[2] Study at high risk of bias
[3] 95% confidence interval crosses one end of a defined MID interval

## ACE-I vs ARB

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **ACE-I** | **ARB** | **Relative (95% CI)** | **Absolute** | |
| **Urinary protein/creatinine ratio (mg/mmol) - Lisinopril vs Candesartan, 3 months (Better indicated by lower values [MID 31.3])** | | | | | | | | | | | |
| 1 | randomised trials[1] | serious[2] | no serious inconsistency | no serious indirectness | serious[3] | none | 14 | 15 | - | MD 66.67 higher (12.68 to 120.66 higher) | LOW |
| **Urinary protein/creatinine ratio (mg/mmol) - Lisinopril vs Candesartan, 6 months (Better indicated by lower values [MID 32.3])** | | | | | | | | | | | |
| 1 | randomised trials[1] | serious[2] | no serious inconsistency | no serious indirectness | very serious[4] | none | 14 | 15 | - | MD 4.52 higher (49.67 lower to 58.71 higher) | VERY LOW |
| **Urinary protein excretion (g/24h), Mean percentage reduction from baseline - ACE-I vs ARB (moderate proteinuria 1.1 to 6.9 g/24h), 3 months (Better indicated by lower values [MID 4])** | | | | | | | | | | | |
| 1 | randomised trials[5] | very serious[6] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 14 | 12 | - | MD 21 higher (15.49 to 26.51 higher) | LOW |
| **Urinary protein excretion (g/24h), Mean percentage reduction from baseline - ACE-I vs ARB (moderate proteinuria 1.1 to 6.9 g/24h), 11 months (Better indicated by lower values [MID 3])** | | | | | | | | | | | |
| 1 | randomised trials[5] | very serious[6] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 14 | 12 | - | MD 13 higher (8 to 18 higher) | LOW |
| **Urinary protein excretion (g/24h), Mean percentage reduction from baseline - Perindopril vs Candesartan, 3 months (Better indicated by lower values [MID 2])** | | | | | | | | | | | |
| 1 | randomised trials[7] | very serious[6] | no serious inconsistency | no serious indirectness | serious[3] | none | 15 | 17 | - | MD 4 higher (0.42 to 7.58 higher) | VERY LOW |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Urinary protein excretion (g/24h), Mean percentage reduction from baseline - Perindopril vs Losartan, 3 months (Better indicated by lower values [MID 1.50])** | | | | | | | | | | | |
| 1 | randomised trials[7] | very serious[6] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 15 | 15 | - | MD 30 higher (26.61 to 33.39 higher) | LOW |
| **Urinary protein excretion (g/24h), Mean percentage reduction from baseline - Trandolapril vs Candesartan, 3 months (Better indicated by lower values [MID 2)** | | | | | | | | | | | |
| 1 | randomised trials[7] | very serious[6] | no serious inconsistency | no serious indirectness | very serious[4] | none | 15 | 17 | - | MD 1 lower (4.58 lower to 2.58 higher) | VERY LOW |
| **Urinary protein excretion (g/24h), Mean percentage reduction from baseline - Trandolapril vs Losartan, 3 months (Better indicated by lower values [MID 1.5])** | | | | | | | | | | | |
| 1 | randomised trials[7] | very serious[6] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 15 | 15 | - | MD 25 higher (21.61 to 28.39 higher) | LOW |
| **Urinary protein excretion (g/24h), Mean percentage reduction from baseline - Perindopril vs Candesartan, 22 months (Better indicated by lower values [MID 2.5])** | | | | | | | | | | | |
| 1 | randomised trials[7] | very serious[6] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 15 | 17 | - | MD 11 higher (6.73 to 15.27 higher) | LOW |
| **Urinary protein excretion (g/24h), Mean percentage reduction from baseline - Perindopril vs Losartan, 22 months (Better indicated by lower values [MID 2])** | | | | | | | | | | | |
| 1 | randomised trials[7] | very serious[6] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 15 | 15 | - | MD 24 higher (19.92 to 28.08 higher) | LOW |
| **Urinary protein excretion (g/24h), Mean percentage reduction from baseline - Trandolapril vs Candesartan, 22 months (Better indicated by lower values [MID 2.5])** | | | | | | | | | | | |
| 1 | randomised trials[7] | very serious[6] | no serious inconsistency | no serious indirectness | serious[3] | none | 15 | 17 | - | MD 4 higher (0.27 lower to 8.27 higher) | VERY LOW |
| **Urinary protein excretion (g/24h), Mean percentage reduction from baseline - Trandolapril vs Losartan, 22 months (Better indicated by lower values [MID 2])** | | | | | | | | | | | |
| 1 | randomised trials[7] | very serious[6] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 15 | 15 | - | MD 17 higher (12.92 to 21.08 higher) | LOW |

[1] Luno 2002
[2] Study at moderate risk of bias
[3] 95% confidence interval crosses one end of a defined MID interval
[4] 95% confidence interval crosses both ends of a defined MID interval
[5] Matsuda 2003a
[6] Study at high risk of bias
[7] Matsuda 2003b

## ARB vs CCB

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | ARB | CCB | Relative (95% CI) | Absolute | |
| **Urinary protein excretion (g/24 h) - Losartan vs Amlodipine, 3 months (Better indicated by lower values [MID 26.93])** | | | | | | | | | | | |
| 1 | randomised trials[1] | very serious[2] | no serious inconsistency | no serious indirectness | serious[3] | none | 26 | 28 | - | MD 27.38 lower (50.22 to 4.54 lower) | VERY LOW |
| **Urinary protein excretion (g/24 h) - Losartan vs Amlodipine (Better indicated by lower values [MID 0.94])** | | | | | | | | | | | |
| 1 | randomised trials[4] | serious[5] | no serious inconsistency | no serious indirectness | serious[3] | none | 50 | 47 | - | MD 1.7 lower (2.47 to 0.93 lower) | LOW |
| **Non-fatal CV events - Losartan vs Amlodipine** | | | | | | | | | | | |
| 1 | randomised trials[1] | very serious[2] | no serious inconsistency | no serious indirectness | very serious[6] | none | 1/47 (2.1%) | 0/46 (0%) | RR 2.94 (0.12 to 70.3) | - | VERY LOW |

[1] Iino 2003
[2] Study at high risk of bias
[3] 95% confidence interval crosses one end of a defined MID interval
[4] Praga 2003
[5] Study at moderate risk of bias
[6] 95% confidence interval crosses both ends of a defined MID interval

## Subcutaneous insulin infusion vs Conventional insulin

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Subcutaneous insulin infusion | Conventional insulin | Relative (95% CI) | Absolute | |
| **Urinary albumin excretion (mcg/min) - Type 1 diabetes (Better indicated by lower values [MID 516.85])** | | | | | | | | | | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials[1] | very serious[2] | no serious inconsistency | no serious indirectness | very serious[3] | none | 5 | 5 | - | MD 195 lower (1353.56 lower to 963.56 higher) | VERY LOW |

[1] Ciavarella 1985
[2] Study at high risk of bias
[3] 95% confidence interval crosses both ends of a defined MID interval

## ACE-I + ARB vs ARB

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **ACE-I + ARB** | **ARB** | **Relative (95% CI)** | **Absolute** | |
| **Urinary protein/creatinine ratio (mg/mmol) - Candesartan + Lisinopril vs Candesartan, 3 months (Better indicated by lower values [MID 31.3])** | | | | | | | | | | | |
| 1 | randomised trials[1] | serious[2] | no serious inconsistency | no serious indirectness | serious[3] | none | 16 | 15 | - | MD 29.38 lower (72.27 lower to 13.51 higher) | LOW |
| **Urinary protein/creatinine ratio (mg/mmol) - Candesartan + Lisinopril vs Candesartan, 6 months (Better indicated by lower values [MID 32.3])** | | | | | | | | | | | |
| 1 | randomised trials[1] | serious[2] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 16 | 15 | - | MD 111.87 lower (153.34 to 70.40 lower) | MODERATE |

[1] Luno 2002
[2] Study at moderate risk of bias
[3] 95% confidence interval crosses one end of a defined MID interval

## ACE-I + ARB vs ACE-I

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **ACE-I + ARB** | **ACE-I** | **Relative (95% CI)** | **Absolute** | |
| **Urinary protein excretion (g/24 h) - Candesartan + ACE-I vs ACE-I (Better indicated by lower values [MID 0.07])** | | | | | | | | | | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials[1] | very serious[2] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 45 | 45 | - | MD 0.83 lower (0.89 to 0.77 lower) | LOW |
| **Urinary protein/creatinine ratio (mg/mmol) - Candesartan + Lisinopril vs Lisinopril, 3 months (Better indicated by lower values [MID 41.6])** | | | | | | | | | | | |
| 1 | randomised trials[3] | serious[4] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 16 | 14 | - | MD 96.05 lower (148.35 to 43.75 lower) | MODERATE |
| **Urinary protein/creatinine ratio (mg/mmol) - Candesartan + Lisinopril vs Lisinopril, 6 months (Better indicated by lower values [MID 41.1])** | | | | | | | | | | | |
| 1 | randomised trials[3] | serious[4] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 16 | 14 | - | MD 116.39 lower (166.48 to 66.30 lower) | MODERATE |

[1] Kanno 2006
[2] Study at high risk of bias
[3] Luno 2002
[4] Study at moderate risk of bias

## ARB + CCB vs ARB

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **ARB + CCB** | **ARB** | **Relative (95% CI)** | **Absolute** | |
| **Urinary albumin/creatinine ratio (mg/mmol) - Valsartan + Amlodipine vs Valsartan (Better indicated by lower values [MID 3.96])** | | | | | | | | | | | |
| 1 | randomised trials[1] | very serious[2] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 70 | 70 | - | MD 9.83 lower (12.58 to 7.08 lower) | LOW |

[1] Ameen 2016
[2] Study at high risk of bias

## ARB + Diuretic vs ARB

| Quality assessment | No of patients | Effect | Quality |
|---|---|---|---|

| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | ARB + Diuretic | ARB | Relative (95% CI) | Absolute | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Urinary protein/creatinine ratio (mg/mmol) - 3 months (Better indicated by lower values [MID 0.05])** | | | | | | | | | | | |
| 1 | randomised trials[1] | serious[2] | no serious inconsistency | no serious indirectness | serious[3] | none | 51 | 48 | - | MD 0.08 lower (0.12 to 0.05 lower) | LOW |
| **Urinary protein/creatinine ratio (mg/mmol) - 6 months (Better indicated by lower values [MID 0.04])** | | | | | | | | | | | |
| 1 | randomised trials[1] | serious[2] | no serious inconsistency | no serious indirectness | serious[3] | None | 51 | 48 | - | MD 0.06 lower (0.10 to 0.03 lower) | LOW |

[1] Fujisaki 2014
[2] Study at moderate risk of bias
[3] 95% confidence interval crosses one end of a defined MID interval

## Spironolactone + conventional therapy vs Conventional therapy

| Quality assessment | | | | | | | No of patients | | Effect | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Spironolactone + conventional therapy | Conventional therapy | Relative (95% CI) | Absolute | |
| **Urinary protein/creatinine ratio (mg/mmol), 3 months - 3 months (Better indicated by lower values [MID 35.5])** | | | | | | | | | | | |
| 1 | randomised trials[1] | very serious[2] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 83 | 82 | - | MD 91.53 lower (113.75 to 69.31 lower) | LOW |
| **Urinary protein/creatinine ratio (mg/mmol), 3 months - 6 months (Better indicated by lower values [MID 35.5])** | | | | | | | | | | | |
| 1 | randomised trials[1] | very serious[2] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 83 | 82 | - | MD 106.22 lower (128.44 to 84.00 lower) | LOW |
| **Urinary protein/creatinine ratio (mg/mmol), 3 months - 12 months (Better indicated by lower values [MID 38.3])** | | | | | | | | | | | |
| 1 | randomised trials[1] | very serious[2] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 83 | 82 | - | MD 149.16 lower (172.24 to 126.08 lower) | LOW |

[1] Bianchi 2006
[2] Study at high risk of bias

# Appendix H – Economic evidence study selection

# Appendix I – Economic evidence tables

## Timing of antihypertensive therapy

### Farmer 2014

| Study | Farmer AJ, Stevens R, Hirst J et al. (2014) Optimal strategies for identifying kidney disease in diabetes: Properties of screening tests, progression of renal dysfunction and impact of treatment - Systematic review and modelling of progression and cost-effectiveness. Health Technology Assessment 18(14): 1-127 | | | |
|---|---|---|---|---|
| **Study details** | **Population & interventions** | **Costs[3]** | **Outcomes** | **Cost effectiveness** |
| **Economic analysis:** Cost utility analysis<br>**Study design:** Systematic review and decision analytic model<br>**Approach to analysis:** The analysis consisted of 2 individual patient simulation models. The type 1 diabetes model simulates 10,000 individuals to evaluate the costs and consequences of CVD (stroke and myocardial infarction) with or without ESRD and death associated with different frequencies of screening for albuminuria. Renal disease progression was associated with increased risk of CVD.<br>The type 2 diabetes model considers individual characteristics and comorbidities to determine the risk of CVD, complications from diabetes and death. It uses an adaptation of the UKPDS outcomes model. Screening interval was varied | **Population:**<br>Type 1 diabetes<br>People with type 1 diabetes aged 12 years and over[1]<br>Type 2 diabetes<br>People with type 2 diabetes aged 40 to 75 years[2]<br><br>**Cohort settings**<br>The base case compared biennial to annual screening<br><br>**Interventions**<br>Annual **s**creening + ACE inhibitor if progression to micro or macroalbuminuria. Alternative frequencies | **Cost differences:**<br>Type 1 diabetes<br>**1-year vs 2-year:** £2,837<br>**2-year vs 3-year:** £2,222<br>**3-year vs 4-year:** £672<br>**4-year vs 5-year:** £337<br>Type 2 diabetes<br>**1-year vs 2-year:** £244<br>**2-year vs 3-year:** £131<br>**3-year vs 4-year:** £82<br>**4-year vs 5-year:** £83<br><br>**Currency & cost year:**<br>Sterling 2011 | **QALY differences:**<br>Type 1 diabetes<br>**1-year vs 2-year:** 0.26<br>**2-year vs 3-year:** 0.39<br>**3-year vs 4-year:** 0.15<br>**4-year vs 5-year:** 0.08<br>Type 2 diabetes<br>**1-year vs 2-year:** 0.42<br>**2-year vs 3-year:** 0.11<br>**3-year vs 4-year:** 0.24<br>**4-year vs 5-year:** 0.09 | **Full incremental analysis:**<br>Type 1 diabetes<br>**1-year vs 2-year:** £11,203/QALY<br>**2-year vs 3-year:** £5,766/QALY<br>**3-year vs 4-year:** £2,943/QALY<br>**4-year vs 5-year:** £4,215/QALY<br>Type 2 diabetes<br>**1-year vs 2-year:** £707/QALY<br>**2-year vs 3-year:** £575/QALY<br>**3-year vs 4-year:** £386/QALY<br>**4-year vs 5-year:** £890/QALY<br>In both models, annual screening was more expensive and produced more QALYs<br><br>**Analysis of uncertainty:**<br>Univariate sensitivity analyses were conducted using the upper and lower levels of the confidence intervals for test cost, ACR progression, CVD and utility.<br>In both models, the results were sensitive to ACR progression, |

| | | | | |
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| between 1 and 10 years using 1 and 5-year increments.<br>Model results are the average of 1,000 simulations used to stabilise individual Monte Carlo simulations.<br>**Perspective:** NHS perspective<br>**Time horizon:** Lifetime<br>**Intervention effect duration:** Lifetime<br>**Discounting:** costs and effects were discounted at 3.5% annually for the initial 30 years and at 3% thereafter | of screening were compared:<br>**1-year versus 2-year**<br>**2-year versus 3-year**<br>**3-year versus 4-year**<br>**4-year versus 5-year** | **Cost components incorporated:**<br>Type 1 diabetes<br>monitoring, further investigations, treating diagnosed kidney disease (appointments, ESRD) and costs of complications (CVD) | | producing ICERs in excess of £40,000/QALY.<br>Type 1 diabetes<br>Annual screening had a 25% probability of being cost saving and an 80% probability of being cost-effective at a threshold below £30,000/QALY.<br>Type 2 diabetes<br>Annual screening had 97% probability of being cost-effective at a threshold below £30,000/QALY. |

**Data sources**

**Outcomes:**

Type 1 diabetes model

The baseline progression from normoalbuminuria to microalbuminuria was modelled in WinBUGS using a linear random-effects model utilising data from the Oxford Regional Prospective Study of Childhood Diabetes (ORPS, Schultz 1999, Oke 2010).

Incidence of CVS disease was sourced from the Diabetes Control and Complications trial (DCCT, Nathan 2005) and mortality associated with CVD from an Australia study following people with complications from diabetes (Hayes 2011). The incidence of ESRD and the risk of progression of micro/macroalbuminuria to ESRD were sourced from analyses of the Swedish Diabetes Registry (Finne 2005, (Kelly 2011). Progression from ESRD to CVD used data from an Italian cohort of people receiving dialysis (Zoccali 2002) and hazard ratios for age and gender used data from the UKPDS-68 (Clarke 2004).

Type 2 diabetes model

This simulation was based on the UKPDS-68 outcomes model (Clarke 2004) which was adapted to accommodate changes to renal disease progression. The model uses a probabilistic discrete-event simulation based on a system of parametric proportional hazard equations estimated over a median time of 11 years from diagnosis. The model can also be used to estimate health care costs related to diabetes. Progression in ACR was modelled at patient level in WinBUGS using a normally distributed random effects model. The analysis used data from the CARDS trial (Colhoun 2004).

In both models, people testing positive for albuminuria were treated with ACE inhibitor using an absolute risk reduction in renal function deterioration estimated in a systematic review and meta-analysis conducted for the purpose of the health technology assessment.

**Quality of life weights:** Utility parameters for no complications, myocardial infarction, stroke and ESRD were sourced from a meta-analysis of health-state valuations for people with diabetes (Lung 2011). The utilities for ischaemic and congestive heart disease, blindness and amputation used estimated from the UKPDS study (Clarke 2004).

**Costs:** All costs were obtained from standard UK sources. The cost of drugs used data from Prescription Cost Analysis 2010. The price and unit costs for screening, appointments and dialysis were sourced from the Unit Costs of Health and Social Care 2010 (Curtis 2010) and from the CKD Costing Report 2008 (NICE 2008). The costs of treating CVD used data from the UKPDS-65 (Clarke 2003).

| Comments |
|---|
| **Source of funding:** National Institute for Health Research Health Technology Assessment programme |
| **Overall applicability:** Partially applicable |
| Conducted from an NHS perspective using a robust methodology, but the study assesses the cost-effectiveness of screening and then treatment, rather than treatment alone, which is the primary focus of this review question. |
| **Overall quality**: Minor limitations |
| The type 1 diabetes model does not include data from people older than 35 years and may not be representative of the entire UK population. |

*[1]The ORPS study (Oke 2010) recruited Young people living in Oxfordshire UK, diagnosed with type 1 diabetes before the age of 16 who were screened annually using 3 consecutive early morning urine samples. Two positive tests of albumin to creatinine ratio (ACR) were required to confirm progression of kidney disease. Annual assessment continued up to 20 years.*

*[2]Used participants inf the CARDS trial (Colhoun 2004) of atorvastatin versus placebo in people with type 2 diabetes aged 40 to 75 years, with low-density lipoprotein cholesterol ≤4.14 mmol/l, fasting triglycerides ≤6.78mmol/l and one or more of the following conditions: hypertension, retinopathy, micro/macro albuminuria and current smoking. Albumin and creatinine levels were measured at 1, 2, 3 and 6 months after randomisation and every 6 months thereafter.*

*[3]Costs inflated from sterling 2011 to sterling 2020 using the EPPI Centre cost converter accessed 23/01/20020, inflation factor 0.857.*

## Adarkwah 2011a

| **Study** | Adarkwah CC, Gandjour A, Akkerman M et al (2011) Cost-effectiveness of angiotensin-converting enzyme inhibitors for the prevention of diabetic nephropathy in the Netherlands: a Markov model. PLOS ONE 10: e26139 | | | |
|---|---|---|---|---|
| **Study details** | **Population & interventions** | **Costs** | **Outcomes** | **Cost effectiveness** |
| **Economic analysis:** Cost utility analysis<br>**Study design:** Decision analytic model<br>**Approach to analysis:** Markov model[1] simulating the progression from normoalbuminuria[2] to microalbuminuria, macroalbuminuria, end-stage renal disease (ESRD) and death. It was assumed people continuously progressed without skipping any health state. Probabilistic sensitivity analysis | **Population:** People aged 50 with type 2 diabetes<br><br>**Cohort settings***<br>**Intervention 1:** ACE inhibitor at time of DM diagnosis (treat all)<br>**Intervention 2:** ACE inhibitor if microalbuminuria<br>**Intervention 3:** ACE inhibitor if macroalbuminuria<br><br>*If cough was developed as side-effect, an angiotensin II receptor blocker was used | **Total costs (mean per individual)[3]:**<br>**Int1:** €98,421 (£94,742)<br>**Int2:** €101,140 (£97,359)<br>**Int3:** €110,777 (£106,636)<br><br>**Currency & cost year:**<br>Euro, 2010<br>**Cost components incorporated:** direct healthcare costs | **QALYs (mean per individual):**<br>**Int1:** 19.63<br>**Int2:** 19.54<br>**Int3:** 19.15 | **Full incremental analysis:**<br>The strategy of treating all patients at the time of diagnosis of DM dominates as it is cheaper and produces more QALYs.<br><br>**Analysis of uncertainty:**<br>The most influential parameters in univariate sensitivity analysis were the baseline risk of progression from micro- to macroalbuminuria, the effect of ACE inhibition in preventing microalbuminuria and the discount rate.<br>When assuming a lower baseline risk of having macroalbuminuria, intervention 2 becomes dominant. |

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| used 1,000 Monte Carlo simulations.<br>**Perspective:** Dutch health system<br>**Time horizon:** 50 years (>99% of cohort dead), 1-year cycle with half-cycle correction<br>**Intervention effect duration:** duration of the analysis<br>**Discounting:** 4% costs, 1.5% QALYs | | (drugs, testing for microalbuminuria, cost dialysis and transplant) | | Compared to intervention 2, treating all patient has a 70% probability of producing savings. |

**Data sources**

**Outcomes:** ACE inhibitors efficacy in people with normoalbuminuria was sourced from the systematic review by Strippoli (2005). For the population with microalbuminuria efficacy parameters were extracted from another systematic review by the same author (Strippoli 2006). These efficacy data were from people with type 1 and type 2 diabetes, but heterogeneity was not a concern. The transition for macroalbuminuria to ESRD was informed by RCT data (Lewis 1993).

Mortality was modelled using age-specific mortality rates in the Dutch population which were adjusted for diabetes-specific deaths. Mortality was assumed not to differ for people in the normo-, micro- and macroalbuminuria states due to lack of contrary evidence. Mortality for people in ESRD and dialysis was calculated from values reported on the Dutch End-Stage Renal Disease Registry data (2011a).

**Quality of life weights:** Preference weights for people with DM were sourced from Brown (2000) who used a time trade-off methodology (TTO). This was assumed to be the same regardless of albuminuria excretion levels. The utility for ESRD was extracted from a systematic review of studies using a time trade-off methodology (Arnesen 2004).

**Costs:** Costing of drugs, screening and ESRD treatment used nationally available sources. The base case analysis used the cost of enalapril, the cheapest and most commonly used ACE inhibitor in the Netherlands. The cost of ibesartan (300 mg) was used if adverse events to the ACE inhibitor were present. Transplants were assumed to last 10 years

**Comments**

**Source of funding:** No support or funding. Authors declared having no conflict of interest.

**Overall applicability:** Partially applicable

Analysis conducted 8 years ago taking a Dutch health system perspective. The analysis does not consider standard practice as one of the comparators. Costs were discounted at a 4% annual rate and benefits at a 1.5% rate. This may have contributed to the cost-effectiveness of the interventions, compared to a scenario were both costs and benefits were subject to 3.5% annual discounting.

**Overall quality**: Potentially serious limitations

The absolute effect of the interventions was assumed constant over the duration of the analysis which may be an oversimplification of reality.

It is likely that technologies such as dialysis and transplant may have different costs and safety profiles since the analysis was conducted.

[1]*Model adapted from a previous analysis of the cost effectiveness of ACE inhibitors in Germany (Adarkwah 2010).*

[2]*Normoalbuminuria – excretion <30 mg/day; microalbuminuria – excretion 30 to 300 mg/day; macroalbuminuria – excretion >300 mg/day; ESRD – treated with dialysis of renal transplant.*

[3]*Euros 2010 converted to sterling 2019 using the EPPI Centre cost converter (accessed 11/12/2019), conversion factor 1.04.*

## Adarkwah 2011b

| **Study** | Adarkwah CC, Gandjour A (2011) Cost-effectiveness of angiotensinconverting enzyme inhibitors in nondiabetic advanced renal disease. PLOS ONE 10.1586/ERP.11.8 | | | |
|---|---|---|---|---|
| **Study details** | **Population & interventions** | **Costs** | **Outcomes** | **Cost effectiveness** |
| **Economic analysis:** Cost utility analysis<br>**Study design:** Decision analytic model<br>**Approach to analysis:** Markov model[1] simulating the progression from normoalbuminuria[2] to microalbuminuria, macroalbuminuria, end-stage renal disease (ESRD) and death. It was assumed people continuously progressed without skipping any health state. Probabilistic sensitivity analysis used 1,000 Monte Carlo simulations.<br>**Perspective:** German health system<br>**Time horizon:** 57 years (>99% of cohort dead), 1-year cycle with half-cycle correction<br>**Intervention effect duration:** duration of the analysis<br>**Discounting:** 3% costs, 3% QALYs | **Population:** People aged 44 with advanced renal insufficiency, proteinuria and hypertension<br><br>**Cohort settings**<br>**Intervention 1:** ACE inhibitor (treat all)<br>**Intervention 2:** No ACE inhibitor | **Total costs (mean per individual)[1]:**<br>**Int1:** €172,676 (£177,233.60)<br>**Int2:** €205,200 (£210,616.03)<br><br>**Currency & cost year:**<br>Euro, 2011<br>**Cost components incorporated:** direct healthcare costs (drugs, cost dialysis and transplant) | **QALYs (mean per individual):**<br>**Int1:** 8.26<br>**Int2:** 6.77 | **Full incremental analysis:**<br>The strategy of treating all patients dominates as it is cheaper and produces more QALYs.<br>**Analysis of uncertainty:**<br>All univariate sensitivity analyses showed that an ACE inhibitor is dominant. |

| Data sources |
|---|
| **Outcomes:** Model was adapted from a previously developed model for diabetic nephropathy. Model based on the results of RCTs by Ihle et al. and Hou et al. The transition probabilities used a review by Terajima et al. and was updated by an additional review. Mortality was calculated as a function of age for patients without ESRD, it was assumed that mortality was independent of age for people with ESRD.<br>**Quality of life weights:** Preference weights for advanced renal disease were sourced from a study in 65 people and used a time trade-off methodology (TTO). For ESRD the preference weights were taken from a systematic review.<br>**Costs:** Only direct cost were considered, this included cost of ACE inhibitors, treatment of ESRD and healthcare expenditure related and unrelated to CKD. The reference cost of the ACE inhibitor was used. Annual costs of ESRD included a weighted average of dialysis and transplant costsx. |
| **Comments** |
| **Source of funding:** No support or funding. Authors declared having no conflict of interest. |
| **Overall applicability:** Partially applicable |
| Analysis conducted 8 years ago taking a Dutch health system perspective. The analysis does not consider standard practice as one of the comparators.<br>Costs were discounted at a 4% annual rate and benefits at a 1.5% rate. This may have contributed to the cost-effectiveness of the interventions, compared to a scenario were both costs and benefits were subject to 3.5% annual discounting. |
| **Overall quality**: Potentially serious limitations |
| The absolute effect of the interventions was assumed constant over the duration of the analysis which may be an oversimplification of reality.<br>It is likely that technologies such as dialysis and transplant may have different costs and safety profiles since the analysis was conducted. |

[1]*Euros 2011 converted to sterling 2019 using the EPPI Centre cost converter (accessed 30/10/2020), conversion factor 1.14.*

## Hoerger 2010

| **Study** | Hoerger TJ, Wittenborn JS, Segel JE et al. (2010) A health policy model of CKD. Part 2: The cost-effectiveness of microalbuminuria screening. American Journal of Kidney Diseases 55(3): 463-473 | | | |
|---|---|---|---|---|
| **Study details** | **Population & interventions** | **Costs**[2] | **Outcomes** | **Cost effectiveness** |
| **Economic analysis:** Cost utility analysis<br>**Study design:** Decision analytic model<br>**Approach to analysis:** Microsimulation modelling the | **Population:** People with 30 years old<br><br>**Intervention 1:** Usual care[1]<br>**Intervention 2:** Universal 1y*<br>**Intervention 3:** Universal 2y*<br>**Intervention 4:** Universal 5y*<br>**Intervention 5:** Universal 10y* | **Total costs (mean per individual):**<br>**Int1**: $146,500 (£130,029)<br>**Int2**: $147,900 (£131,271)<br>**Int3**: $147,900 (£130,650) | **QALYs (mean per individual):**<br>**Int1**: 17.685<br>**Int2**: 17.695<br>**Int3**: 17.693<br>**Int4**: 17.691<br>**Int5**: 17.690<br>**Int6**: 17.682 | **Full incremental analysis**[3]**:**<br>(Each strategy compared to usual care)<br>Full population<br>**Int2 vs Int1:** $145,000 (£128,697)<br>**Int3 vs Int1:** $91,000 (£80,769)<br>**Int4 vs Int 1:** $52,000 (£46,153)<br>**Int5 vs Int 1:** $34,000 (£30,177)<br>**Int6 vs Int 1:** $29,000 (£25,739) |

| | | | | |
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| progression of renal disease through the stages of no-CKD, CKD stages 1 to 5 and death.<br>**Perspective:** US Health system<br>**Time horizon:** lifetime<br>**Intervention effect duration:** lifetime<br>**Discounting:** Costs and effect at 3% annually | **Intervention 6:** Universal at age 50y only<br><br>*all from age 50 | **Int4**: $146,800 (£130,295)<br>**Int5**: $146,700 (£130,206)<br>**Int6**: $146,400 (£129,940)<br><br>**Currency & cost year**:**<br>US dollars 2006<br>**Cost components incorporated:** annual medical management of CKD, direct screening and treatment costs.<br><br>**Author rounded costs to the nearest $100 and ICERS to the nearest $1000 | | People with DM<br>All strategies are more expensive and produce more QALYs than usual care ranging from $40,000/QALY (£35,503/QALY) for annual screening to $2,000/QALY (£1,775/QALY) when screening every 5 years.<br>People with HTN<br>All strategies are more expensive than usual care and produce more QALYs ranging from $67,000/QALY (£59,467/QALY) for annual screening to $6,000/QALY (5,325/QALY) when screening every 10 years. The exception was universal screening at age 50 years only which was cost saving.<br>People without diabetes or hypertension<br>All strategies produce more QALYS but were associated with ICERs in excess of $52,000/QALY (£46,153/QALY, Int5) to $253,000/QALY (£224,554/QALY, Int2)<br>**Analysis of uncertainty:**<br>Univariate sensitivity analysis used a (+ -)25% variation on the rate of albuminuria, treatment adherence, costs of screening and discount rate, these being the most influential parameters in the model. This did not substantially change the conclusions of the analysis in the total population with annual screening being more effective and more expensive than usual care at over $55,000/QALY (£48,816/QALY).<br>Probabilistic sensitivity analysis was not conducted. |

**Data sources**

**Outcomes:** The usual care strategy used data from the US Renal Data System (2006) to inform the probability of microalbuminuria in people with (or without) diabetes and hypertension. The sensitivity and specificity of screening used data from a study assessing diagnostic accuracy of a rapid urine test in people with risk factors for cardiovascular and kidney disease (Sarafidis 2008). Treatment compliance was sourced from a cost-utility analysis of albuminuria screening in a population with CKD (Boulware 2003). The efficacy of ACE and ARB therapy was extracted from a meta-analysis on the use of ACE inhibitors and ARBs in people with diabetic nephropathy (Strippoli 2004). Probability of death was sourced from the cost-effectiveness analysis by

Boulware (2003) sourced from the US Renal Data System (2006). It was assumed that people enter ESRD (dialysis or transplant) 1 year after being in CKD stage 5.

**Quality of life weights:** Background utility was assumed to be 1. Utilities for subsequent health states were adjusted (decreased) using data from a study eliciting quality of life estimates from people with CKD using the Kidney Disease Quality of Life Short Form 36 and a time trade-off methodology (Gorodetskaya 2005). Macroalbuminuria was associated with a disutility of 0.01 (Boulware 2003). Disutilities from myocardial infarction and coronary heart disease from other causes were also applied to the stages of CKD, which were sourced from publications assessing quality of life using standard gamble (Nease 1995) or time trade-off (Tsevat 1993)

**Costs:** The costs of CKD are inferred from a privately insured population (Smith 20007). For stage 5 CKD costs from Smith (2007) were adjusted using the US Renal Data System data (2006). Costs of ESRD were also sourced from the US Renal Data System (2006). Screening included a visit to the physician for albumin and creatinine measurement, costs were informed by publications from the Centres for Medicare and Medicaid services (2007). Additional costs of screening after positive albuminuria and renal biopsy were informed by Boulware 2003. Drug costs used average wholesale prices from the Red Book (2007). Diagnosed patients were seen annually by a medical specialist, people with neither diabetes of hypertension were assumed to attend 3 annual medical appointments.

**Comments**

**Source of funding:** Funded by the Centers for Disease Control and Prevention

**Overall applicability:** Partially applicable

Study conducted 10 years ago from an US health system perspective. Costs and utilities discounted at 3% annually.
Study assesses the cost-effectiveness of screening and then treatment, rather than treatment alone, which is the primary focus of this review question.

**Overall quality**: Potentially serious limitations.

Background utilities were not adjusted for the population characteristics and were assumed to be equal to 1.
Probabilistic sensitivity analysis was not conducted.

*[1]Usual care assumed annual screening rates of 22% for people with diabetes, 2% for people with hypertension, 23% for people with both and 0% for people with neither.*

*[2]US dollars 2006 converted to sterling 2020 using the EPPI Centre cost converter (accessed 28/01/2020), conversion factor 1.127.[3]Results presented for each strategy compared to usual care in turn. Author also reported results using no treatment and no screening as the common comparator. These were not presented by the analyst as they were found not to be representative of the UK context were some degree of screening and treatment is in place.*

## Howard 2010

| **Study** | Howard K, White S, Salkeld G et al. (2010) Cost-effectiveness of screening and optimal management for diabetes, hypertension, and chronic kidney disease: a modeled analysis. Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research 13: 196-208 | | | |
|---|---|---|---|---|
| **Study details** | **Population & interventions**[1] | **Costs**[2] | **Outcomes** | **Cost effectiveness** |
| **Economic analysis:** Cost utility analysis | Treatment model (known risk factors) | **Total costs (mean per individual):** | **QALYs (mean per individual):** | **Full incremental analysis:** Treatment model |

| | | | | |
|---|---|---|---|---|
| **Study design:** Decision analytic model<br><br>**Approach to analysis:** Two Markov models simulating cohort progression through no albuminuria, microalbuminuria, macroalbuminuria, ESRD and death states. People could also experience non-fatal cardiac events. One model compared the effect of 3 strategies of intensive management of known risk factors versus standard care. The second model analysed the effect of 3 screening and intensive management of risk factors strategies versus standard care in people aged over 25 years. The optimal management of CKD, hypertension and diabetes was modelled separately due to lack of evidence on the efficacy of combined interventions. Probabilistic sensitivity analysis used a Monte Carlo simulation.<br><br>**Perspective:** Australian health system<br><br>**Time horizon:** lifetime, 1-year cycle<br><br>**Intervention effect duration:** lifetime<br><br>**Discounting:** costs and effects at 5% annually | **Population:** People aged >25 years with sub-optimally managed type 2 diabetes or hypertension and<br><br>**Intervention 1**. Intensive glycaemic control in people with known type 2 diabetes<br>**Intervention 2** Addition of ACE inhibitor in people with known type 2 diabetes<br>**Intervention 3:** Intensive blood pressure control in people with known hypertension<br><br>Screening model (unknown risk factors)<br>**Population:** Entire people over 25 years<br><br>**Intervention 4:** Screening for diabetes and intensive glycaemic control in know and screen-detected people with type 2 diabetes<br>**Intervention 5:** Screening for hypertension and intensive hypertension control in known and screen-detected people with hypertension<br>**Intervention 6:** Screening for proteinuria and addition of ACE inhibitor in people with known diabetes and screen-detected proteinuria | Treatment model<br>**Int1:** $40,144 (£23,530)<br>**SC:** $40,277 (£23,608)<br><br>**Int2:** $37,781 (£22,145)<br>**SC:** $38,606 (£22,629)<br><br>**Int3:** $39,716 (£23,279)<br>**SC:** $39,364 (£23,073)<br><br>Screening model:<br>**Int4:** $17,832 (£10,452) **SC:** $16,487 (£9,664)<br><br>**Int5:** $14,061 (£8,242)<br>**SC:** $14,004 (8,208)<br><br>**Int6:** $16,974 (£9,949)<br>**SC:** $16,821 (£9,860)<br><br>**Currency & cost year:**<br>Australian dollars 2008<br>**Cost components incorporated:** costs of treatment, screening, diabetes, hypertension and coronary care, dialysis, renal transplantation and graft failure. | Treatment model<br>**Int1:** 9.942<br>**SC:** 9.867<br><br>**Int2:** 10.111<br>**SC:** 9.987<br><br>**Int3:** 10.070<br>**SC:** 9.934<br><br>Screening model:<br>**Int4:** 12.798<br>**SC:** 12.701<br><br>**Int5:** 12.947<br>**SC:** 12.831<br><br>**Int6:** 12.763<br>**SC:** 12.731 | **Int1:** Dominates SC<br>**Int2:** Dominates SC<br>**Int3:** $2,588/QALY (£1,517/QALY<br><br>Screening model:<br>**Int4:** $13,866/QALY (£8,128/QALY)<br>**Int5:** $491/QALY (£288/QALY)<br>**Int6:** $4,781/QALY (£2,803/QALY)<br><br>**Analysis of uncertainty:**<br>Univariate sensitivity analysis showed that the cost-effectiveness of screening improved as starting age increased. The ICER increased slightly as participation increase due to more utilisation of services. This did not change the conclusions of the analysis.<br>**Probabilistic sensitivity analysis**<br>Probability cost effective at $50,000/QALY (£29,307/QALY) threshold:<br>Treatment model<br>**Int1:** 85%<br>**Int2:** 88%<br>**Int3:** 82%<br>Screening model:<br>**Int4:** 57%<br>**Int5:** 55%<br>**Int6:** 50% |
| **Data sources** | | | | |

**Outcomes:**

Treatment model

The profile of the modelled population (known risk factors) followed that of the AusDiab study, a cohort representative of the Australian population. The study was used to define diagnosed and undiagnosed cases of type 2 diabetes, age specific risk factors, comorbidities, controlled and uncontrolled disease status (Briganti 2003, Colagiuri 2004, Chadban 2003).

Screening model

The screening model used a distribution of the entire Australian population sourced from a report by the Australian Bureau of Statistics (2003). Both arms could still be clinically diagnosed with risk factors, as per standard care, but screening allowed the identification of additional individuals at risk in the intervention arm. Screening was assumed to occur annually in a primary care setting, being offered to individuals aged 50 to 69 years.

Benefits of intensive management strategies were applied only to people with uncontrolled risk factors in both models. All event rates and outcomes for people with ESRD were sourced from the Australian national cohort of ESRD (Cass 2006).

**Quality of life weights:** Age and health state-specific utility weights were calculated from individual patients SF-36 responses from the AusDiab study (Brazier 2002). Utility values for ESRD (dialysis and transplant) were sourced from (Lee 2005, Laupacis 1996).

**Costs:** The cost of non-pharmacologic diabetes and hypertension care was sourced from the UKPDS study (Gray 2000). The weighting of antidiabetic medication use was sourced from an Australian and New Zealand study (Patel 2008). Intensive hypertension management was based on data from the NEFRON study (Thomas 2009). Drug cost and usage was informed by national reference documents (Pharmaceutic Benefits Scheme 2008 utilization and unit cost). The cost of nonfatal cardiovascular events was informed by data from the Australian population (Clarke 2006). Costs of ESRD were sourced form the Australian National Cohort of ESRD (11).

**Comments**

**Source of funding:** Study was financed by Kidney Health Australia. Design, interpretation, writing and publishing was not conditional on sponsor approval.

**Overall applicability:** Partially applicable

Study conducted 9 years ago from an Australian health system perspective.

Costs and effects were discounted at a 5% annual rate.

Study assesses the cost-effectiveness of screening and then treatment, rather than treatment alone, which is the primary focus of this review question.

**Overall quality**: Minor limitations

Transition probabilities used data from individual RCTs but these were specific to the Australian context.

Calculation of age and condition specific utility weights used patient data collected with the SF-36 tool.

[1]*Each intervention was compared to standard care (SC)*

[2]*Australian dollars 2008 converted to sterling 2019 using the EPPI Centre cost converter (accessed 17/12/2019), conversion factor 1.71*

1 **Dong 2004**

| **Study** | Dong FB, Sorensen SW, Manninen DL et al. (2004) Cost effectiveness of ACE inhibitor treatment for patients with Type 1 diabetes mellitus. Pharmacoeconomics 22(15): 1015-1027 | | | |
|---|---|---|---|---|
| **Study details** | **Population & interventions** | **Costs** | **Outcomes** | **Cost effectiveness** |
| **Economic analysis:** Cost utility analysis<br>**Study design:** Decision analytic model<br>**Approach to analysis:** Discrete event simulation of type 1 diabetes emphasising progression from normoalbuminuria through microalbuminuria, macroalbuminuria, ESRD and death. In addition to nephropathy, the model considered retinopathy and neuropathy as microvascular complications of diabetes.<br>**Perspective:** US healthcare payer<br>**Time horizon:** 70 years or death<br>**Intervention effect duration:** lifetime<br>**Discounting:** costs and effects at 3% annually | **Population:** People with type 1 diabetes aged 20 or older<br><br>**Cohort settings**<br>**Intervention 1:** ACE inhibitor 1 year after diagnosis of type 1 diabetes (Early)<br>**Intervention 2**: Annual screening for microalbuminuria [1] **+** ACE inhibitor (Standard) | **Total costs (mean per individual):**<br>**Int1:** $130,460 (£136,558)<br>**Int2:** $127,768 (£133,740)<br><br>**Currency & cost year:** US dollars 1999<br><br>**Cost components incorporated:** screening for microalbuminuria, ACE inhibitor, management of diabetes and routine medical costs | **QALYs (mean per individual):**<br>**Int1:** 20.456<br>**Int2:** 20.357 | **Full incremental analysis:**<br>The strategy using early ACE inhibition 1 year after diagnosis of diabetes was more expensive and produced more QALYS at a cost of $27,192 (£28,463) per QALY<br>**Analysis of uncertainty:**<br>Increasing the age at diagnosis and decreasing the level of HbA1c would raise the ICER but did not change conclusions of the analysis. This was explored in bivariate scenario analysis. For people diagnosed at age 20 and with HbA1c of 9%, intervention 1 was associated with an ICER of $13, 814 (£14,460)/QALY. For those diagnosed at 30 years with HbA1c of 7% Early administration of ACE inhibitors was priced at $32,972 (£34,513)/QALY.<br>Univariate sensitivity analyses used alternative discount rate, cost and accuracy of the screening test, efficacy and costs of ACE inhibition. The results were particularly sensitive to ACE inhibitor efficacy. A relative risk reduction of 10% (instead of 24%) originated an ICER of $75,276 (£78,794) per QALY. A relative risk reduction of 50% originated an ICER of $8,814 (£9,226) per QALY.<br>The results were overall robust to one-way sensitivity analysis.<br><br>Probabilistic sensitivity analysis was not conducted. |
| **Data sources** | | | | |
| **Outcomes:** Transition probabilities in the nephropathy states were based on a previous cost-effectiveness analysis of the Diabetes Control and Complications Trial (DCCT research group 1996), assessing the role of tight glucose control in preventing complications of diabetes. The transition | | | | |

probabilities were made conditional to glycaemic level (HbA1c), antihypertensive therapy status and duration of diabetes. The model assumed an average HbA1c of 8% with a normal distribution and a standard deviation of 1.2. ACE inhibitor efficacy was used to determine the transition probability from normoalbuminuria to microalbuminuria. This parameter was calculated based on the adjusted relative risk reduction of albumin excretion ratio from the EUCLID trial (lisinopril versus placebo, Lewis 1993) divided by the increase in AER over 2 years from the DCCT trial (1996). Mortality was modelled as a competing risk between lower-extremity amputation, ESRD and cardiovascular disease and was also informed by EUCLID trial.

**Quality of life weights:** The health state utility of blindness was sourced from Dasbach 1992 (abstract not available online). The utility for ESRD was sourced from a study assessing quality of life using SF-36 and a time trade-off methodology (Fryback 1992). The utility of lower limb amputation used a parameter from a cost-effectiveness analysis of long-term antibiotics in diabetic foot infection (Eckman 1995). When multiple complications were present, the lower utility parameter was used.

**Costs**: The analysis included the costs of managing side-effects of diabetes (DCCT research group 1996), microalbuminuria testing, routine diabetes care and intensive glucose control (DCCT research group 1995), cardiovascular disease (American heart Association 1999), cost of ACE inhibitors (Red Book 2000) and lower extremity amputation (Eckman 1995). The costs associated with ESRD were based on data from the US Health Care Financing Administration (1999).

**Comments**

**Source of funding:** Analysis funded by the Centre for Disease Control and Prevention. No conflict of interest.

**Overall applicability:** Partially applicable

Analysis conducted 16 years ago from an US healthcare payer perspective. The clinical management of diabetes and renal disease is likely to have progressed since publication. Discounting was applied at a 3% annual rate for costs and effects.

Study assesses the cost-effectiveness of screening and then treatment, rather than treatment alone, which is the primary focus of this review question. The analysis did not consider screening adherence.

**Overall quality**: Very serious limitations

The parameter informing ACE inhibitor efficacy in preventing microalbuminuria was calculated by the authors based on relative risks from 2 trials. This assumption is likely to have affected the conclusions of the analysis.

Probabilistic sensitivity analysis was not conducted.

[1]*Details of albuminuria screening were not provided by the author, sensitivity and specificity assumed to be 100%.*

[2]*US dollars 1999 converted to sterling 2020 using the EPPI Centre cost converter (accessed 22/01/2020), conversion factor 0.955*

## Boulware 2003

| **Study** | Boulware LE, Jaar BG, Brancati FL et al. (2003) Screening for proteinuria in US adults: a cost-effectiveness analysis. JAMA 23: 3101-3114 | | | |
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| **Study details** | **Population & interventions** | **Costs**[2] | **Outcomes** | **Cost effectiveness** |

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| **Economic analysis:** Cost utility analysis<br>**Study design:** Decision analytical model<br>**Approach to analysis:** Markov model simulating the clinical path of people with normal kidney function through chronic kidney insufficiency and ESRD. Probabilistic sensitivity analysis used a Monte Carlo simulation with 1,000 iterations. Scenario analyses used alternative starting age for screening, screening frequencies, and separate effects of ACE inhibitors and ARBs on ESRD progression and death.<br>**Perspective:** Societal perspective<br>**Time horizon:** lifetime<br>**Intervention effect duration:** lifetime<br>**Discounting:** 3% annually for costs and effects | **Population:** US adults aged 50 without hypertension or diabetes or with hypertension<br><br>**Cohort settings**<br>**Intervention 1:** Annual screening for proteinuria[1] + treatment with ACE inhibitor or ARB therapy<br>**Intervention 2:** No screening (standard care) | **Total costs (mean per individual):**<br>Neither hypertension nor diabetes<br>**Int1:** $13,745 (£14,192)<br>**Int2:** $13,129 (£13,556)<br>Hypertension<br>**Int1:** $23,927 (£24,706)<br>**Int2:** $23,451 (£24,214)<br><br>**Currency & cost year:**<br>US dollars 2002<br>**Cost components incorporated:** direct medical costs (screening, medical appointments, radiology, pathology, antihypertensive therapy, cost of adverse events, ESRD, dialysis and renal transplantation) and indirect costs from loss of productivity | **QALYs (mean per individual):**<br>Neither hypertension nor diabetes<br>**Int1:** 19.461<br>**Int2:** 19.459<br>Hypertension<br>**Int1:** 17.241<br>**Int2:** 17.215 | **Full incremental analysis:**<br>Neither hypertension nor diabetes<br>The screening strategy was more expensive and produced more QALYs at $280,000 (£289,114)/QALY<br>Hypertension<br>The screening strategy was more expensive and produced more QALYs at $18,594 (£19,999)/QALY<br>**Analysis of uncertainty:**<br>Neither hypertension nor diabetes<br>The screening strategy was not cost-effective when screening started between the ages of 30 to 50 years.<br>Screening less frequently was associated with lower ICERs, $120,727 (£124,657) if done every 5 years and $80,700 (£83,327) is done every 10 years.<br>Screening was associated with a 1.5% probability of being cost-effective at a threshold less than $50,000 (£51,628) per QALY.<br>Hypertension<br>Screening was cost-effective irrespectively of the age at which screening was started (range 30 to 70 years). After the age of 40, screening was associated with a cost of $18,589 (£19,194)/QALY, decreasing thereafter.<br>The screening strategy remained cost-effective with less frequent screening produced lower ICERs.<br>In univariate sensitivity analysis the most influential parameters were adherence to antihypertensive therapy and reduction in all-cause mortality. These were likely to make screening moderately favourable in the population with hypertension.<br>Screening was associated with a 50.3% probability of being cost-effective at a threshold less than $50,000 (£51,628) per QALY). |
| **Data sources** | | | | |

**Outcomes:** Natural disease progression was obtained from published cohorts and clinical studies relevant to the US context. Baseline use of ACE inhibitors or ARDs was informed by publications on national prescription and medication usage. The distribution of people in the chronic insufficiency state (GFR 15 to 89 ml/min per 1.73 $m^2$) and the baseline probability of positive dipstick proteinuria were informed by the National Health and Nutrition Examination Survey (NHANES III) (Coresh 2003, Garg 2002). Sensitivity and specificity of proteinuria detection were obtained from primary research studies of test characteristics in different subpopulations. The authors considered adherence to screening and antihypertensive therapy, obtaining data from primary care screening services reports and other published literature. Symptom development and incidental testing in the no screening group was sourced from a national medical care survey (Cherry 2002). The benefits of screening (all-cause mortality) and harms (unnecessary procedures) were drawn from multiple publications reporting on people with (or without) diabetes and hypertension.

The effect of ACE inhibitors in reducing the incidence of ESRD used data from a meta-analysis by Jafar 2001. For people with diabetes, the effect of ARB therapy in reducing CKD progression was drawn from 2 RCTs comparing irbesartan (Lewis 2001) or losartan (Brenner 2001) to placebo in people with nephropathy. The effects of ACE inhibitors on mortality reduction were drawn from a cohort of people with and without diabetes (Gerstein 2001), for ARBs this parameter was sourced from a multicentre RCT comparing losartan to atenolol in people with diabetes (Lindholm 2002).

**Quality of life weights:** The health state utilities used in the model were sourced from two studies using standard gamble (Tengs 2000) or time trade-off methodologies (de Wit 2002). The disutility associated with the side-effects of antihypertensive therapy was sourced from (Tengs 2000).

**Costs:** Costs of screening included dipstick testing, medical appointments, pathology and biochemistry tests and were estimated from Medicare usage (Centers for Medicare and Medicaid Services 2003, 2003a). Antihypertensive therapy used a weighted average of wholesale prices for ACE inhibitors and ARBs available from national sources. Costs of appointments due to adverse events of therapy or renal biopsies was also sourced from Medicare data. The costs of ESRD were sourced from the US Renal Data System (USRDS 2002).

Annual wage loss for people with ESRD used a weighted average of published estimates with the proportion of people working full-time while receiving dialysis or transplantation. It was assumed that people on other states were working full-time until the age of 65. These costs were informed by average US wages from the US Department of Labour (2002).

**Comments**

**Source of funding:** The study was funded by the National Kidney Foundation of Maryland, the National Institute of Diabetes and Digestive and Kidney Diseases, and from the Robert Wood Johnson Minority Medical Faculty Development program

**Overall applicability:** Partially applicable

Study conducted 17 years ago from an US societal perspective. Lost wages due to renal failure were considered in the analysis and were associated with high cost. Comparatively, the monetary value of productivity losses was equivalent to 60% of the cost of ESRD, an important parameter offsetting the costs of the intervention. This is likely to have influenced the study's conclusions and its generalisability to the UK context.

Costs and effects discounted at a 3% annual rate.

Study assesses the cost-effectiveness of screening and then treatment, rather than treatment alone, which is the primary focus of this review question.

**Overall quality**: Minor limitations

Included papers were ranked for quality and described in detail. No sensitivity analysis was conducted using wage loss costs.

[1] *Initial screening for proteinuria consisted of a urine dipstick. Positive results were followed by a second physician appointment to assess protein levels using albumin to creatinine ratio or timed urine specimens in addition to serum creatinine level and eGFR. Screening occurred annually until age 75, development of ESRD or death.*

[2] *US dollars 2002 converted to sterling 2020 using the EPPI Centre cost converter (accessed 22/01/2020), conversion factor 0.968.*

[3]*The author assumed an ICERs below $50,000/QALY (£51,628/QALY) to be highly favourable, between $50,000 and $100,000/QALY (£103,255/QALY) moderately favourable and greater than $100,000/QALY unfavourable*

## Golan 1999

| **Study** | Golan L, Birkmeyer JD and Welch HG (1999) The cost-effectiveness of treating all patients with type 2 diabetes with angiotensin-converting enzyme inhibitors. Annals of Internal Medicine 131: 660-667 | | | |
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| **Study details** | **Population & interventions** | **Costs** | **Outcomes** | **Cost effectiveness** |
| **Economic analysis:** Cost utility analysis<br>**Study design:** Decision analytic model<br>**Approach to analysis:** Markov model simulating progression of kidney disease from normoalbuminuria through microalbuminuria, macroalbuminuria, gross proteinuria, ESRD and death. Adherence to screening and compliance with medication were also modelled by subdividing the health states. No probabilistic sensitivity analysis was conducted.<br>**Perspective:** US societal<br>**Time horizon:** Lifetime horizon, 1-year cycle<br>**Intervention effect duration:**<br>**Discounting:** 3% annually for costs and QALYs | **Population:** 50-year-old people with type 2 diabetes<br>**Cohort settings**<br>**Intervention 1:** Treat all with ACE inhibitor (no screening)<br>**Intervention 2:** ACE inhibitor if microalbuminuria<br>**Intervention 3:** ACE inhibitor if gross proteinuria | **Total costs (mean per individual):**<br>**Int1:** $15,240 (£15,874)<br>**Int2:** $14,940 (£15,562)<br>**Int3:** $19,520 (£20,333)<br><br>**Currency & cost year:**<br>US dollars 1998<br><br>**Cost components incorporated:** Direct medical cost (ACE inhibitor therapy, monitoring, screening, treatment of ESRD) | **QALYs (mean per individual):**<br>**Int1:** 11.82<br>**Int2:** 11.78<br>**Int3:** 11.59 | **Full incremental analysis:**<br>In the base case treating all without screening was the most cost-effective strategy with an ICER of $7500/QALY (£7,812/QALY). Int 3 was dominated being more expensive and producing less QALYs.<br>**Analysis of uncertainty:**<br>In univariate sensitivity analysis the ICER was sensitive to age at diagnosis of diabetes, drug costs, effectiveness and quality of life associated with ACE inhibitor.<br>Increasing the age at diagnosis to 55 years, increasing the cost of ACE inhibitor from $320 to $420/year and increasing the rate for progression from 0.32 to 0.46 all generated an ICER in excess of £20,000/QALY for treat all compared to the microalbuminuria strategy. This did not change the overall conclusions of the analysis. |
| **Data sources** | | | | |
| **Outcomes:** It was modelled that the cohort had a recent diagnosis of type 2 diabetes with 70% having normoalbuminuria, 18% microalbuminuria and 3% gross albuminuria. ACE inhibitor efficacy was sourced from 3 RCTs reporting on populations with normoalbuminuria (Ravid 1998), microalbuminuria (Ravid 1993) and gross proteinuria (Lewis 1993). The probability of transiting to the ESRD state was extrapolated from a trial assessing the efficacy of ACE inhibitors in people with type 1 diabetes. Transition to death was age adjusted and could occur from any health state. The probability of dying in the | | | | |

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| initial states was that of the general population adjusted using a standardised mortality rate for people with diabetes (Walters 1994). In the ESRD state mortality was sourced from US Renal Data System (1998) and assumed to be age independent. It was assumed that nephropathy would not regress, and progression would not skip health states. It was modelled that only 50% of clinicians would adhere to the annual screening and that people on ACE inhibitor or in which treatment has failed were not re-screened. It was assumed that discontinuation due to adverse effects (2%) and non-compliance (25%) would occur within 3 months of starting ACE inhibition. These people did not incur the therapeutic benefit and would be at higher risk of renal disease progression.<br><br>**Quality of life weights:** Utility states for the initial kidney disease states was sourced from the Beaver Dam Health Outcomes Study (Fryback 1993). The utility in the ESRD state was calculated using a weighted average of conditions such as dialysis and transplant (Lovell 1998).<br><br>**Costs:** The analysis used the wholesale price of lisinopril. The cost of screening, dialysis and renal transplantation was based on the Medicare data estimated by the US Renal Database System (1998). |
| **Comments** |
| **Source of funding:** The analysis was financed by the Veterans Affair Fellowship in Ambulatory Care. There were no conflicts of interest. |
| **Overall applicability:** Partially applicable |
| Conducted 20 years ago using an US societal perspective. Progression of chronic kidney disease was informed by individual RCTs.<br>Analysis took a societal perspective of costs.<br>The analysis does not consider standard practice as one of the comparators.<br>Study assesses the cost-effectiveness of screening and then treatment, rather than treatment alone, which is the primary focus of this review question. |
| **Overall quality**: Very serious limitations |
| Transition to the ESRD state was sourced from a trial of ACE inhibitors in a population with type 1 diabetes which may have influenced the incidence of ESRD and overall costs. The analysis did not consider test accuracy which could affect the number of people allocated to treatment. The efficacy of ACE inhibition was informed by individual trials.<br>It is likely that the cost of medicines, screening practices and the clinical management of people with ESRD has changed substantially since the analysis was conducted which may limits the generalisability of the study results to the UK context.<br>No probabilistic sensitivity analysis was conducted. |

*[1]Normoalbuminuria –excretion < 30 mg/day; microalbuminuria –excretion 30 to 100 mg/day; gross proteinuria – excretion > 300 mg/day*

*[2]US dollars 1998 converted to sterling 2019 using the EPPI Centre cost converter (accessed 17/12/2019), conversion factor 0.98*

## Kiberd 1998

| Study | Kiberd BA and Jindal KK (1998) Routine treatment of insulin-dependent diabetic patients with ACE inhibitors to prevent renal failure: an economic evaluation. American Journal of Kidney Diseases 31: 49-54 | | | |
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| **Study details** | **Population & interventions** | **Costs[4]** | **Outcomes** | **Cost effectiveness** |

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| **Economic analysis:** Cost utility analysis<br>**Study design:** Decision analytic model simulating CKD progression through the stages of normoalbuminuria, microalbuminuria, macroalbuminuria, ESRD and death.<br>**Approach to analysis:** Markov model[1]<br>**Perspective:** US, third party<br>**Time horizon:** 60 years<br>**Intervention effect duration:**<br>**Discounting:** Costs and effects at 3% annually | **Population:** People with type 1 diabetes 43 years of age<br>**Intervention 1:** Current recommendations (annual screening for microalbuminuria plus ACE inhibitor)[2]<br>**Intervention 2:** Routine treatment of all people 5 years after diagnosis of diabetes<br>**Intervention 3:** Treat people at high risk 5 years after diagnosis of diabetes and screen people at low risk and treat with ACE inhibitor accordingly[3] | **Total costs (mean per individual):**<br>**Int1:** $29,350 (£32,646)<br>**Int2:** $29,180 (£32,457)<br>**Int3:** $29,236 (£32,520)<br>**Currency & cost year:** US dollars 1995<br><br>**Cost components incorporated:** Costs of screening, ACE inhibitor and ESRD | **QALYs (mean per individual):**<br><br>**Int1:** 19.15<br>**Int2:** 19.34<br>**Int3:** 19.17 | **Full incremental analysis:**<br>The routine treatment strategy dominated Int1 and Int3, being cheaper and producing more QALYs<br>**Analysis of uncertainty:**<br>The results were robust to univariate sensitivity analyses.<br>Probabilistic sensitivity analysis was not conducted. |
| **Data sources** | | | | |
| **Outcomes:** The model assumed that 40% of people were high risk and were assigned a fourfold higher risk of CKD progression compared to low-risk individuals. The probability of CKD progression was sourced from (The Microalbuminuria Captopril Study Group 1996, Diabetes Control and Complications Trial Research Group 1996). The probability transition to the macroalbuminuria in high-risk patients was sourced from (Warram 1995). This reference is from an abstract and is no longer available. The positive predictive value of microalbuminuria screening was sourced from Kimberd (1995). Mortality in the model was that for the general US population (National Centre for Health Statistics 1995) adjusted for diabetes specific mortality (Portuese 1995) and progressed CKD (Rossing 1996). In the ESRD state the probability of death was informed by the US Renal Data System (1995).<br>**Quality of life weights:** The utilities were sourced from Kimberd (1995) who used 6 health states (present health, hypertension requiring medication, insulin dependent diabetes, hypertension and diabetes requiring insulin and antihypertensive, renal transplant and dialysis) to elicited preferences from 17 health care workers using time-trade-off.<br>**Costs:** Cost of medicines was sourced from the Red Book (1993) and increased by 25% to account for dispensing fees, overheads and monitoring costs. The cost of ESRD used a pooled average of all patients and treatments including transplantation (US Renal Data System, 1995). | | | | |
| **Comments** | | | | |
| **Source of funding:** None, no conflict of interest. | | | | |
| **Overall applicability:** Partly applicable | | | | |
| Study conducted 22 years ago from an US third party perspective. What constituted current practice for the purposes of the study may not be comparable to the current UK context. Utility values were obtained from a sample of 17 US health professionals using a time-trade-off methodology.<br>Study assesses the cost-effectiveness of screening and then treatment, rather than treatment alone, which is the primary focus of this review question. | | | | |

| **Overall quality**: Very serious limitations |
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| It is likely that technologies such as dialysis and transplant may have different costs since the analysis was conducted. It is also likely that the management of people with hypertension and diabetes has substantially changed since publication of the economic analysis. Efficacy data was sourced from 2 RCTs and an abstract paper which is no longer available. Probabilistic sensitivity analysis was not conducted. Costing is loosely described which limits model validation. |

[1]*Adapted from a previous model (Kimberd 1995) analysing the effect of 2 screening strategies on kidney disease progression in people with insulin dependent diabetes mellitus.*

[2]*Screening in people with diagnosis of diabetes for more than 5 years and treatment with the equivalent to captopril 25 mg 3 times a day if 2 of 3 tests were positive (>20 mcg/min or 30 mg albumin/g creatinine)*

[3]*People with low risk were screened for hypertension and macroproteinuria (dipstick >0.3 g/L or positive albustick confirmed with >3000 mg/day or >200 mcg/min proteinuria)*

[4]*US dollars 1995 converted to sterling 2020 using the EPPI Centre cost converter (accessed 14/01/2020), conversion factor 0.90*

# Comparison of antihypertensive therapies

## Adarkwah 2013

| **Study** | Adarkwah CC, Gandjour A, Akkerman M et al. (2013) To treat or not to treat? Cost-effectiveness of ace inhibitors in non-diabetic advanced renal disease: a Dutch perspective. Kidney and Blood Pressure Research 37: 168-180 | | | |
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| **Study details** | **Population & interventions** | **Costs** | **Outcomes** | **Cost effectiveness** |
| **Economic analysis:** Cost utility analysis<br>**Study design:** Decision analytic model<br>**Approach to analysis:** Markov model[1] simulating the progression of 1000 people through 3 health states: advanced renal disease, ESRD and death. Probabilistic sensitivity analysis used 1,000 Monte Carlo simulations.<br>**Perspective:** Dutch health system<br>**Time horizon:** Until cohort age of 100 (>99% of cohort dead), 1-year cycle with half-cycle correction<br>**Intervention effect duration:** duration of the analysis<br>**Discounting:** 4% costs, 1.5% QALYs | **Population:** People aged 44 with advanced renal disease[2]<br><br>**Cohort settings**<br>**Intervention 1:** ACE inhibitor<br>**Intervention 2:** No treatment (Antihypertensives not acting on the renin-angiotensin-system[3]) | **Total costs (mean per individual)[4]:**<br>**Int 1:** €183, 535 (£176,674)<br>**Int2**: €220,942 (£212,683)<br>**Currency & cost year:** Euros, 2010<br><br>**Cost components incorporated:** direct healthcare costs (ACE inhibitor, chronic kidney disease costs, transplant and dialysis) | **QALYs (mean per individual):**<br>**Int1**: 14.66<br>**Int 2:** 13.38 | **Full incremental analysis:**<br>The ACE inhibitor strategy dominates the no treatment strategy having a lower cost and higher benefit.<br>**Analysis of uncertainty:**<br>Parameters with largest impact in univariate sensitivity analysis were the effectiveness of ACE inhibitor, cost of ESRD and discount rate. The conclusions of the analysis did not change when these were varied.<br>The probability of producing savings was 83%. |

| Data sources |
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| **Outcomes:** The author conducted a literature review from 2001 to September 2012 to update an existing systematic review on the effect of ACE inhibitors (Terajima 2003). Two RCTs met the inclusion criteria (Ihle 1996 and Hou 2006) and informed the probability of transition to the ESRD state in people receiving ACE inhibitor, and in the no treatment arm (baseline risk). In the advanced renal disease group mortality was modelled using national age specific national rates adjusted for disease specific mortality using cohort data (Hemmelgarn 2010). For people with ESRD mortality was assumed to be age independent.<br><br>**Quality of life weights:** The utility for people in the advanced renal disease stage was sourced from a survey using TTO (Hoerger 2010). ESRD state preferences were sourced from a publication applying a TTO methodology in 272 people in ESRD (Churchill 1987).<br><br>**Costs:** The base case used the cost of the cheapest generic of benazepil 10 mg available in the Netherlands. The annual cost of renal transplant and different types of dialysis was sourced from was sourced from a Dutch study (de Wit 1998) and prevalence data from a The Dutch End-Stage Renal Disease registry (2011b). Transplant survival was assumed to be 10 years. |
| **Comments** |
| **Source of funding:** None. No conflicts of interest. |
| **Overall applicability:** Partially applicable |
| Analysis conducted 6 years ago taking a Dutch health system perspective. The analysis considers only one class of antihypertensive medication in CKD progression.<br>Costs were discounted at a 4% annual rate and benefits at a 1.5% rate. This may have contributed to the cost-effectiveness of the intervention, compared to a scenario were both costs and benefits were subject to 3.5% annual discounting. |
| **Overall quality**: Potentially serious complications |
| The absolute effect of the intervention was assumed constant over the duration of the analysis as was the risk of progressing to ESRD.<br>It is likely that technologies such as dialysis and transplant may have different costs and safety profiles since the analysis was conducted. |

[1]*Model adapted from previous analysis of the cost effectiveness of ACE inhibitors in Germany (Adarkwah 2010) and the Netherlands (Adarkwah 2011)*

[2]*Serum creatinine: > 3.0 mg/dl, glomerular filtration rate (GFR): 15-26 ml/min/1.73 m²), proteinuria, and hypertension (> 150/85 mm Hg), but without severe heart failure (New York Heart Association III or IV) or diabetes.*

[3]*People in the control arm were allowed diuretics, calcium-channel antagonists, alpha- or beta-blockers, or a combination of these, excluding ACE inhibitors and angiotensin II–receptor antagonists.*

[4]*Euros 2010 converted to sterling 2019 using the EPPI Centre cost converter (accessed 12/12/2019), conversion factor 1.04*

## Delea 2009

| **Study** | Delea TE, Sofrygin O, Palmer JL et al. (2009) Cost-effectiveness of aliskiren in type 2 diabetes, hypertension, and albuminuria. Journal of the American Society of Nephrology 20: 2205-13 | | | |
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| **Study details** | **Population & interventions** | **Costs** | **Outcomes** | **Cost effectiveness** |

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| **Economic analysis:** Cost utility analysis<br>**Study design:** Decision analytic model<br>**Approach to analysis:** Markov model[1] simulating progressive kidney disease using several health states: microalbuminuria, early overt nephropathy, advanced overt nephropathy, doubling serum creatinine, dialysis, transplant and death. Probabilistic sensitivity analysis used 1,000 Monte Carlo simulations.<br>**Perspective:** US health system<br>**Time horizon:** lifetime, 6-month cycles<br>**Intervention effect duration:** lifetime<br>**Discounting:** Cost and QALYs at 3% annually | **Population:** People with type 2 diabetes and microalbuminuria<br><br>**Cohort settings**<br>**Intervention 1:** Aliskiren 300 mg/day plus losartan 100 mg/day*<br>**Intervention 2:** Losartan 100 mg/day*<br><br>*Plus optimal antihypertensive therapy | **Total costs (mean per individual)[2]:**<br>**Int1:** $64,746 (£53,849)<br>**Int 2:** $61,794 (£51,394)<br>**Currency & cost year:** US dollars, 2008<br>**Cost components incorporated:** direct healthcare costs (intervention costs, additional antihypertensive costs, | **QALYs (mean per individual):**<br>**Int1:** 5.9775<br>**Int2:** 5.8808<br>**Other:**<br>Incidence of ESRD:<br>**Int1:** 23.43%<br>**Int2:** 20.74%<br>(2.69% reduction, favours intervention 1)<br>Time free of ESRD:<br>Increased by 0.1772 years, favours intervention 1 | **Full incremental analysis[3]:**<br>In the base case aliskiren combined with losartan was more expensive and produced more QALYs than the strategy using losartan alone producing an ICER of $30,527/QALY (£25,390/QALY).<br>**Analysis of uncertainty:**<br>In univariate sensitivity analysis the results were sensitive to the duration of effect and price of aliskiren but the intervention remained cost-effective at the $50,000 to $100,000/QALY (£41,585 to £83,170/QALY) threshold.<br>Interventions 1 had a 60% probability of being cost-effective at a $50,000/QALY threshold and a 72% probability of being cost-effective at a threshold of $100,000. |

**Data sources**

**Outcomes:** In the initial 6 months the distribution of people and probability of transiting between the microalbuminuria, early overt nephropathy and advanced overt nephropathy states was estimated using patient level data from the AVOID trial (Parving 2008). After 6 months the probabilities were estimated using Bayesian conjugate analyses of these data not allowing for backward or double forward transitions. The probability of transiting to the double serum creatinine state and ESRD dialysis was sourced from the cost-effectiveness analysis by Palmer (2004). The probability of transplant and graft failure for those on dialysis was sourced from the US Renal Data System (2007). Mortality on those without ESRD was implemented using US lifetables (WHO 2008) adjusted for diabetic nephropathy specific mortality using a risk ratio (diabetic nephropathy versus general population) from Palmer (2004). Age-specific mortality for those on the ESRD stages was estimated from the US Renal Data System (2007). Adverse events were not modelled as they were similar between arms of the AVOID trial.

**Quality of life weights:** Health state utilities were calculated by multiplying age-specific utilities in the US population by health state disutilities. The disutilities for early chronic kidney disease and renal transplantation were sourced from cohort studies using TTO to elicit preferences (Fryback 1993 and Kiberd 1995, respectively). The disutility for dialysis was sourced from a study eliciting utility values from 2,048 people with diabetes using a self-administer questionnaire (Coffey 2002).

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| **Costs:** The use of aliskiren, losartan and additional antihypertensive medicines was estimated during the AVOID trial (Parving 2008). Unit costs used wholesale drug prices and the IMS National prescription audit (2008). The cost of routine healthcare in people with diabetes used data from a cost-effectiveness analysis of diabetes screening (Centres for Disease Control and Prevention, 1998) and from the Diabetes Control and Complications Trial (1996). Costs of dialysis, renal transplantation and graft failure were obtained from the US Renal Data System (2007). |
| **Comments** |
| **Source of funding:** The analysis was funded by the drug manufacturers. Several authors have received consulting fees from drugs manufacturers. |
| **Overall applicability:** Partially applicable |
| Conducted 10 years ago from an US health system perspective. The analysis does not compare all medicines available in this decision space.<br>The analysis was sponsored by the drug manufacturer.<br>Aliskiren is not a drug in routine use in the UK. |
| **Overall quality**: Potentially serious limitations |
| Progression in the model is essentially sourced from a single RCTs, adverse events were not modelled because RCT found incidence to be identical in the comparator included in the trial. |

*[1]Markov model adapted from US cost effectiveness analysis of ACE inhibitors in people with diabetes, hypertension and renal disease (Palmer 2004)*

*[2]US dollars 2008 converted to sterling 2019 using the EPPI Centre cost converter (accessed 17/12/2019), conversion factor 1.20*

### Smith 2004

| **Study** | Smith DG, Nguyen AB, Peak CN et al. (2004) Markov modeling analysis of health and economic outcomes of therapy with valsartan versus amlodipine in patients with Type 2 diabetes and microalbuminuria. Journal of Managed Care Pharmacy 10: 26-32 | | | |
|---|---|---|---|---|
| **Study details** | **Population & interventions** | **Costs**[1] | **Outcomes** | **Cost effectiveness** |
| **Economic analysis:** Cost utility analysis<br>**Study design:** Decision analytic model<br>**Approach to analysis:** Markov model simulating kidney disease progression through 7 states: normoalbuminuria, microalbuminuria, nephropathy, ESRD (transplant and dialysis), death, cardiovascular disease and withdrawal. The model assumed people in the microalbuminuria and nephropathy states could return to earlier states (improve), once | **Population:** People with type 2 diabetes<br>**Cohort settings**<br>**Intervention 1:** Valsartan<br>**Intervention 2:** Amlodipine | **Total costs (mean per individual):**<br>**Int1:** $92,058 (£92,231)<br>**Int2:** $124,470 (£124,703)<br>**Currency & cost year:** US dollars 2001<br>**Cost components incorporated:** Study drugs, routine healthcare services to manage | **QALYs (mean per individual):**<br>**Int1:** 6.390<br>**Int2:** 5.835 | **Full incremental analysis:** The intervention using valsartan dominated amlodipine being cheaper and producing more QALYs.<br>**Analysis of uncertainty:** The results were robust to univariate sensitivity analyses on discount rate, health state costs, and medication costs |

| | | | | |
|---|---|---|---|---|
| ESRD was achieved, model progression was unidirectional.<br>**Perspective:** US third party perspective<br>**Time horizon:** 8 years, 3-month cycles<br>**Intervention effect duration:** 8 years<br>**Discounting: C**osts and effects at a 3% annual rate | | hypertension, dialysis, renal transplantation | | Probabilistic sensitivity analysis was not conducted. |
| **Data sources** | | | | |
| **Outcomes:** Transition probabilities of withdrawal and transiting from normoalbuminuria used data from the MARVAL study (Viberti 2002, Syne Qua Non 2001). Transition probabilities for the microalbuminuria, nephropathy, ESRD and cardiovascular disease were sourced from additional RCTs in people with nephropathy: Bernner 2001 (losartan versus placebo), Lewis 1993 (captopril versus placebo) and Parving 2001 (ibesartan versus placebo). Transplantation failure was informed by data from the US Renal Data System (2003).<br>**Quality of life weights:** Health state utilities for the renal disease states used values from a published cost-effectiveness analysis of benazepril versus placebo (Hogan 2002). Hogan (2002) cites several primary studies assessing quality of life and health state preferences from people at different states of chronic kidney disease but there is not enough detail to precise the source for each parameter. The utility for the cardiovascular disease state was sourced from a study using a time-trade off methodology to elicit state preferences from US survivors of myocardial infarction (Tsevat 1993).<br>**Costs:** Costs were assumed to increase 2.8% annually based on the consumer price index. Drug costs used prices from the Red Book (2001). The costs of hypertension management appointment used data from insurance company payments (ADP Context 2001). The costs associated with each health state were sourced Brown (1999) who used routine healthcare data to quantify resource use by people with renal and cardiovascular disease in the US. The costs of terminal care (death) used values published from Hogan (2003). | | | | |
| **Comments** | | | | |
| **Source of funding:** The study was funded by co-authored by the manufacturers of valsartan. | | | | |
| **Overall applicability:** Partially applicable | | | | |
| Analysis conducted 16 years ago from an US third party perspective. The time horizon of the analysis is limited to the 8-year follow-up of the study.<br>No probabilistic sensitivity analysis was conducted. | | | | |
| **Overall quality**: Very serious limitations | | | | |
| Evidence on the efficacy of valsartan is drawn from a single RCT. The analysis does not consider standard care as one of the comparators of interest. The analysis does not consider the lifelong costs as benefits of the comparators. Potential conflict of interest (funded by the manufacturer of valsartan). | | | | |

[1]*US dollars 2001 converted to sterling 2020 using the EPPI Centre cost converter (accessed 15/01/2020), conversion factor 0.998*

# Diet interventions

## You 2015

| Study | You JHS, Ming WK, Lin WA et al. (2015) Early supplemented low-protein diet restriction for chronic kidney disease patients in Taiwan - A cost-effectiveness analysis. Clinical nephrology 88:189-96 | | | |
|---|---|---|---|---|
| **Study details** | **Population & interventions** | **Costs**[4] | **Outcomes** | **Cost effectiveness** |
| **Economic analysis:** Cost utility analysis<br>**Study design:** Decision analytic model<br>**Approach to analysis:** Markov model simulating the progression of CKD to ESRD, dialysis and death.<br>**Perspective:** Taiwanese health system<br>**Time horizon:** 10 years<br>**Intervention effect duration:**<br>**Discounting:** Costs and effects at 3% annually | **Population:** People with CKD stage 4[1]<br><br>**Cohort settings**<br>**Intervention 1:** Low protein diet[2] + supplementation with ketoanalogues[3] in people with CKD stage 4<br><br>**Intervention 2:** Low protein diet and watchful waiting (CKD stage 4) + supplementation with ketoanalogues if CKD stage 5 | **Total costs (mean per individual):**<br>**Int1**: $564,637 (£430,741)<br>**Int2**: $914,236 (£697,437)<br>**Currency & cost year:**<br>US dollars 2015<br>**Cost components incorporated:** | **QALYs (mean per individual):**<br>**Int1**: 3.926<br>**Int2**: 3.787 | **Full incremental analysis**[5]**:**<br>The intervention delivering early low protein diet supplemented with ketoanalogues dominates the watchful waiting strategy, being both cheaper and producing more QALYs.<br><br>**Analysis of uncertainty:**<br>The analysis was robust to univariate sensitivity analysis of the treatment efficacy parameter.<br><br>Probabilistic sensitivity analysis used 10,000 iterations of each of the model's parameters using a triangular distribution. This analysis suggested a statistically significant difference in cost and QALYs between comparators. |
| **Data sources** | | | | |
| **Outcomes:** Baseline distribution of CKD progression was informed by a study correlating glomerular filtration rates and renal disease outcomes in Taiwan (Weng 2014). Incidence and prevalence of dialysis was sourced from an analysis of the national Taiwanese haemodialysis database (Hwang 2010). Treatment effect of ketoanalogues was sourced from a retrospective study assessing the effect of supplemented low protein diet in Korean people with stage 4 or 5 CKD (Chang 2009).<br>**Quality of life weights: U**tilities were sourced from a study assessing quality of life in people with CKD using the Kidney Disease Quality of Life Short Form 36 and a time trade-off methodology (Gorodetskaya 2005).<br>**Costs:** The cost of medical management of CKD stages 4 and 5 and the costs of dialysis used data from the Taiwanese National Health System (2014). | | | | |
| **Comments** | | | | |

| |
|---|
| **Source of funding:** The study was funded by a manufacturer of ketoanalogues. |
| **Overall applicability:** Partially applicable |
| Analysis conducted 5 years ago from a Taiwanese health system perspective.<br>The analysis did not include standard of care as one of the comparators so it may give a biased estimate of the cost-effectiveness of the intervention when implemented in current practice. |
| **Overall quality**: Very serious limitations |
| The efficacy of ketoanalogues used evidence from a retrospective analysis of people with stage 4 or 5 CKD treated with supplemented low protein diet.<br>The study was funded by a manufacturer of ketoanalogues.<br>Probabilistic sensitivity analysis used a triangular distribution for all parameters which may have affected the estimation of uncertainty in the analysis. |

[1] *CKD stage 4 defined as estimated glomerular filtration rate (eGFR) 15 – 29 mL/min/1.73 $m^2$ and CKD stage 5 defined as eGFR < 15 mL/min/1.73 $m^2$.*

[2] *Defined as a protein intake of ≤ 0.6 g/kg/day*

[3] *Combination of essential amino acids and essential amino acid analogues*

[4] *US dollars 2015 converted to sterling 2020 using the EPPI Centre cost converter (accessed 27/01/2020), conversion factor 1.311.*

[5] *The analysis used the threshold for cost-effectiveness defined by the World Health Organisation, 3-fold the gross domestic product (GDP) per capita. In Taiwan this value was calculated as US $20,726 (£15,811)*

## Mennini 2014

| **Study** | Mennini FS, Russo S, Marcellusi A et al. (2014) Economic effects of treatment of chronic kidney disease with low-protein diet. Journal of renal nutrition: the official journal of the Council on Renal Nutrition of the National Kidney Foundation 24: 313-21 | | | |
|---|---|---|---|---|
| **Study details** | **Population & interventions** | **Costs**[2] | **Outcomes** | **Cost effectiveness** |
| **Economic analysis:** Cost utility analysis<br>**Study design:** Decision analytic model<br>**Approach to analysis:** Markov model simulating CKD (state 4 and 5) progression to ESRD (dialysis) and death.<br>**Perspective:** Italian National Health Service<br>**Time horizon:** 2, 3,5 or 10 years | **Population:** People with CKD stage 4 and 5<br>**Cohort settings**<br>**Intervention 1:** Very low protein diet[1]<br>**Intervention 2:** Moderately low protein diet[2] | **Total costs (mean per individual):**<br>**Int1:** € 55,109 (£56,391)<br>**Int2:** € 65,483 (£67,007)<br>**Currency & cost year:** Euros 2014<br>**Cost components incorporated:** medical and non-medical direct costs of dialysis, | **QALYs (mean per individual):**<br>**Int1:** 5.75<br>**Int2:** 4.77 | **Full incremental analysis:**<br>The very low protein diet strategy dominated the moderately low protein diet being both cheaper and producing more QALYs.<br>**Analysis of uncertainty:**<br>The analysis was robust to univariate analysis of discount rates, transition probability to ESRD, probability of death from ESRD, utility parameters, cost of dialysis and cost of diet. |

| | | | | |
|---|---|---|---|---|
| **Intervention effect duration:** up to 10 years<br>**Discounting:** 3% for costs and 1.5% for effects | | reimbursement tariff for low-protein diet | | In probabilistic sensitivity analysis the very low protein diet had 100% probability of being cost-effective (dominant). |
| **Data sources** | | | | |
| **Outcomes:** The model assumed that half of the existing patients were already treated with low protein diet and the other half with very low protein diet. Baseline data was sourced from national CKD prevalence data (Gambaro2010). Treatment efficacy used data from a Cochrane systematic review of RCTs comparing protein intake in people with CKD (Fouque 2009). Probability of death used data from an Italian RCT also included in the Fouque 2009 review (Cianciaruso 2008). The probability of death whilst on dialysis used data from De Nicola (2010) and epidemiological study of CKD in Italy. Risk of death was adjusted to age group and glomerular filtration rate (O'Hare 2006)<br>**Quality of life weights:** Utility parameters were sourced from a study eliciting quality of life estimates from people with CKD using the Kidney Disease Quality of Life Short Form 36 and using a time trade-off methodology (Gorodetskaya 2005).<br>**Costs:** The cost of dialysis was sourced from a report on renal replacement therapy from the Italian Centre of Studies for Social Investment (CENSIS 2009). | | | | |
| **Comments** | | | | |
| **Source of funding:** Funded by the National Kidney Foundation**.** No conflict of interest. | | | | |
| **Overall applicability:** Partially applicable | | | | |
| Study conducted 6 years ago from the Italian NHS perspective. Effects were discounted at 1.5% and costs at 3% annual rates.<br>Analysis accounted for direct medical and non-medical costs of dialysis but did not report on breakdown of costs making it difficult to extrapolate to the UK context. | | | | |
| **Overall quality**: Very serious limitations | | | | |
| The analysis was limited to a 10-year time horizon which may affect the cost-effectiveness conclusion about the long-term use of the intervention.<br>Costs included in the model were not described in enough detail to infer if all the relevant costs were included, for example, follow-up and nutritionist appointments seem not to have been included in the costs.<br>Compliance with diet was not explored in the analysis. Baseline mortality was not included in the analysis. | | | | |

[1]*Low protein diet defined as 0.6 g/kg/day; very low protein diet defined as 0.3 g/kg/day.*

[2]*Euros 2014 converted to sterling 2020 using the EPPI Centre cost converter (accessed 27/01/2020), conversion factor 0.977.*

# Appendix J : Economic evaluation checklists

## Timing of antihypertensive therapy

### Farmer 2014

Farmer AJ, Stevens R, Hirst J et al. (2014) Optimal strategies for identifying kidney disease in diabetes: Properties of screening tests, progression of renal dysfunction and impact of treatment - Systematic review and modelling of progression and cost-effectiveness. Health Technology Assessment 18(14): 1-127

| Category | Rating | Comments |
|---|---|---|
| **Applicability** | | |
| 1.1 Is the study population appropriate for the review question? | Partly | Study assesses the cost effectiveness of screening and then treatment, rather than treatment alone |
| 1.2 Are the interventions appropriate for the review question? | Yes | |
| 1.3 Is the system in which the study was conducted sufficiently similar to the current UK context? | Yes | |
| 1.4 Is the perspective for costs appropriate for the review question? | Yes | |
| 1.5 Is the perspective for outcomes appropriate for the review question? | Yes | |
| 1.6 Are all future costs and outcomes discounted appropriately? | Yes | |
| 1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above). | Yes | |
| **1.8 OVERALL JUDGEMENT** | **PARTIALLY APPLICABLE** | |
| **Limitations** | | |
| 2.1 Does the model structure adequately reflect the nature of the topic under evaluation? | Yes | |
| 2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes? | Yes | |
| 2.3 Are all important and relevant outcomes included? | Yes | |

| Farmer AJ, Stevens R, Hirst J et al. (2014) Optimal strategies for identifying kidney disease in diabetes: Properties of screening tests, progression of renal dysfunction and impact of treatment - Systematic review and modelling of progression and cost-effectiveness. Health Technology Assessment 18(14): 1-127 | | |
|---|---|---|
| **Category** | **Rating** | **Comments** |
| 2.4 Are the estimates of baseline outcomes from the best available source? | Yes | |
| 2.5 Are the estimates of relative intervention effects from the best available source? | Yes | |
| 2.6 Are all important and relevant costs included? | Yes | |
| 2.7 Are the estimates of resource use from the best available source? | Yes | |
| 2.8 Are the unit costs of resources from the best available source? | Yes | |
| 2.9 Is an appropriate incremental analysis presented or can it be calculated from the data? | Yes | |
| 2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis? | Yes | |
| 2.11 Has no potential financial conflict of interest been declared? | Yes | |
| **2.12 OVERALL ASSESSMENT** | **MINOR LIMITATIONS** | |

1 **Adarkwah 2011a**

| Adarkwah CC, Gandjour A, Akkerman M et al (2011) Cost-effectiveness of angiotensin-converting enzyme inhibitors for the prevention of diabetic nephropathy in the Netherlands: a Markov model. PLOS ONE 10: e26139 | | |
|---|---|---|
| **Category** | **Rating** | **Comments** |
| **Applicability** | | |
| 1.1 Is the study population appropriate for the review question? | Yes | In a diabetic subpopulation |
| 1.2 Are the interventions appropriate for the review question? | Partly | Does not include all comparators available in this decision space. Standard care is not considered. |
| 1.3 Is the system in which the study was conducted sufficiently similar to the current UK context? | Partly | Dutch healthcare perspective, analysis is 8 years old |
| 1.4 Is the perspective for costs appropriate for the review question? | Yes | |

| Adarkwah CC, Gandjour A, Akkerman M et al (2011) Cost-effectiveness of angiotensin-converting enzyme inhibitors for the prevention of diabetic nephropathy in the Netherlands: a Markov model. PLOS ONE 10: e26139 | | |
|---|---|---|
| **Category** | **Rating** | **Comments** |
| 1.5 Is the perspective for outcomes appropriate for the review question? | Yes | |
| 1.6 Are all future costs and outcomes discounted appropriately? | Partly | Cost discounted at 4%, outcomes at 1.5% |
| 1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above). | Yes | |
| **1.8 OVERALL JUDGEMENT** | **PARTIALLY APPLICABLE** | |
| **Limitations** | | |
| 2.1 Does the model structure adequately reflect the nature of the topic under evaluation? | Yes | |
| 2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes? | Yes | |
| 2.3 Are all important and relevant outcomes included? | Partly | Cardiovascular risk and antihypertensive cardiovascular benefits were not accounted for |
| 2.4 Are the estimates of baseline outcomes from the best available source? | Yes | |
| 2.5 Are the estimates of relative intervention effects from the best available source? | Partly | Absolute effect of the interventions assumed constant throughout the time horizon of the analysis |
| 2.6 Are all important and relevant costs included? | Yes | |
| 2.7 Are the estimates of resource use from the best available source? | Yes | |
| 2.8 Are the unit costs of resources from the best available source? | Yes | |
| 2.9 Is an appropriate incremental analysis presented or can it be calculated from the data? | Yes | |
| 2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis? | Yes | |

| Adarkwah CC, Gandjour A, Akkerman M et al (2011) Cost-effectiveness of angiotensin-converting enzyme inhibitors for the prevention of diabetic nephropathy in the Netherlands: a Markov model. PLOS ONE 10: e26139 | | |
|---|---|---|
| **Category** | **Rating** | **Comments** |
| 2.11 Has no potential financial conflict of interest been declared? | Yes | |
| **2.12 OVERALL ASSESSMENT** | **POTENTIALLY SERIOUS LIMITATIONS** | |

1 **Adarkwah 2011b**

| Adarkwah CC, Gandjour A (2011) Cost-effectiveness of angiotensinconverting enzyme inhibitors in nondiabetic advanced renal disease. PLOS ONE 10.1586/ERP.11.8 | | |
|---|---|---|
| **Category** | **Rating** | **Comments** |
| **Applicability** | | |
| 1.1 Is the study population appropriate for the review question? | Yes | |
| 1.2 Are the interventions appropriate for the review question? | Partly | Does not include all comparators available in this decision space. |
| 1.3 Is the system in which the study was conducted sufficiently similar to the current UK context? | Partly | German healthcare perspective, 8 years old |
| 1.4 Is the perspective for costs appropriate for the review question? | Yes | |
| 1.5 Is the perspective for outcomes appropriate for the review question? | Yes | |
| 1.6 Are all future costs and outcomes discounted appropriately? | Yes | |
| 1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above). | Yes | |
| **1.8 OVERALL JUDGEMENT** | **PARTIALLY APPLICABLE** | |
| **Limitations** | | |
| 2.1 Does the model structure adequately reflect the nature of the topic under evaluation? | Yes | |
| 2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes? | Yes | |

| Adarkwah CC, Gandjour A (2011) Cost-effectiveness of angiotensinconverting enzyme inhibitors in nondiabetic advanced renal disease. PLOS ONE 10.1586/ERP.11.8 | | |
|---|---|---|
| **Category** | **Rating** | **Comments** |
| 2.3 Are all important and relevant outcomes included? | Partly | Cardiovascular risk and antihypertensive cardiovascular benefits were not accounted for |
| 2.4 Are the estimates of baseline outcomes from the best available source? | Yes | |
| 2.5 Are the estimates of relative intervention effects from the best available source? | Partly | Absolute effect of the interventions assumed constant throughout the time horizon of the analysis |
| 2.6 Are all important and relevant costs included? | Yes | |
| 2.7 Are the estimates of resource use from the best available source? | Yes | |
| 2.8 Are the unit costs of resources from the best available source? | Yes | |
| 2.9 Is an appropriate incremental analysis presented or can it be calculated from the data? | Yes | |
| 2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis? | Yes | |
| 2.11 Has no potential financial conflict of interest been declared? | No | |
| **2.12 OVERALL ASSESSMENT** | **POTENTIALLY SERIOUS LIMITATIONS** | |

1 **Hoerger 2010**

| Hoerger TJ, Wittenborn JS, Segel JE et al. (2010) A health policy model of CKD. Part 2: The cost-effectiveness of microalbuminuria screening. American Journal of Kidney Diseases 55(3): 463-473 | | |
|---|---|---|
| **Category** | **Rating** | **Comments** |
| **Applicability** | | |
| 1.1 Is the study population appropriate for the review question? | Partly | Focuses on people who do not yet have CKS |
| 1.2 Are the interventions appropriate for the review question? | Partly | Study assesses the cost-effectiveness of screening and then treatment, rather than treatment alone |
| 1.3 Is the system in which the study was conducted sufficiently similar to the current UK context? | Partly | US |
| 1.4 Is the perspective for costs appropriate for the review question? | Yes | |

| Hoerger TJ, Wittenborn JS, Segel JE et al. (2010) A health policy model of CKD. Part 2: The cost-effectiveness of microalbuminuria screening. American Journal of Kidney Diseases 55(3): 463-473 | | |
|---|---|---|
| **Category** | **Rating** | **Comments** |
| 1.5 Is the perspective for outcomes appropriate for the review question? | Yes | |
| 1.6 Are all future costs and outcomes discounted appropriately? | Partly | Uses 3% discount rate |
| 1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above). | Partly | Background utilities were not adjusted for the population characteristics and were assumed to be equal to 1. |
| **1.8 OVERALL JUDGEMENT** | **PARTIALLY APPLICABLE** | |
| **Limitations** | | |
| 2.1 Does the model structure adequately reflect the nature of the topic under evaluation? | Yes | |
| 2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes? | Yes | |
| 2.3 Are all important and relevant outcomes included? | Yes | |
| 2.4 Are the estimates of baseline outcomes from the best available source? | Partly | Background utilities were not adjusted for the population characteristics and were assumed to be equal to 1 |
| 2.5 Are the estimates of relative intervention effects from the best available source? | Yes | |
| 2.6 Are all important and relevant costs included? | Yes | |
| 2.7 Are the estimates of resource use from the best available source? | Yes | |
| 2.8 Are the unit costs of resources from the best available source? | Yes | |
| 2.9 Is an appropriate incremental analysis presented or can it be calculated from the data? | No | All intervention compared to standard care |
| 2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis? | Partly | No PSA |
| 2.11 Has no potential financial conflict of interest been declared? | No | |

| Hoerger TJ, Wittenborn JS, Segel JE et al. (2010) A health policy model of CKD. Part 2: The cost-effectiveness of microalbuminuria screening. American Journal of Kidney Diseases 55(3): 463-473 | | |
|---|---|---|
| **Category** | **Rating** | **Comments** |
| **2.12 OVERALL ASSESSMENT** | **POTENTIALLY SERIOUS LIMITATIONS** | |

1 **Howard 2010**

| Howard K, White S, Salkeld G et al. (2010) Cost-effectiveness of screening and optimal management for diabetes, hypertension, and chronic kidney disease: a modeled analysis. Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research 13: 196-208 | | |
|---|---|---|
| **Category** | **Rating** | **Comments** |
| **Applicability** | | |
| 1.1 Is the study population appropriate for the review question? | Yes | |
| 1.2 Are the interventions appropriate for the review question? | Yes | |
| 1.3 Is the system in which the study was conducted sufficiently similar to the current UK context? | Partly | Australia |
| 1.4 Is the perspective for costs appropriate for the review question? | Yes | |
| 1.5 Is the perspective for outcomes appropriate for the review question? | Yes | |
| 1.6 Are all future costs and outcomes discounted appropriately? | Partly | Costs and effects discounted at 5% annually |
| 1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above). | Partly | Quality of life measured using SF-36 |
| **1.8 OVERALL JUDGEMENT** | **PARTIALLY APPLICABLE** | |
| **Limitations** | | |
| 2.1 Does the model structure adequately reflect the nature of the topic under evaluation? | Yes | |
| 2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes? | Yes | |
| 2.3 Are all important and relevant outcomes included? | Yes | |

| Howard K, White S, Salkeld G et al. (2010) Cost-effectiveness of screening and optimal management for diabetes, hypertension, and chronic kidney disease: a modeled analysis. Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research 13: 196-208 | | |
|---|---|---|
| **Category** | **Rating** | **Comments** |
| 2.4 Are the estimates of baseline outcomes from the best available source? | Yes | |
| 2.5 Are the estimates of relative intervention effects from the best available source? | Partly | Transition probabilities were based in data from individual trials but these were specific to the Australian context |
| 2.6 Are all important and relevant costs included? | Yes | |
| 2.7 Are the estimates of resource use from the best available source? | Yes | |
| 2.8 Are the unit costs of resources from the best available source? | Yes | |
| 2.9 Is an appropriate incremental analysis presented or can it be calculated from the data? | Yes | |
| 2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis? | Yes | |
| 2.11 Has no potential financial conflict of interest been declared? | Yes | |
| **2.12 OVERALL ASSESSMENT** | **MINOR LIMITATIONS** | |

1 **Dong 2004**

| Dong FB, Sorensen SW, Manninen DL et al. (2004) Cost effectiveness of ACE inhibitor treatment for patients with Type 1 diabetes mellitus. Pharmacoeconomics 22(15): 1015-1027 | | |
|---|---|---|
| **Category** | **Rating** | **Comments** |
| **Applicability** | | |
| 1.1 Is the study population appropriate for the review question? | Yes | |
| 1.2 Are the interventions appropriate for the review question? | Yes | |
| 1.3 Is the system in which the study was conducted sufficiently similar to the current UK context? | Partly | US |
| 1.4 Is the perspective for costs appropriate for the review question? | Yes | |

| Dong FB, Sorensen SW, Manninen DL et al. (2004) Cost effectiveness of ACE inhibitor treatment for patients with Type 1 diabetes mellitus. Pharmacoeconomics 22(15): 1015-1027 | | |
|---|---|---|
| **Category** | **Rating** | **Comments** |
| 1.5 Is the perspective for outcomes appropriate for the review question? | Yes | |
| 1.6 Are all future costs and outcomes discounted appropriately? | Partly | 3% Discount rate |
| 1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above). | Partly | This is not clearly documented, some of the references are no longer available online (cited as abstracts) |
| **1.8 OVERALL JUDGEMENT** | **PARTIALLY APPLICABLE** | |
| **Limitations** | | |
| 2.1 Does the model structure adequately reflect the nature of the topic under evaluation? | Yes | |
| 2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes? | Yes | |
| 2.3 Are all important and relevant outcomes included? | Yes | |
| 2.4 Are the estimates of baseline outcomes from the best available source? | Partly | Uses data from individual RCTs |
| 2.5 Are the estimates of relative intervention effects from the best available source? | Partly | From individual RCTs |
| 2.6 Are all important and relevant costs included? | Yes | |
| 2.7 Are the estimates of resource use from the best available source? | Yes | |
| 2.8 Are the unit costs of resources from the best available source? | Yes | |
| 2.9 Is an appropriate incremental analysis presented or can it be calculated from the data? | Yes | |
| 2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis? | Partly | No PSA |
| 2.11 Has no potential financial conflict of interest been declared? | No | |

| Dong FB, Sorensen SW, Manninen DL et al. (2004) Cost effectiveness of ACE inhibitor treatment for patients with Type 1 diabetes mellitus. Pharmacoeconomics 22(15): 1015-1027 | | |
|---|---|---|
| **Category** | **Rating** | **Comments** |
| **2.12 OVERALL ASSESSMENT** | **VERY SERIOUS LIMITATIONS** | |

## 1 Boulware 2003

| Boulware LE, Jaar BG, Brancati FL et al. (2003) Screening for proteinuria in US adults: a cost-effectiveness analysis. JAMA 23: 3101-3114 | | |
|---|---|---|
| **Category** | **Rating** | **Comments** |
| **Applicability** | | |
| 1.1 Is the study population appropriate for the review question? | Yes | |
| 1.2 Are the interventions appropriate for the review question? | Yes | |
| 1.3 Is the system in which the study was conducted sufficiently similar to the current UK context? | Partly | US |
| 1.4 Is the perspective for costs appropriate for the review question? | Partly | Study takes a societal perspective |
| 1.5 Is the perspective for outcomes appropriate for the review question? | Yes | |
| 1.6 Are all future costs and outcomes discounted appropriately? | Partly | 3% discount rate |
| 1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above). | Yes | |
| **1.8 OVERALL JUDGEMENT** | **PARTIALLY APPLICABLE** | |
| **Limitations** | | |
| 2.1 Does the model structure adequately reflect the nature of the topic under evaluation? | Yes | |
| 2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes? | Yes | |
| 2.3 Are all important and relevant outcomes included? | Yes | |
| 2.4 Are the estimates of baseline outcomes from the best available source? | Yes | |

| Boulware LE, Jaar BG, Brancati FL et al. (2003) Screening for proteinuria in US adults: a cost-effectiveness analysis. JAMA 23: 3101-3114 | | |
|---|---|---|
| **Category** | **Rating** | **Comments** |
| 2.5 Are the estimates of relative intervention effects from the best available source? | Yes | |
| 2.6 Are all important and relevant costs included? | Partly | Loss of productivity wages included in the analysis |
| 2.7 Are the estimates of resource use from the best available source? | Yes | |
| 2.8 Are the unit costs of resources from the best available source? | Yes | |
| 2.9 Is an appropriate incremental analysis presented or can it be calculated from the data? | Yes | |
| 2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis? | Yes | |
| 2.11 Has no potential financial conflict of interest been declared? | No | |
| **2.12 OVERALL ASSESSMENT** | **VERY SERIOUS LIMITATIONS** | |

1 **Golan 1999**

| Golan L, Birkmeyer JD and Welch HG (1999) The cost-effectiveness of treating all patients with type 2 diabetes with angiotensin-converting enzyme inhibitors. Annals of Internal Medicine 131: 660-667 | | |
|---|---|---|
| **Category** | **Rating** | **Comments** |
| **Applicability** | | |
| 1.1 Is the study population appropriate for the review question? | Yes | |
| 1.2 Are the interventions appropriate for the review question? | Partly | Current practice is not considered as one of the comparators |
| 1.3 Is the system in which the study was conducted sufficiently similar to the current UK context? | Partly | US |
| 1.4 Is the perspective for costs appropriate for the review question? | Partly | Societal perspective |
| 1.5 Is the perspective for outcomes appropriate for the review question? | Yes | |
| 1.6 Are all future costs and outcomes discounted appropriately? | Partly | Costs and effects discounted at 3% annually. |

| Golan L, Birkmeyer JD and Welch HG (1999) The cost-effectiveness of treating all patients with type 2 diabetes with angiotensin-converting enzyme inhibitors. Annals of Internal Medicine 131: 660-667 | | |
|---|---|---|
| **Category** | **Rating** | **Comments** |
| 1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above). | Yes | |
| **1.8 OVERALL JUDGEMENT** | **PARTIALLY APPLICABLE** | |
| **Limitations** | | |
| 2.1 Does the model structure adequately reflect the nature of the topic under evaluation? | Yes | |
| 2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes? | Yes | |
| 2.3 Are all important and relevant outcomes included? | Yes | |
| 2.4 Are the estimates of baseline outcomes from the best available source? | Partly | Informed by individual RCTs |
| 2.5 Are the estimates of relative intervention effects from the best available source? | Partly | Informed by individual RCTs |
| 2.6 Are all important and relevant costs included? | Yes | |
| 2.7 Are the estimates of resource use from the best available source? | Yes | |
| 2.8 Are the unit costs of resources from the best available source? | Yes | |
| 2.9 Is an appropriate incremental analysis presented or can it be calculated from the data? | Yes | |
| 2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis? | No | Probabilistic sensitivity analysis was not conducted |
| 2.11 Has no potential financial conflict of interest been declared? | Yes | |
| **2.12 OVERALL ASSESSMENT** | **VERY SERIOUS LIMITATIONS** | |

## 1 Kiberd 1998

| Kiberd BA and Jindal KK (1998) Routine treatment of insulin-dependent diabetic patients with ACE inhibitors to prevent renal failure: an economic evaluation. American Journal of Kidney Diseases 31: 49-54 | | |
|---|---|---|
| **Category** | **Rating** | **Comments** |
| **Applicability** | | |
| 1.1 Is the study population appropriate for the review question? | Partly | Considers people before development of CKD |
| 1.2 Are the interventions appropriate for the review question? | Partly | Study assesses the cost-effectiveness of screening and then treatment, rather than treatment alone |
| 1.3 Is the system in which the study was conducted sufficiently similar to the current UK context? | Partly | US |
| 1.4 Is the perspective for costs appropriate for the review question? | Yes | |
| 1.5 Is the perspective for outcomes appropriate for the review question? | Yes | |
| 1.6 Are all future costs and outcomes discounted appropriately? | Partly | Uses 3% discount rate |
| 1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above). | No | Utility values were obtained from a sample of 17 US health professionals using a time-trade-off methodology |
| **1.8 OVERALL JUDGEMENT** | **PARTIALLY APPLICABLE** | |
| **Limitations** | | |
| 2.1 Does the model structure adequately reflect the nature of the topic under evaluation? | Yes | |
| 2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes? | Yes | |
| 2.3 Are all important and relevant outcomes included? | Yes | |
| 2.4 Are the estimates of baseline outcomes from the best available source? | Partly | Single RCT |
| 2.5 Are the estimates of relative intervention effects from the best available source? | Partly | Single RCTs |
| 2.6 Are all important and relevant costs included? | Unclear | Costing is poorly described |

| Kiberd BA and Jindal KK (1998) Routine treatment of insulin-dependent diabetic patients with ACE inhibitors to prevent renal failure: an economic evaluation. American Journal of Kidney Diseases 31: 49-54 | | |
|---|---|---|
| **Category** | **Rating** | **Comments** |
| 2.7 Are the estimates of resource use from the best available source? | Unclear | Costing is poorly described |
| 2.8 Are the unit costs of resources from the best available source? | Partly | Old papers, different health system costs |
| 2.9 Is an appropriate incremental analysis presented or can it be calculated from the data? | Yes | |
| 2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis? | Partly | PSA not conducted |
| 2.11 Has no potential financial conflict of interest been declared? | Yes | |
| **2.12 OVERALL ASSESSMENT** | **VERY SERIOUS LIMITATIONS** | |

# 1 Comparison of antihypertensive therapies

## 2 Adarkwah 2013

| Adarkwah CC, Gandjour A, Akkerman M et al. (2013) To treat or not to treat? Cost-effectiveness of ace inhibitors in non-diabetic advanced renal disease: a Dutch perspective. Kidney and Blood Pressure Research 37: 168-180 | | |
|---|---|---|
| **Category** | **Rating** | **Comments** |
| **Applicability** | | |
| 1.1 Is the study population appropriate for the review question? | Yes | In a diabetic subpopulation |
| 1.2 Are the interventions appropriate for the review question? | Partly | Does not include all comparators available in this decision space. |
| 1.3 Is the system in which the study was conducted sufficiently similar to the current UK context? | Partly | Dutch healthcare perspective, analysis is 8 years old |
| 1.4 Is the perspective for costs appropriate for the review question? | Yes | |
| 1.5 Is the perspective for outcomes appropriate for the review question? | Yes | |
| 1.6 Are all future costs and outcomes discounted appropriately? | Partly | Cost discounted at 4%, outcomes at 1.5% |
| 1.7 Are QALYs, derived using NICE's preferred methods, or | Yes | |

| Adarkwah CC, Gandjour A, Akkerman M et al. (2013) To treat or not to treat? Cost-effectiveness of ace inhibitors in non-diabetic advanced renal disease: a Dutch perspective. Kidney and Blood Pressure Research 37: 168-180 | | |
|---|---|---|
| **Category** | **Rating** | **Comments** |
| an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above). | | |
| **1.8 OVERALL JUDGEMENT** | **PARTIALLY APPLICABLE** | |
| **Limitations** | | |
| 2.1 Does the model structure adequately reflect the nature of the topic under evaluation? | Yes | |
| 2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes? | Yes | |
| 2.3 Are all important and relevant outcomes included? | Partly | Cardiovascular risk and antihypertensive cardiovascular benefits were not accounted for |
| 2.4 Are the estimates of baseline outcomes from the best available source? | Yes | |
| 2.5 Are the estimates of relative intervention effects from the best available source? | Partly | Absolute effect of the interventions assumed constant throughout the time horizon of the analysis |
| 2.6 Are all important and relevant costs included? | Yes | |
| 2.7 Are the estimates of resource use from the best available source? | Yes | |
| 2.8 Are the unit costs of resources from the best available source? | Yes | |
| 2.9 Is an appropriate incremental analysis presented or can it be calculated from the data? | Yes | |
| 2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis? | Yes | |
| 2.11 Has no potential financial conflict of interest been declared? | No | |
| **2.12 OVERALL ASSESSMENT** | **POTENTIALLY SERIOUS LIMITATIONS** | |

1

## 1 Delea 2009

| Delea TE, Sofrygin O, Palmer JL et al. (2009) Cost-effectiveness of aliskiren in type 2 diabetes, hypertension, and albuminuria. Journal of the American Society of Nephrology 20: 2205-13 | | |
|---|---|---|
| **Category** | **Rating** | **Comments** |
| **Applicability** | | |
| 1.1 Is the study population appropriate for the review question? | Yes | |
| 1.2 Are the interventions appropriate for the review question? | Partly | Analysis compared aliskiren + losartan to losartan alone.<br>Does not include all comparators available in this decision space. |
| 1.3 Is the system in which the study was conducted sufficiently similar to the current UK context? | Partly | US |
| 1.4 Is the perspective for costs appropriate for the review question? | Yes | |
| 1.5 Is the perspective for outcomes appropriate for the review question? | Yes | |
| 1.6 Are all future costs and outcomes discounted appropriately? | Partly | Cost and QALYs discounted at 3% annualy |
| 1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above). | Yes | |
| **1.8 OVERALL JUDGEMENT** | **PARTIALLY APPLICABLE** | |
| **Limitations** | | |
| 2.1 Does the model structure adequately reflect the nature of the topic under evaluation? | Yes | |
| 2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes? | Yes | |
| 2.3 Are all important and relevant outcomes included? | Yes | |
| 2.4 Are the estimates of baseline outcomes from the best available source? | Partly | baseline data from a single RCT |
| 2.5 Are the estimates of relative intervention effects from the best available source? | Partly | Efficacy data from a single RCT |
| 2.6 Are all important and relevant costs included? | Yes | |

| Delea TE, Sofrygin O, Palmer JL et al. (2009) Cost-effectiveness of aliskiren in type 2 diabetes, hypertension, and albuminuria. Journal of the American Society of Nephrology 20: 2205-13 | | |
|---|---|---|
| **Category** | **Rating** | **Comments** |
| 2.7 Are the estimates of resource use from the best available source? | Yes | |
| 2.8 Are the unit costs of resources from the best available source? | Yes | |
| 2.9 Is an appropriate incremental analysis presented or can it be calculated from the data? | Yes | |
| 2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis? | Yes | |
| 2.11 Has no potential financial conflict of interest been declared? | Yes | Funded by manufacturer |
| **2.12 OVERALL ASSESSMENT** | **POTENTIALLY SERIOUS LIMITATIONS** | |

1 **Smith 2004**

| Smith DG, Nguyen AB, Peak CN et al. (2004) Markov modeling analysis of health and economic outcomes of therapy with valsartan versus amlodipine in patients with Type 2 diabetes and microalbuminuria. Journal of Managed Care Pharmacy 10: 26-32 | | |
|---|---|---|
| **Category** | **Rating** | **Comments** |
| **Applicability** | | |
| 1.1 Is the study population appropriate for the review question? | Yes | |
| 1.2 Are the interventions appropriate for the review question? | Partly | The analysis does not consider standard practice in the uk |
| 1.3 Is the system in which the study was conducted sufficiently similar to the current UK context? | Partly | Conducted from a US third party perspective |
| 1.4 Is the perspective for costs appropriate for the review question? | Yes | |
| 1.5 Is the perspective for outcomes appropriate for the review question? | Yes | |
| 1.6 Are all future costs and outcomes discounted appropriately? | Partly | Costs and effects discounted at a 3% annual rate |
| 1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe | Partly | It is not clear from the publication (and after backreferencing on cited papers) the source and methodology of the utility parameters. It is likely they were collected in primary research from a relevant population using a mixture of TTO |

| Smith DG, Nguyen AB, Peak CN et al. (2004) Markov modeling analysis of health and economic outcomes of therapy with valsartan versus amlodipine in patients with Type 2 diabetes and microalbuminuria. Journal of Managed Care Pharmacy 10: 26-32 | | |
|---|---|---|
| **Category** | **Rating** | **Comments** |
| rationale and outcomes used in line with analytical perspectives taken (item 1.5 above). | | methodology and other quality of life questionnaires. |
| **1.8 OVERALL JUDGEMENT** | **PARTIALLY APPLICABLE** | |
| **Limitations** | | |
| 2.1 Does the model structure adequately reflect the nature of the topic under evaluation? | Yes | |
| 2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes? | Partly | Time horizon of the analysis is limited to the 8 years of the RCT informing the efficacy of valsartan |
| 2.3 Are all important and relevant outcomes included? | Yes | |
| 2.4 Are the estimates of baseline outcomes from the best available source? | Partly | The efficacy of valsartan is drawn from a single RCT comparing valsartan with placebo |
| 2.5 Are the estimates of relative intervention effects from the best available source? | Partly | The efficacy of valsartan is drawn from a single RCT comparing valsartan with placebo |
| 2.6 Are all important and relevant costs included? | Yes | |
| 2.7 Are the estimates of resource use from the best available source? | Yes | |
| 2.8 Are the unit costs of resources from the best available source? | Yes | |
| 2.9 Is an appropriate incremental analysis presented or can it be calculated from the data? | Yes | |
| 2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis? | Partly | Univariate sensitivity analysis is done on several model parameters. No probabilistic sensitivity analysis was done. |
| 2.11 Has no potential financial conflict of interest been declared? | Yes | Study funded and co-authored by the manufacturers of valsartan |
| **2.12 OVERALL ASSESSMENT** | **VERY SERIOUS LIMITATIONS** | |

# 1 Diet interventions

## 2 You 2015

| You JHS, Ming WK, Lin WA et al. (2015) Early supplemented low-protein diet restriction for chronic kidney disease patients in Taiwan - A cost-effectiveness analysis. Clinical nephrology 88:189-96 | | |
|---|---|---|
| **Category** | **Rating** | **Comments** |
| **Applicability** | | |
| 1.1 Is the study population appropriate for the review question? | Partly | CKD stage 4 |
| 1.2 Are the interventions appropriate for the review question? | Yes | |
| 1.3 Is the system in which the study was conducted sufficiently similar to the current UK context? | No | Taiwan |
| 1.4 Is the perspective for costs appropriate for the review question? | Yes | |
| 1.5 Is the perspective for outcomes appropriate for the review question? | Yes | |
| 1.6 Are all future costs and outcomes discounted appropriately? | Partly | Uses 3% discount rate |
| 1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above). | Partly | Does not use EQ-5D |
| **1.8 OVERALL JUDGEMENT** | **PARTIALLY APPLICABLE** | |
| **Limitations** | | |
| 2.1 Does the model structure adequately reflect the nature of the topic under evaluation? | Partially | Standard of care not part of the comparators |
| 2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes? | Yes | |
| 2.3 Are all important and relevant outcomes included? | Yes | |
| 2.4 Are the estimates of baseline outcomes from the best available source? | Yes | |
| 2.5 Are the estimates of relative intervention effects from the best available source? | Partly | Single trial |

| You JHS, Ming WK, Lin WA et al. (2015) Early supplemented low-protein diet restriction for chronic kidney disease patients in Taiwan - A cost-effectiveness analysis. Clinical nephrology 88:189-96 | | |
|---|---|---|
| **Category** | **Rating** | **Comments** |
| 2.6 Are all important and relevant costs included? | Yes | |
| 2.7 Are the estimates of resource use from the best available source? | Yes | |
| 2.8 Are the unit costs of resources from the best available source? | Yes | |
| 2.9 Is an appropriate incremental analysis presented or can it be calculated from the data? | Yes | |
| 2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis? | Partly | Uses triangular distribution for all parameters in the model |
| 2.11 Has no potential financial conflict of interest been declared? | Yes | Funded by manufacturer of ketoanalogue diet |
| **2.12 OVERALL ASSESSMENT** | **VERY SERIOUS LIMITATIONS** | |

1 **Mennini 2014**

| Mennini FS, Russo S, Marcellusi A et al. (2014) Economic effects of treatment of chronic kidney disease with low-protein diet. Journal of renal nutrition: the official journal of the Council on Renal Nutrition of the National Kidney Foundation 24: 313-21 | | |
|---|---|---|
| **Category** | **Rating** | **Comments** |
| **Applicability** | | |
| 1.1 Is the study population appropriate for the review question? | Yes | |
| 1.2 Are the interventions appropriate for the review question? | Yes | |
| 1.3 Is the system in which the study was conducted sufficiently similar to the current UK context? | Partly | Italian NHS perspective |
| 1.4 Is the perspective for costs appropriate for the review question? | Yes | |
| 1.5 Is the perspective for outcomes appropriate for the review question? | Partly | Model accounts for costs of dialysis and costs of the interventions only |
| 1.6 Are all future costs and outcomes discounted appropriately? | Partly | QALYs 1.5%<br>Costs 3% |
| 1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care- | Yes | |

| Mennini FS, Russo S, Marcellusi A et al. (2014) Economic effects of treatment of chronic kidney disease with low-protein diet. Journal of renal nutrition: the official journal of the Council on Renal Nutrition of the National Kidney Foundation 24: 313-21 | | |
|---|---|---|
| **Category** | **Rating** | **Comments** |
| related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above). | | |
| **1.8 OVERALL JUDGEMENT** | **PARTIALLY APPLICABLE** | |
| **Limitations** | | |
| 2.1 Does the model structure adequately reflect the nature of the topic under evaluation? | Yes | |
| 2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes? | Partly | 2, 3, 5 and 10-year time horizon were explored in the model |
| 2.3 Are all important and relevant outcomes included? | Partly | Compliance with diet was not explored in the model |
| 2.4 Are the estimates of baseline outcomes from the best available source? | Yes | |
| 2.5 Are the estimates of relative intervention effects from the best available source? | Yes | |
| 2.6 Are all important and relevant costs included? | Partly | Analysis accounted for direct medical and non-medical costs of dialysis and cost of the interventions only. Report did not break down cost categories. |
| 2.7 Are the estimates of resource use from the best available source? | Yes | |
| 2.8 Are the unit costs of resources from the best available source? | Yes | |
| 2.9 Is an appropriate incremental analysis presented or can it be calculated from the data? | Yes | |
| 2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis? | Yes | |
| 2.11 Has no potential financial conflict of interest been declared? | No | |
| **2.12 OVERALL ASSESSMENT** | **VERY SERIOUS LIMITATIONS** | |

1

# Appendix K – Health economic model

No health economic modelling was undertaken for this review question.

# 1 Appendix L – Excluded studies

## 2 Effectiveness studies

| Reference | Reason for exclusion |
|---|---|
| Aart-van der Beek, A.B.V., Clegg, L.E., Penland, R.C. et al. (2020) Effect of once-weekly exenatide on eGFR slope depends on baseline renal risk: a post-hoc analysis of the EXSCEL trial. Diabetes, obesity & metabolism | - Does not contain a population of people with proteinuria or albuminuria<br>[Albuminuria was not an inclusion criteria] |
| Abbott, K; Smith, A; Bakris, G L (1996) Effects of dihydropyridine calcium antagonists on albuminuria in patients with diabetes. Journal of clinical pharmacology 36(3): 274-9 | - Does not contain a population of people with CKD or suspected CKD |
| Abe, Masanori, Maruyama, Noriaki, Suzuki, Hiroko et al. (2013) L/N-type calcium channel blocker cilnidipine reduces plasma aldosterone, albuminuria, and urinary liver-type fatty acid binding protein in patients with chronic kidney disease. Heart and vessels 28(4): 480-9 | - Study does not contain a relevant intervention<br>[Cilnidipine (not available in the UK)] |
| Abe, Masanori, Okada, Kazuyoshi, Maruyama, Noriaki et al. (2011) Benidipine reduces albuminuria and plasma aldosterone in mild-to-moderate stage chronic kidney disease with albuminuria. Hypertension research : official journal of the Japanese Society of Hypertension 34(2): 268-73 | - Secondary publication of an included study that does not provide any additional relevant information |
| Abe, Masanori, Okada, Kazuyoshi, Suzuki, Hiroko et al. (2013) T/L-type calcium channel blocker reduces the composite ranking of relative risk according to new KDIGO guidelines in patients with chronic kidney disease. BMC nephrology 14: 135 | - Study does not contain a relevant intervention<br>[Benidipine (not available in the UK)] |
| Agarwal, R (2001) Add-on angiotensin receptor blockade with maximized ACE inhibition. Kidney international 59(6): 2282-9 | - Data not reported in an extractable format<br>[Data reported only in graph] |
| Agha, Adnan, Amer, Wasim, Anwar, Eram et al. (2009) Reduction of microalbuminuria by using losartan in normotensive patients with type 2 diabetes mellitus: A randomized controlled trial. Saudi journal of kidney diseases and transplantation : an official publication of the Saudi Center for Organ Transplantation, Saudi Arabia 20(3): 429-35 | - Not a relevant study design<br>[Non-randomised study] |
| Amara, Alieu B, Sharma, Asheesh, Alexander, John L et al. (2010) Randomized controlled trial: lisinopril reduces proteinuria, ammonia, and renal polypeptide tubular catabolism in patients with chronic allograft nephropathy. Transplantation 89(1): 104-14 | - Does not contain a population of people with CKD or suspected CKD<br>[Participants were receiving renal replacement therapy (renal transplant))] |
| Anand, Inder S, Bishu, Kalkidan, Rector, Thomas S et al. (2009) Proteinuria, chronic kidney disease, and the effect of an angiotensin receptor blocker in addition to an angiotensin-converting enzyme inhibitor in patients with moderate to severe heart failure. Circulation 120(16): 1577-84 | - Does not contain a population of people with proteinuria or albuminuria<br>[Proteinuria was measured via dipstick urinalysis] |

| Reference | Reason for exclusion |
|---|---|
| Ando, Katsuyuki, Nitta, Kosaku, Rakugi, Hiromi et al. (2014) Comparison of the antialbuminuric effects of benidipine and hydrochlorothiazide in Renin-Angiotensin System (RAS) inhibitor-treated hypertensive patients with albuminuria: the COSMO-CKD (COmbination Strategy on Renal Function of Benidipine or Diuretics TreatMent with RAS inhibitOrs in a Chronic Kidney Disease Hypertensive Population) study. International journal of medical sciences 11(9): 897-904 | - Study does not contain a relevant intervention [Benidipine (not available in the UK)] |
| Andress, Dennis L, Coll, Blai, Pritchett, Yili et al. (2012) Clinical efficacy of the selective endothelin A receptor antagonist, atrasentan, in patients with diabetes and chronic kidney disease (CKD). Life sciences 91(1314): 739-42 | - Secondary publication of an included study that does not provide any additional relevant information [Kohan 2011] |
| Anonymous. (2005) ACE inhibitors beneficial in diabetics. South African Family Practice 47(1): 18 | - Conference abstract |
| Antlanger, Marlies, Bernhofer, Sebastian, Kovarik, Johannes J et al. (2017) Effects of direct renin inhibition versus angiotensin II receptor blockade on angiotensin profiles in non-diabetic chronic kidney disease. Annals of medicine 49(6): 525-533 | - Study does not contain a relevant intervention [Aliskiren (BNF license highly limiting in CKD)] |
| Aranda, Pedro, Segura, Julian, Ruilope, Luis M et al. (2005) Long-term renoprotective effects of standard versus high doses of telmisartan in hypertensive nondiabetic nephropathies. American journal of kidney diseases : the official journal of the National Kidney Foundation 46(6): 1074-9 | - Study does not contain a relevant intervention [Dosing RCT] |
| Atmaca, Aysegul and Gedik, Olcay (2006) Effects of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and their combination on microalbuminuria in normotensive patients with type 2 diabetes. Advances in Therapy 23(4): 615-622 | - Does not contain a population of people with CKD or suspected CKD |
| Baba, S (2001) Nifedipine and enalapril equally reduce the progression of nephropathy in hypertensive type 2 diabetics. Diabetes Research and Clinical Practice 54(3): 191-201 | - Does not contain a population of people with CKD or suspected CKD |
| Baek, Seon Ha, Kim, Sejoong, Kim, Dong Ki et al. (2014) A low-salt diet increases the estimated net endogenous acid production in nondiabetic chronic kidney disease patients treated with angiotensin receptor blockade. Nephron. Clinical practice 128(34): 407-13 | - Study does not contain a relevant intervention [Education] |
| Bakris, George L., Slataper, Richard, Vicknair, Nancy et al. (1994) ACE inhibitor mediated reductions in renal size and microalbuminuria in normotensive, diabetic subjects. Journal of Diabetes and its Complications 8(1): 2-6 | - Data not reported in an extractable format [microalbuminuria was not reported by arm] |
| Bakris, George L, Agarwal, Rajiv, Chan, Juliana C et al. (2015) Effect of Finerenone on Albuminuria in Patients With Diabetic | - Study does not contain a relevant intervention [Finerenone (not available in the UK)] |

| Reference | Reason for exclusion |
|---|---|
| Nephropathy: A Randomized Clinical Trial. JAMA 314(9): 884-94 | |
| Bakris, George L, Weir, Matthew R, Secic, Michelle et al. (2004) Differential effects of calcium antagonist subclasses on markers of nephropathy progression. Kidney international 65(6): 1991-2002 | - Does not contain a population of people with proteinuria or albuminuria<br>[Proteinuria was not an inclusion criteria] |
| Bakris, George, Burgess, Ellen, Weir, Matthew et al. (2008) Telmisartan is more effective than losartan in reducing proteinuria in patients with diabetic nephropathy. Kidney international 74(3): 364-9 | - Comparator in study does not match that specified in protocol [Intra-class comparison between ARBs] |
| Balamuthusamy, Saravanan, Srinivasan, Lavanya, Verma, Meenakshi et al. (2008) Renin angiotensin system blockade and cardiovascular outcomes in patients with chronic kidney disease and proteinuria: a meta-analysis. American heart journal 155(5): 791-805 | - Does not contain a population of people with proteinuria or albuminuria<br>[Proteinuria was not an inclusion criteria] |
| Barnett, A H (2005) Preventing renal complications in diabetic patients: the Diabetics Exposed to Telmisartan And enalaprIL (DETAIL) study. Acta diabetologica 42suppl1: 42-9 | - Not a relevant study design<br>[Review] |
| Berger, Elke D, Bader, Birgit D, Ebert, Carola et al. (2002) Reduction of proteinuria; combined effects of receptor blockade and low dose angiotensin-converting enzyme inhibition. Journal of hypertension 20(4): 739-743 | - Not a relevant study design<br>[intra-individual study] |
| Bilic, Marija, Munjas-Samarin, Radenka, Ljubanovic, Danica et al. (2011) Effects of ramipril and valsartan on proteinuria and renal function in patients with nondiabetic proteinuria. Collegium antropologicum 35(4): 1061-6 | - Data not reported in an extractable format<br>[Mean 24-hour protein excretion reported without standard deviations, standard errors, or confidence intervals] |
| Boesby, Lene, Elung-Jensen, Thomas, Klausen, Tobias Wirenfeldt et al. (2011) Moderate antiproteinuric effect of add-on aldosterone blockade with eplerenone in non-diabetic chronic kidney disease. A randomized cross-over study. PloS one 6(11): e26904 | - Data not reported in an extractable format<br>[Crossover trial without parallel data reported] |
| Bohlen, L; de Courten, M; Weidmann, P (1994) Comparative study of the effect of ACE-inhibitors and other antihypertensive agents on proteinuria in diabetic patients. American journal of hypertension 7(9pt2): 84s-92s | - Not a relevant study design<br>[Uncontrolled studies were included] |
| Bolignano, Davide and Zoccali, Carmine (2013) Effects of weight loss on renal function in obese CKD patients: a systematic review. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 28suppl4: iv82-98 | - Not a relevant study design<br>[Non-randomised studies were included] |
| Bomback, Andrew S, Kshirsagar, Abhijit V, Amamoo, M Ahinee et al. (2008) Change in proteinuria after adding aldosterone blockers to ACE inhibitors or angiotensin receptor blockers in CKD: a systematic review. American journal | - Not a relevant study design<br>[Non-randomised controlled trials were included] |

| Reference | Reason for exclusion |
|---|---|
| of kidney diseases : the official journal of the National Kidney Foundation 51(2): 199-211 | |
| Burgess, E., Muirhead, N., De Cotret, P.R. et al. (2009) Supramaximal dose of candesartan in proteinuric renal disease. Journal of the American Society of Nephrology 20(4): 893-900 | - Study does not contain a relevant intervention [Dosing RCT] |
| Chaturvedi, Nish (1997) Randomised placebo-controlled trial of lisinopril in normotensive patients with insulin-dependent diabetes and normoalbuminuria or microalbuminuria. The Lancet 349(9068): 1787-1792 | - Does not contain a population of people with CKD or suspected CKD |
| Cheng, I.K.P., Fang, G.X., Wong, M.C. et al. (1998) A randomized prospective comparison of nadolol, captopril with or without ticlopidine on disease progression in IgA nephropathy. Nephrology 4(12): 19-26 | - Data not reported in an extractable format [Data reported only in graph] |
| Cherney, David Z I, Dekkers, Claire C J, Barbour, Sean J et al. (2020) Effects of the SGLT2 inhibitor dapagliflozin on proteinuria in non-diabetic patients with chronic kidney disease (DIAMOND): a randomised, double-blind, crossover trial. The lancet. Diabetes & endocrinology 8(7): 582-593 | - Data not reported in an extractable format [Crossover trial without parallel data reported] |
| Ciavarella, A, Di Mizio, G, Stefoni, S et al. (1987) Reduced albuminuria after dietary protein restriction in insulin-dependent diabetic patients with clinical nephropathy. Diabetes care 10(4): 407-13 | - Does not contain a relevant outcome |
| Cohen, D.; Dodds, R.; Viberti, G. (1987) Effect of protein restriction in insulin dependent diabetics at risk of nephropathy. British Medical Journal 294(6575): 795-798 | - Does not contain a population of people with proteinuria or albuminuria [urinary albumin excretion rate in a timed overnight sample was 15-200 mcg/min on three successive occasions during a six week run in period.] |
| Coleman, C.I., Weeda, E.R., Kharat, A. et al. (2019) Impact of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers on renal and mortality outcomes in people with Type 2 diabetes and proteinuria. Diabetic Medicine | - Systematic review used as source of primary studies |
| Cooper, M.E., Rosenstock, J., Kadowaki, T. et al. (2020) Cardiovascular and kidney outcomes of linagliptin treatment in older people with type 2 diabetes and established cardiovascular disease and/or kidney disease: A prespecified subgroup analysis of the randomized, placebo-controlled CARMELINA trial. Diabetes, Obesity and Metabolism 22(7): 1062-1073 | - Does not contain a population of people with proteinuria or albuminuria [Around 20% of participants had urinary albumin:creatinine ratio <30 mg/g at baseline] |
| Crepaldi, G, Carta, Q, Deferrari, G et al. (1998) Effects of lisinopril and nifedipine on the progression to overt albuminuria in IDDM patients with incipient nephropathy and normal blood pressure. The Italian Microalbuminuria Study Group in IDDM. Diabetes care 21(1): 104-10 | - Does not contain a population of people with proteinuria or albuminuria [albumin excretion rate between 20 and 200 mcg/min from 3 timed overnight urine collections] |

| Reference | Reason for exclusion |
|---|---|
| Crowe, Alexander V, Howse, Matthew, Vinjamuri, Sobhan et al. (2003) The antiproteinuric effect of losartan is systemic blood pressure dependent. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 18(10): 2160-4 | - Study does not contain a relevant intervention [Dosing RCT] |
| Dalla Vestra, M, Pozza, G, Mosca, A et al. (2004) Effect of lercanidipine compared with ramipril on albumin excretion rate in hypertensive Type 2 diabetic patients with microalbuminuria: DIAL study (diabete, ipertensione, albuminuria, lercanidipina). Diabetes, nutrition & metabolism 17(5): 259-266 | - Does not contain a population of people with CKD or suspected CKD |
| De Cesaris, R, Ranieri, G, Andriani, A et al. (1996) Effects of benazepril and nicardipine on microalbuminuria in normotensive and hypertensive patients with diabetes. Clinical pharmacology and therapeutics 60(4): 472-8 | - Study does not contain a relevant intervention [Benazepril (not available in the UK)] |
| de Zeeuw, Dick, Remuzzi, Giuseppe, Parving, Hans-Henrik et al. (2004) Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: lessons from RENAAL. Kidney international 65(6): 2309-20 | - Secondary publication of an included study that does not provide any additional relevant information [RENAAL trial] |
| Demarie, B.K. and Bakris, G.L. (1990) Effects of different calcium antagonists on proteinuria associated with diabetes mellitus. Annals of Internal Medicine 113(12): 987-988 | - Data not reported in an extractable format [Number of participants per arm in the initial period was not reported] |
| Dhaun, Neeraj, MacIntyre, Iain M, Kerr, Debbie et al. (2011) Selective endothelin-A receptor antagonism reduces proteinuria, blood pressure, and arterial stiffness in chronic proteinuric kidney disease. Hypertension (Dallas, Tex. : 1979) 57(4): 772-9 | - Data not reported in an extractable format [Crossover trial without parallel data reported] |
| Dhaun, Neeraj, Macintyre, Iain M, Melville, Vanessa et al. (2009) Blood pressure-independent reduction in proteinuria and arterial stiffness after acute endothelin-a receptor antagonism in chronic kidney disease. Hypertension (Dallas, Tex. : 1979) 54(1): 113-9 | - Study does not contain a relevant intervention [BQ-123 Clinalfa] |
| Dhaun, Neeraj, Yuzugulen, Jale, Kimmitt, Robert A et al. (2015) Plasma pro-endothelin-1 peptide concentrations rise in chronic kidney disease and following selective endothelin A receptor antagonism. Journal of the American Heart Association 4(3): e001624 | - Secondary publication of an included study that does not provide any additional relevant information [Dhaun 2011] |
| Douglas, Janice G and Agodoa, Lawrence (2003) ACE inhibition is effective and renoprotective in hypertensive nephrosclerosis: the African American Study of Kidney Disease and Hypertension (AASK) trial. Kidney international. Supplement: 74-6 | - Does not contain a population of people with proteinuria or albuminuria [Proteinuria was not an inclusion criteria] |
| Ecder, T, Chapman, A B, Brosnahan, G M et al. (2000) Effect of antihypertensive therapy on renal function and urinary albumin excretion in hypertensive patients with autosomal dominant | - Does not contain a population of people with proteinuria or albuminuria [Albuminuria was not an inclusion criteria] |

| Reference | Reason for exclusion |
|---|---|
| polycystic kidney disease. American journal of kidney diseases : the official journal of the National Kidney Foundation 35(3): 427-32 | |
| Erley, CM, Komini, E, Nicaeus, T et al. (1994) The effect of angiotensin-converting enzyme inhibitors on proteinuria in chronic glomerulonephritis. Deutsche medizinische wochenschrift (1946) 119(4): 89-95 | - Study not reported in English [German] |
| Esnault, V.L.M., Brown, E.A., Apetrei, E. et al. (2008) The effects of amlodipine and enalapril on renal function in adults with hypertension and nondiabetic nephropathies: A 3-year, randomized, multicenter, double-blind, placebo-controlled study. Clinical Therapeutics 30(3): 482-498 | - Does not contain a relevant outcome [Relevant outcomes were not reported in the subgroup of participants with proteinuria >1 g/d] |
| Esnault, Vincent L M, Ekhlas, Amr, Delcroix, Catherine et al. (2005) Diuretic and enhanced sodium restriction results in improved antiproteinuric response to RAS blocking agents. Journal of the American Society of Nephrology : JASN 16(2): 474-81 | - Data not reported in an extractable format [Crossover trial without parallel data reported] |
| Esnault, Vincent L M, Ekhlas, Amr, Nguyen, Jean-Michel et al. (2010) Diuretic uptitration with half dose combined ACEI + ARB better decreases proteinuria than combined ACEI + ARB uptitration. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 25(7): 2218-24 | - Data not reported in an extractable format [Crossover trial without parallel data reported] |
| Fogari, R, Zoppi, A, Corradi, L et al. (1999) Long-term effects of ramipril and nitrendipine on albuminuria in hypertensive patients with type II diabetes and impaired renal function. Journal of human hypertension 13(1): 47-53 | - Study does not contain a relevant intervention [Nitrendipine (not available in the UK)] |
| Fogari, R, Zoppi, A, Pasotti, C et al. (1995) Comparative effects of ramipril and nitrendipine on albuminuria in hypertensive patients with non-insulin-dependent diabetes mellitus and impaired renal function. Journal of human hypertension 9(2): 131-135 | - Study does not contain a relevant intervention [Nitrendipine (not available in the UK)] |
| Fogari, Roberto, Corradi, Luca, Zoppi, Annalisa et al. (2007) Addition of Manidipine Improves the Antiproteinuric Effect of Candesartan in Hypertensive Patients With Type II Diabetes and Microalbuminuria:. ajh 20(10): 1092-1096 | - Does not contain a population of people with CKD or suspected CKD |
| Fogari, Roberto, Derosa, Giuseppe, Zoppi, Annalisa et al. (2014) Comparative effect of canrenone or hydrochlorothiazide addition to valsartan/amlodipine combination on urinary albumin excretion in well-controlled type 2 diabetic hypertensive patients with microalbuminuria. Expert Opinion on Pharmacotherapy 15(4): 453-459 | - Study does not contain a relevant intervention [Canrenone (not available in the UK)] |
| Fogari, Roberto, Mugellini, Amedeo, Zoppi, Annalisa et al. (2005) Effect of successful hypertension control by manidipine or lisinopril | - Does not contain a population of people with CKD or suspected CKD |

| Reference | Reason for exclusion |
|---|---|
| on albuminuria and left ventricular mass in diabetic hypertensive patients with microalbuminuria. European Journal of Clinical Pharmacology 61(7): 483-490 | |
| Fogari, Roberto, Preti, Paola, Zoppi, Annalisa et al. (2002) Effects of amlodipine fosinopril combination on microalbuminuria in hypertensive type 2 diabetic patients. American Journal of Hypertension 15(12): 1042-1049 | - Does not contain a population of people with CKD or suspected CKD |
| Fogari, Roberto, Zoppi, A., Malamani, G. D. et al. (1997) Effects of Amlodipine vs Enalapril on Microalbuminuria in Hypertensive Patients with Type II Diabetes. Clinical Drug Investigation 13(1): 42-49 | - Does not contain a population of people with CKD or suspected CKD |
| Fogari, Roberto, Zoppi, Annalisa, Corradi, Luca et al. (2000) Long-term effects of amlodipine versus fosinopril on microalbuminuria in elderly hypertensive patients with type 2 diabetes mellitus. Current Therapeutic Research 61(3): 163-173 | - Does not contain a population of people with CKD or suspected CKD |
| Galle, J., Schwedhelm, E., Pinnetti, S. et al. (2008) Antiproteinuric effects of angiotensin receptor blockers: Telmisartan versus valsartan in hypertensive patients with type 2 diabetes mellitus and overt nephropathy. Nephrology Dialysis Transplantation 23(10): 3174-3183 | - Comparator in study does not match that specified in protocol [Intra-class comparison between ARBs] |
| Gant, Christina M, Laverman, Gozewijn D, Vogt, Liffert et al. (2017) Renoprotective RAAS inhibition does not affect the association between worse renal function and higher plasma aldosterone levels. BMC nephrology 18(1): 370 | - Data not reported in an extractable format [Crossover trial without parallel data reported] |
| Garg, Jay P, Ellis, Renee, Elliott, William J et al. (2005) Angiotensin receptor blockade and arterial compliance in chronic kidney disease: a pilot study. American journal of nephrology 25(4): 393-9 | - Does not contain a relevant outcome |
| Greene, T., Tighiouart, H., Gansevoort, R.T. et al. (2019) Change in albuminuria as a surrogate endpoint for progression of kidney disease: a meta-analysis of treatment effects in randomised clinical trials. The Lancet Diabetes and Endocrinology 7(2): 128-139 | - Data not reported in an extractable format [Results were not reported by intervention] |
| Hase, M., Babazono, T., Ujihara, N. et al. (2013) Comparison of spironolactone and trichlormethiazide as add-on therapy to renin-angiotensin blockade for reduction of albuminuria in diabetic patients. Journal of Diabetes Investigation 4(3): 316-319 | - Study does not contain a relevant intervention [Trichlormethiazide (not available in the UK)] |
| Hayashi, Koichi; Kumagai, Hiroo; Saruta, Takao (2003) Effect of efonidipine and ACE inhibitors on proteinuria in human hypertension with renal impairment. American journal of hypertension 16(2): 116-22 | - Study does not contain a relevant intervention [Efonidipine (not available in the UK)] |
| Hebert, L A, Bain, R P, Verme, D et al. (1994) Remission of nephrotic range proteinuria in type | - Does not contain a relevant outcome [Remission of proteinuria] |

| Reference | Reason for exclusion |
|---|---|
| I diabetes. Collaborative Study Group. Kidney international 46(6): 1688-93 | |
| Heerspink, Hiddo J L, Parving, Hans-Henrik, Andress, Dennis L et al. (2019) Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR): a double-blind, randomised, placebo-controlled trial. Lancet (London, England) 393(10184): 1937-1947 | - Study does not contain a relevant intervention [Atrasentan (not available in the UK)] |
| Hollenberg, N.K., Parving, H.-H., Viberti, G. et al. (2007) Albuminuria response to very high-dose valsartan in type 2 diabetes mellitus. Journal of Hypertension 25(9): 1921-1926 | - Does not contain a population of people with proteinuria or albuminuria [Urinary albumin excretion rate between 20 and 700 mcg/min at the time of randomisation] |
| Horita, Yoshio, Tadokoro, Masato, Taura, Koichi et al. (2004) Low-dose combination therapy with temocapril and losartan reduces proteinuria in normotensive patients with immunoglobulin a nephropathy. Hypertension research : official journal of the Japanese Society of Hypertension 27(12): 963-970 | - Study does not contain a relevant intervention [Temocapril (not available in the UK)] |
| Hou, Fan Fan, Xie, Di, Zhang, Xun et al. (2007) Renoprotection of Optimal Antiproteinuric Doses (ROAD) Study: a randomized controlled study of benazepril and losartan in chronic renal insufficiency. Journal of the American Society of Nephrology : JASN 18(6): 1889-98 | - Data not reported in an extractable format [Data reported only in graph] |
| Huang, Rongzhong, Feng, Yuxing, Wang, Ying et al. (2017) Comparative Efficacy and Safety of Antihypertensive Agents for Adult Diabetic Patients with Microalbuminuric Kidney Disease: A Network Meta-Analysis. PloS one 12(1): e0168582 | - Systematic review used as source of primary studies |
| Iino, Yasuhiko, Hayashi, Matsuhiko, Kawamura, Tetsuya et al. (2004) Renoprotective effect of losartan in comparison to amlodipine in patients with chronic kidney disease and hypertension--a report of the Japanese Losartan Therapy Intended for the Global Renal Protection in Hypertensive Patients (JLIGHT) study. Hypertension research : official journal of the Japanese Society of Hypertension 27(1): 21-30 | - Data not reported in an extractable format [Data reported only in graph] |
| Janssen, J J, Gans, R O, van der Meulen, J et al. (1998) Comparison between the effects of amlodipine and lisinopril on proteinuria in nondiabetic renal failure: a double-blind, randomized prospective study. American journal of hypertension 11(9): 1074-9 | - Data not reported in an extractable format [Data reported only in graph] |
| Katayama, Shigehiro, Kikkawa, Ryuichi, Isogai, Syo et al. (2002) Effect of captopril or imidapril on the progression of diabetic nephropathy in Japanese with type 1 diabetes mellitus: a randomized controlled study (JAPAN-IDDM). Diabetes Research and Clinical Practice 55(2): 113-121 | - Does not contain a population of people with CKD or suspected CKD |
| Kim, M.-J., Song, J.H., Suh, J.H. et al. (2003) Additive antiproteinuric effect of combination | - Data not reported in an extractable format |

| Reference | Reason for exclusion |
|---|---|
| therapy with ACE inhibitor and angiotensin II receptor antagonist: Differential short-term response between IgA nephropathy and diabetic nephropathy. Yonsei Medical Journal 44(3): 463-472 | [Crossover trial without parallel data reported] |
| Kim-Mitsuyama, Shokei, Soejima, Hirofumi, Yasuda, Osamu et al. (2018) Cardiovascular and renal protective role of angiotensin blockade in hypertension with advanced CKD: a subgroup analysis of ATTEMPT-CVD randomized trial. Scientific reports 8(1): 3150 | - Does not contain a population of people with proteinuria or albuminuria<br>[mixed population G3b and/or A3] |
| Kincaid-Smith, Priscilla; Fairley, Kenneth; Packham, David (2002) Randomized controlled crossover study of the effect on proteinuria and blood pressure of adding an angiotensin II receptor antagonist to an angiotensin converting enzyme inhibitor in normotensive patients with chronic renal disease and proteinuria. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 17(4): 597-601 | - Data not reported in an extractable format<br>[Crossover trial without parallel data reported] |
| Knoll, Greg A, Fergusson, Dean, Chasse, Michael et al. (2016) Ramipril versus placebo in kidney transplant patients with proteinuria: a multicentre, double-blind, randomised controlled trial. The lancet. Diabetes & endocrinology 4(4): 318-26 | - Does not contain a population of people with CKD or suspected CKD<br>[Participants were receiving renal replacement therapy (kidney transplant)] |
| Kohan, D.E., Pritchett, Y., Molitch, M. et al. (2011) Addition of atrasentan to renin-angiotensin system blockade reduces albuminuria in diabetic nephropathy. Journal of the American Society of Nephrology 22(4): 763-772 | - Study does not contain a relevant intervention<br>[Atrasentan (not available in the UK)] |
| Kohan, Donald E, Lambers Heerspink, Hiddo J, Coll, Blai et al. (2015) Predictors of Atrasentan-Associated Fluid Retention and Change in Albuminuria in Patients with Diabetic Nephropathy. Clinical journal of the American Society of Nephrology : CJASN 10(9): 1568-74 | - Data not reported in an extractable format<br>[UACR reported as median] |
| Kojima, Masayoshi, Ohashi, Masuo, Dohi, Yasuaki et al. (2013) Titration of telmisartan, but not addition of amlodipine, reduces urine albumin in diabetic patients treated with telmisartan-diuretic. Journal of hypertension 31(1): 186-191 | - Study does not contain a relevant intervention<br>[Trichlormethiazide (not available in the UK)] |
| Kowey, Peter R, Dickson, Tania Z, Zhang, Zhongxin et al. (2005) Losartan and end-organ protection--lessons from the RENAAL study. Clinical cardiology 28(3): 136-42 | - Secondary publication of an included study that does not provide any additional relevant information |
| Kshirsagar, A V, Joy, M S, Hogan, S L et al. (2000) Effect of ACE inhibitors in diabetic and nondiabetic chronic renal disease: a systematic overview of randomized placebo-controlled trials. American journal of kidney diseases : the | - Systematic review used as source of primary studies |

| Reference | Reason for exclusion |
|---|---|
| official journal of the National Kidney Foundation 35(4): 695-707 | |
| Kunz, Regina, Friedrich, Chris, Wolbers, Marcel et al. (2008) Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin angiotensin system on proteinuria in renal disease. Annals of internal medicine 148(1): 30-48 | - Does not contain a population of people with proteinuria or albuminuria<br>[Some RCTs were included based on creatinine levels] |
| Kwakernaak, Arjan J, Waanders, Femke, Slagman, Maartje C J et al. (2013) Sodium restriction on top of renin-angiotensin-aldosterone system blockade increases circulating levels of N-acetyl-seryl-aspartyl-lysyl-proline in chronic kidney disease patients. Journal of hypertension 31(12): 2425-32 | - Data not reported in an extractable format<br>[Crossover trial without parallel data reported] |
| Lea, Janice, Greene, Tom, Hebert, Lee et al. (2005) The relationship between magnitude of proteinuria reduction and risk of end-stage renal disease: results of the African American study of kidney disease and hypertension. Archives of internal medicine 165(8): 947-53 | - Does not contain a population of people with proteinuria or albuminuria<br>[Proteinuria was not an inclusion criteria] |
| | |
| Lewis, E J, Hunsicker, L G, Rodby, R A et al. (2001) A clinical trial in type 2 diabetic nephropathy. American journal of kidney diseases : the official journal of the National Kidney Foundation 38(4suppl1): 191-4 | - Does not contain a relevant outcome<br>[The outcome was correlation between baseline 24 hour urine protein and baseline characteristics] |
| Lizakowski, Slawomir, Tylicki, Leszek, Renke, Marcin et al. (2012) Effect of aliskiren on proteinuria in non-diabetic chronic kidney disease: a double-blind, crossover, randomised, controlled trial. International urology and nephrology 44(6): 1763-70 | - Data not reported in an extractable format<br>[Crossover trial without parallel data reported] |
| Lizakowski, Slawomir, Tylicki, Leszek, Rutkowski, Przemyslaw et al. (2013) Safety of enhanced renin-angiotensin-aldosterone system inhibition with aliskiren in nondiabetic patients with chronic kidney disease. Polskie Archiwum Medycyny Wewnetrznej 123(5): 221-7 | - Data not reported in an extractable format<br>[Crossover trial without parallel data reported] |
| Lubrano, Riccardo, Soscia, Francesca, Elli, Marco et al. (2006) Renal and cardiovascular effects of angiotensin-converting enzyme inhibitor plus angiotensin II receptor antagonist therapy in children with proteinuria. Pediatrics 118(3): e833-8 | - Conference abstract |
| MacKinnon, M., Shurraw, S., Akbari, A. et al. (2006) Combination Therapy With an Angiotensin Receptor Blocker and an ACE Inhibitor in Proteinuric Renal Disease: A Systematic Review of the Efficacy and Safety Data. American Journal of Kidney Diseases 48(1): 8-20 | - Systematic review used as source of primary studies |
| Maione, Ausilia, Navaneethan, Sankar D, Graziano, Giusi et al. (2011) Angiotensin-converting enzyme inhibitors, angiotensin | - Does not contain a population of people with proteinuria or albuminuria |

| Reference | Reason for exclusion |
|---|---|
| receptor blockers and combined therapy in patients with micro- and macroalbuminuria and other cardiovascular risk factors: a systematic review of randomized controlled trials. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 26(9): 2827-47 | [Albuminuria values were not reported as one of the inclusion criteria of the RCTs] |
| Makhlough, A., Kashi, Z., Akha, O. et al. (2014) Effect of spironolactone on diabetic nephropathy compared to the combination of spironolactone and losartan. Nephro-Urology Monthly 6(1): e12148 | - Does not contain a population of people with proteinuria or albuminuria<br>[urinary albumin to creatinine ratio of 20 - 200 mg/g] |
| Makino, Hirofumi, Haneda, Masakazu, Babazono, Tetsuya et al. (2007) Prevention of Transition From Incipient to Overt Nephropathy With Telmisartan in Patients With Type 2 Diabetes. Diabetes Care 30(6): 1577 | - Does not contain a relevant outcome<br>[Transition rates to overt nephropathy; reduced urinary albumin-to-creatinine ratio at final observation without baseline data.] |
| Mann, J.F.E., Fonseca, V.A., Poulter, N.R. et al. (2020) Safety of liraglutide in type 2 diabetes and chronic kidney disease. Clinical Journal of the American Society of Nephrology 15(4): 465-473 | - Does not contain a population of people with proteinuria or albuminuria<br>[Albuminuria was not an inclusion criteria] |
| Marre, M., Chatellier, G., Leblanc, H. et al. (1988) Prevention of diabetic nephropathy with enalapril in normotensive diabetics with microalbuminuria. British Medical Journal 297(6656): 1092 | - Does not contain a population of people with CKD or suspected CKD |
| Marre, Michel, Lievre, Michel, Chatellier, Gilles et al. (2004) Effects of low dose ramipril on cardiovascular and renal outcomes in patients with type 2 diabetes and raised excretion of urinary albumin: randomised, double blind, placebo controlled trial (the DIABHYCAR study). BMJ (Clinical research ed.) 328(7438): 495 | - Does not contain a population of people with proteinuria or albuminuria<br>[urinary albumin excretion ≥20 mg/l in two successive random urine samples] |
| Maschio, G, Alberti, D, Locatelli, F et al. (1999) Angiotensin-converting enzyme inhibitors and kidney protection: the AIPRI trial. The ACE Inhibition in Progressive Renal Insufficiency (AIPRI) Study Group. Journal of cardiovascular pharmacology 33suppl1: 16-3 | - Does not contain a population of people with proteinuria or albuminuria<br>[Proteinuria was not an inclusion criteria] |
| Matos, J P S, de Lourdes Rodrigues, M, Ismerim, VL et al. (2005) Effects of dual blockade of the renin angiotensin system in hypertensive type 2 diabetic patients with nephropathy. Clinical nephrology 64(3): 180-189 | - Data not reported in an extractable format<br>[Crossover trial without parallel data reported] |
| Matsuba, I., Kawata, T., Iemitsu, K. et al. (2020) Effects of ipragliflozin on the development and progression of kidney disease in patients with type 2 diabetes: An analysis from a multicenter prospective intervention study. Journal of Diabetes Investigation | - Does not contain a population of people with proteinuria or albuminuria<br>[Albuminuria was not an inclusion criteria] |
| McGuire, Darren K., Shih, Weichung J., Cosentino, Francesco et al. (2020) Association of SGLT2 Inhibitors With Cardiovascular and | - Does not contain a population of people with proteinuria or albuminuria<br>[Proteinuria was not an inclusion criteria] |

| Reference | Reason for exclusion |
|---|---|
| Kidney Outcomes in Patients With Type 2 Diabetes: A Meta-analysis. JAMA Cardiol | |
| Mishima, E.; Haruna, Y.; Arima, H. (2019) Renin-angiotensin system inhibitors in hypertensive adults with non-diabetic CKD with or without proteinuria: a systematic review and meta-analysis of randomized trials. Hypertension research : official journal of the Japanese Society of Hypertension 42(4): 469-482 | - Does not contain a population of people with proteinuria or albuminuria<br>[Proteinuria was not an inclusion criteria] |
| Morales, E., Caro, J., Gutierrez, E. et al. (2015) Diverse diuretics regimens differentially enhance the antialbuminuric effect of renin-angi in patients with chronic kidney disease. Kidney International 88(6): 1434-1441 | - Data not reported in an extractable format<br>[Crossover trial without parallel data reported] |
| Morales, E., Huerta, A., Gutierrez, E. et al. (2009) The antiproteinuric effect of the blockage of the renin-angiotensin-aldosterone system (RAAS) in obese patients. Which treatment option is the most effective?. Nefrologia 29(5): 421-429 | - Data not reported in an extractable format<br>[Crossover trial without parallel data reported] |
| Morales, E, Gutiérrez, E, Caro, J et al. (2015) Beneficial long-term effect of aldosterone antagonist added to a traditional blockade of the renin-angiotensin-aldosterone system among patients with obesity and proteinuria. Nefrologia 35(6): 554-561 | - Not a relevant study design<br>[Prospective cohort study] |
| Muirhead, Norman, Feagan, Brian F., Mahon, Jeffrey et al. (1999) The effects of valsartan and captopril on reducing microalbuminuria in patients with type 2 diabetes mellitus: a placebo-controlled trial. Current Therapeutic Research 60(12): 650-660 | - Does not contain a population of people with proteinuria or albuminuria<br>[albuminuria 20 to 300 mcg/min] |
| Ohishi, Mitsuru, Takeya, Yasushi, Tatara, Yuji et al. (2010) Strong suppression of the renin-angiotensin system has a renal-protective effect in hypertensive patients: high-dose ARB with ACE inhibitor (Hawaii) study. Hypertension research : official journal of the Japanese Society of Hypertension 33(11): 1150-4 | - Does not contain a population of people with CKD or suspected CKD |
| Parving, Hans-Henrik, Lehnert, Hendrik, Bröchner-Mortensen, Jens et al. (2001) The Effect of Irbesartan on the Development of Diabetic Nephropathy in Patients with Type 2 Diabetes. New England Journal of Medicine 345(12): 870-878 | - Does not contain a population of people with proteinuria or albuminuria<br>[Albumin excretion rate 20 to 200 mcg/min] |
| Perkovic, V., Toto, R., Cooper, M.E. et al. (2020) Effects of linagliptin on cardiovascular and kidney outcomes in people with normal and reduced kidney function: Secondary analysis of the carmelina randomized trial. Diabetes Care 43(8): 1803-1812 | - Does not contain a population of people with proteinuria or albuminuria<br>[20% of participants had urinary albumin:creatinine ratio <30 mg/g at baseline] |
| Pérez-Maraver, Manuel, Carrera, Maria José, Micaló, Teresa et al. (2005) Renoprotective effect of diltiazem in hypertensive type 2 diabetic patients with persistent microalbuminuria despite | - Does not contain a population of people with CKD or suspected CKD |

| Reference | Reason for exclusion |
|---|---|
| ACE inhibitor treatment. Diabetes Research and Clinical Practice 70(1): 13-19 | |
| Ravid, M, Lang, R, Rachmani, R et al. (1996) Long-term renoprotective effect of angiotensin-converting enzyme inhibition in non-insulin-dependent diabetes mellitus. A 7-year follow-up study. Archives of internal medicine 156(3): 286-9 | - Does not contain a population of people with CKD or suspected CKD |
| Ravid, Mordchai, Savin, Hilel, Jutrin, Itzhak et al. (1993) Long-Term Stabilizing Effect of Angiotensin-Converting Enzyme Inhibition on Plasma Creatinine and on Proteinuria in Normotensive Type II Diabetic Patients. AIM 118(8): 577-581 | - Does not contain a population of people with CKD or suspected CKD |
| Remuzzi, Giuseppe; Macia, Manuel; Ruggenenti, Piero (2006) Prevention and treatment of diabetic renal disease in type 2 diabetes: the BENEDICT study. Journal of the American Society of Nephrology : JASN 17(4suppl2): 90-7 | - Review article but not a systematic review |
| Rodby, R A, Rohde, R D, Clarke, W R et al. (2000) The Irbesartan type II diabetic nephropathy trial: study design and baseline patient characteristics. For the Collaborative Study Group. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 15(4): 487-97 | - Secondary publication of an included study that does not provide any additional relevant information<br>[Lewis 2001] |
| Rosenstock, Julio, Perkovic, Vlado, Johansen, Odd Erik et al. (2019) Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk: The CARMELINA Randomized Clinical Trial. JAMA 321(1): 69-79 | - Does not contain a population of people with proteinuria or albuminuria<br>[20% of participants had urinary albumin:creatinine ratio <30 mg/g at baseline] |
| Rosman, J B and ter Wee, P M (1989) Relationship between proteinuria and response to low protein diets early in chronic renal failure. Blood purification 7(1): 52-7 | - Data not reported in an extractable format<br>[Proteinuria reported as median] |
| Rossing, Kasper, Christensen, Per K., Jensen, Berit R. et al. (2002) Dual Blockade of the Renin-Angiotensin System in Diabetic Nephropathy. Diabetes Care 25(1): 95 | - Data not reported in an extractable format<br>[Crossover trial without parallel data reported] |
| Ruggenenti, P., Perna, A., Benini, R. et al. (1999) In chronic nephropathies prolonged ACE inhibition can induce remission: Dynamics of time-dependent changes in GFR. Journal of the American Society of Nephrology 10(5): 997-1006 | - Secondary publication of an included study that does not provide any additional relevant information<br>[GISEN group 1997] |
| Ruggenenti, P, Perna, A, Gherardi, G et al. (1998) Renal function and requirement for dialysis in chronic nephropathy patients on long-term ramipril: REIN follow-up trial. Gruppo Italiano di Studi Epidemiologici in Nefrologia (GISEN). Ramipril Efficacy in Nephropathy. Lancet (London, England) 352(9136): 1252-6 | - Secondary publication of an included study that does not provide any additional relevant information<br>[GISEN group 1997] |

| Reference | Reason for exclusion |
|---|---|
| Ruggenenti, P, Perna, A, Mosconi, L et al. (1997) Proteinuria predicts end-stage renal failure in non-diabetic chronic nephropathies. The "Gruppo Italiano di Studi Epidemiologici in Nefrologia" (GISEN). Kidney international. Supplement 63: 54-7 | - Does not contain a relevant outcome<br>[GFR and kidney survival per tertile of baseline 24 h urine protein ] |
| Ruilope, L M, Aldigier, J C, Ponticelli, C et al. (2000) Safety of the combination of valsartan and benazepril in patients with chronic renal disease. European Group for the Investigation of Valsartan in Chronic Renal Disease. Journal of hypertension 18(1): 89-95 | - Duplicate reference |
| Ruilope, L.M., Aldigier, J.C., Ponticelli, C. et al. (2000) Safety of the combination of valsartan and benazepril in patients with chronic renal disease. Journal of Hypertension 18(1): 89-95 | - Does not contain a population of people with proteinuria or albuminuria<br>[Proteinuria was not an inclusion criteria] |
| Rutkowski, Przemyslaw, Tylicki, Leszek, Renke, Marcin et al. (2004) Low-dose dual blockade of the renin-angiotensin system in patients with primary glomerulonephritis. American journal of kidney diseases : the official journal of the National Kidney Foundation 43(2): 260-8 | - Data not reported in an extractable format<br>[Crossover trial without parallel data reported] |
| Sato, Atsuhisa; Hayashi, Koichi; Saruta, Takao (2005) Antiproteinuric effects of mineralocorticoid receptor blockade in patients with chronic renal disease. American journal of hypertension 18(1): 44-9 | - Not a relevant study design<br>[Before-after study] |
| Sato, Atsuhisa, Tabata, Mitsuhisa, Hayashi, Koichi et al. (2003) Effects of the angiotensin II type 1 receptor antagonist candesartan, compared with angiotensin-converting enzyme inhibitors, on the urinary excretion of albumin and type IV collagen in patients with diabetic nephropathy. Journal of Clinical and Experimental Nephrology 7(3): 215-220 | - Not a relevant study design<br>[Non-randomised study] |
| Schnack, Ch., Capek, M., Banyai, M. et al. (1994) Long-term treatment with nifedipine reduces urinary albumin excretion and glomerular filtration rate in normotensive type 1 diabetic patients with microalbuminuria. Acta Diabetologica 31(1): 14-18 | - Does not contain a population of people with CKD or suspected CKD |
| Scholtes, R.A., van Raalte, D.H., Correa-Rotter, R. et al. (2020) The effects of dapagliflozin on cardio-renal risk factors in patients with type 2 diabetes with or without renin-angiotensin system inhibitor treatment: a post hoc analysis. Diabetes, Obesity and Metabolism 22(4): 549-556 | - Aim of study does not match protocol<br>[Lowering proteinuria was not the aim of the trials in this pooled analysis] |
| Segura, Julián, Praga, Manuel, Campo, Carlos et al. (2003) Combination is better than monotherapy with ACE inhibitor or angiotensin receptor antagonist at recommended doses. Journal of the Renin-Angiotensin-Aldosterone System 4(1): 43-47 | - Study does not contain a relevant intervention<br>[Benazepril (not available in the UK)] |

| Reference | Reason for exclusion |
|---|---|
| Sengul, Ahmet M., Altuntas, Yüksel, Kürklü, Akın et al. (2006) Beneficial effect of lisinopril plus telmisartan in patients with type 2 diabetes, microalbuminuria and hypertension. Diabetes Research and Clinical Practice 71(2): 210-219 | - Does not contain a population of people with CKD or suspected CKD |
| Shahinfar, Shahnaz, Dickson, Tania Z, Ahmed, Tultul et al. (2002) Losartan in patients with type 2 diabetes and proteinuria: observations from the RENAAL Study. Kidney international. Supplement: 64-7 | - Secondary publication of an included study that does not provide any additional relevant information<br>[Brenner 2001] |
| Slagman, Maartje C J, Nguyen, Tri Q, Waanders, Femke et al. (2011) Effects of antiproteinuric intervention on elevated connective tissue growth factor (CTGF/CCN-2) plasma and urine levels in nondiabetic nephropathy. Clinical journal of the American Society of Nephrology : CJASN 6(8): 1845-50 | - Data not reported in an extractable format<br>[Crossover trial without parallel data reported] |
| Slagman, Maartje C J, Waanders, Femke, Vogt, Liffert et al. (2012) Elevated N-terminal pro-brain natriuretic peptide levels predict an enhanced anti-hypertensive and anti-proteinuric benefit of dietary sodium restriction and diuretics, but not angiotensin receptor blockade, in proteinuric renal patients. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 27(3): 983-90 | - Secondary publication of an included study that does not provide any additional relevant information<br>[Slagman 2011] |
| Song, J.H., Cha, S.H., Lee, H.J. et al. (2006) Effect of low-dose dual blockade of renin-angiotensin system on urinary TGF-beta in type 2 diabetic patients with advanced kidney disease. Nephrology Dialysis Transplantation 21(3): 683-689 | - Data not reported in an extractable format<br>[Crossover trial without parallel data reported] |
| Song, J.H., Lee, S.W., Suh, J.H. et al. (2003) The effects of dual blockade of the renin-angiotensin system on urinary protein and transforming growth factor-beta excretion in 2 groups of patients with IgA and diabetic nephropathy. Clinical Nephrology 60(5): 318-326 | - Data not reported in an extractable format<br>[Crossover trial without parallel data reported] |
| Takahara, S., Moriyama, T., Kokado, Y. et al. (2002) Randomized prospective study of effects of benazepril in renal transplantation: An analysis of safety and efficacy. Clinical and Experimental Nephrology 6(4): 242-247 | - Does not contain a population of people with CKD or suspected CKD<br>[Post-transplant patients] |
| Takebayashi, Kohzo, Matsumoto, Sachiko, Aso, Yoshimasa et al. (2006) Aldosterone Blockade Attenuates Urinary Monocyte Chemoattractant Protein-1 and Oxidative Stress in Patients with Type 2 Diabetes Complicated by Diabetic Nephropathy. jcem 91(6): 2214-2217 | - Data not reported in an extractable format<br>[Urinary albumin/creatinine ratio reported as geometric means (interquartile range, 25th and 75th percentiles)] |
| Tang, S.C.W., Chan, K.W., Ip, D.K.M. et al. (2020) Direct Renin Inhibition in Non-diabetic chronic Kidney disease (DRINK): a prospective randomized trial. Nephrology, dialysis, transplantation : official publication of the | - Does not contain a population of people with proteinuria or albuminuria<br>[Proteinuria/albuminuria was not an inclusion criteria] |

| Reference | Reason for exclusion |
|---|---|
| European Dialysis and Transplant Association - European Renal Association | |
| Tang, Sydney C W, Lin, Miao, Tam, Sidney et al. (2012) Aliskiren combined with losartan in immunoglobulin A nephropathy: an open-labeled pilot study. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 27(2): 613-8 | - Not a relevant study design [Before-after study] |
| Titan, S M, M Vieira, J Jr, Dominguez, W V et al. (2011) ACEI and ARB combination therapy in patients with macroalbuminuric diabetic nephropathy and low socioeconomic level: a double-blind randomized clinical trial. Clinical nephrology 76(4): 273-83 | - Data not reported in an extractable format [Urinary protein excretion (g/24 h) reported as median and interquartile range] |
| Trachtman, H., Nelson, P., Adler, S. et al. (2018) DUET: A phase 2 study evaluating the efficacy and safety of sparsentan in patients with FSGS. Journal of the American Society of Nephrology 29(11): 2745-2754 | - Aim of study does not match protocol [Dose-escalation study] |
| Tylicki, L, Renke, M, Rutkowski, P et al. (2008) Dual blockade of the renin-angiotensin-aldosterone system with high-dose angiotensin-converting enzyme inhibitor for nephroprotection: an open, controlled, randomized study. Scandinavian journal of urology and nephrology 42(4): 381-388 | - Data not reported in an extractable format [Crossover trial without parallel data reported] |
| Tylicki, Leszek, Lizakowski, Slawomir, Rutkowski, Przemyslaw et al. (2012) The enhanced renin-angiotensin-aldosteron system pharmacological blockade--which is the best?. Kidney & blood pressure research 36(1): 335-43 | - Data not reported in an extractable format [Crossover trial without parallel data reported] |
| Tylicki, Leszek, Rutkowski, Przemyslaw, Renke, Marcin et al. (2008) Triple pharmacological blockade of the renin-angiotensin-aldosterone system in nondiabetic CKD: an open-label crossover randomized controlled trial. American journal of kidney diseases : the official journal of the National Kidney Foundation 52(3): 486-93 | - Data not reported in an extractable format [Crossover trial without parallel data reported] |
| Tütüncü, N. B.; Gürlek, A.; Gedik, O. (2001) Efficacy of ACE inhibitors and ATII receptor blockers in patients with microalbuminuria: a prospective study. Acta Diabetologica 38(4): 157-161 | - Does not contain a population of people with CKD or suspected CKD |
| Uzu, Takashi, Araki, Shin-Ichi, Kashiwagi, Atsunori et al. (2016) Comparative Effects of Direct Renin Inhibitor and Angiotensin Receptor Blocker on Albuminuria in Hypertensive Patients with Type 2 Diabetes. A Randomized Controlled Trial. PloS one 11(12): e0164936 | - Study does not contain a relevant intervention [Aliskiren (BNF license highly limiting in CKD)] |
| Viberti, Giancarlo, Mogensen, Carl Erik, Groop, Leif C. et al. (1994) Effect of Captopril on Progression to Clinical Proteinuria in Patients With Insulin-Dependent Diabetes Mellitus and Microalbuminuria. JAMA 271(4): 275-279 | - Does not contain a population of people with CKD or suspected CKD |

| Reference | Reason for exclusion |
|---|---|
| Waanders, Femke, Vaidya, Vishal S, van Goor, Harry et al. (2009) Effect of renin-angiotensin-aldosterone system inhibition, dietary sodium restriction, and/or diuretics on urinary kidney injury molecule 1 excretion in nondiabetic proteinuric kidney disease: a post hoc analysis of a randomized controlled trial. American journal of kidney diseases : the official journal of the National Kidney Foundation 53(1): 16-25 | - Data not reported in an extractable format<br>[Crossover trial without parallel data reported] |
| Wang, Kanran, Hu, Jinbo, Luo, Ting et al. (2018) Effects of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers on All-Cause Mortality and Renal Outcomes in Patients with Diabetes and Albuminuria: a Systematic Review and Meta-Analysis. Kidney & blood pressure research 43(3): 768-779 | - Does not contain a population of people with proteinuria or albuminuria<br>[urine albumin excretion rate 20–199 mcg/min was also used to define microalbuminuria] |
| Wanner, C., Inzucchi, S.E., Zinman, B. et al. (2020) Consistent Effects of Empagliflozin on Cardiovascular and Kidney Outcomes Irrespective of Diabetic Kidney Disease Categories - Insights from the EMPA-REG OUTCOME trial. Diabetes, obesity & metabolism | - Does not contain a population of people with proteinuria or albuminuria<br>[Albuminuria was not an inclusion criteria] |
| Wanner, Christoph, Lachin, John M, Inzucchi, Silvio E et al. (2018) Empagliflozin and Clinical Outcomes in Patients With Type 2 Diabetes Mellitus, Established Cardiovascular Disease, and Chronic Kidney Disease. Circulation 137(2): 119-129 | - Does not contain a population of people with proteinuria or albuminuria<br>[Albuminuria was not an inclusion criteria] |
| Webb, Nicholas J A, Shahinfar, Shahnaz, Wells, Thomas G et al. (2012) Losartan and enalapril are comparable in reducing proteinuria in children. Kidney international 82(7): 819-26 | - Does not contain a population of people with CKD or suspected CKD<br>[Not all participants had CKD or suspected CKD] |
| Weil, E. Jennifer, Fufaa, Gudeta, Jones, Lois I. et al. (2013) Effect of Losartan on Prevention and Progression of Early Diabetic Nephropathy in American Indians With Type 2 Diabetes. Diabetes 62(9): 3224 | - Does not contain a population of people with CKD or suspected CKD |
| Weir, M.R., McCullough, P.A., Buse, J.B. et al. (2020) Renal and Cardiovascular Effects of Sodium Glucose Co-Transporter 2 Inhibitors in Patients with Type 2 Diabetes and Chronic Kidney Disease: Perspectives on the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation Trial Results. American Journal of Nephrology 51(4): 276-288 | - Review article but not a systematic review |
| Xie, Di, Hou, Fan Fan, Fu, Bi Ling et al. (2011) High level of proteinuria during treatment with renin-angiotensin inhibitors is a strong predictor of renal outcome in nondiabetic kidney disease. Journal of clinical pharmacology 51(7): 1025-34 | - Secondary publication of an included study that does not provide any additional relevant information<br>[Hou 2007] |
| Yang, Pingping, Zou, Honghong, Xiao, Bufan et al. (2018) Comparative Efficacy and Safety of Therapies in IgA Nephropathy: A Network Meta-analysis of Randomized Controlled Trials. Kidney international reports 3(4): 794-803 | - Study does not contain a relevant intervention<br>[Network meta-analysis also including steroids, urokinase and tonsillectomy] |

| Reference | Reason for exclusion |
|---|---|
| Zimering, M.B., Zhang, J.H., Guarino, P.D. et al. (2014) Endothelial cell autoantibodies in predicting declining renal function, end-stage renal disease, or death in adult type 2 diabetic nephropathy. Frontiers in Endocrinology 5(aug): 128 | - Secondary publication of an included study that does not provide any additional relevant information<br>[Fried 2013] |

## 1 Economic studies

| Author (year) | Title | Reason for exclusion |
|---|---|---|
| Ambrosioni 2005 | Pharmacoeconomic study of first-line perindopril/indapamide combination in lowering blood pressure and reducing albuminuria | Cost benefit analysis |
| Annemans 2008 | An Asian regional analysis of cost-effectiveness of early irbesartan treatment versus conventional antihypertensive, late amlodipine, and late irbesartan treatments in patients with type 2 diabetes, hypertension, and nephropathy | Not conducted in an OECD country, cost benefit analysis |
| Clark 2000 | To pay or not to pay? A decision and cost-utility analysis of angiotensin-converting-enzyme inhibitor therapy for diabetic nephropathy. | Intervention does not meet PICO criteria, Not a medical intervention |
| Chen 2001 | A computer simulation model for cost-effectiveness analysis of mass screening for type 2 diabetes mellitus | Not conducted in an OECD country, not a cost utility analysis |
| Coyle 2004 | Economic evaluation of the use of irbesartan and amlodipine in the treatment of diabetic nephropathy in patients with hypertension in Canada | Not a cost-utility analysis, outcomes reported as life-years |
| Gerth 2002 | Losartan reduces the burden and cost of ESRD: public health implications from the RENAAL study for the European Union | Cost consequences analysis |
| Herman 2003 | Losartan reduces the costs associated with diabetic end-stage renal disease: the RENAAL study economic evaluation | Cost consequences analysis |
| Palmer 2007 | Irbesartan treatment of patients with type 2 diabetes, hypertension and renal disease: a UK health economics analysis | Cost consequences analysis |
| Palmer 2005 | Irbesartan is projected to be cost and life saving in a Spanish setting for treatment of patients with type 2 diabetes, hypertension, and microalbuminuria | Cost consequences analysis |
| Palmer 2006 | Health economic implications of irbesartan plus conventional antihypertensive medications versus conventional blood pressure control alone in patients with type 2 diabetes, hypertension, and renal disease in Switzerland | Cost consequences analysis |
| Palmer 2006a | Palmer AJ Valentine WJ, Tucker DMD et al. (2006) A French cost-consequence analysis of the renoprotective benefits of irbesartan in patients with type 2 diabetes and hypertension | Cost consequences analysis |
| Palmer 2004 | Health economics studies assessing irbesartan use in patients with hypertension, type 2 diabetes, and microalbuminuria | Cost consequences analysis |

| Author (year) | Title | Reason for exclusion |
|---|---|---|
| Palmer 2004a | Cost-effectiveness of early irbesartan treatment versus control (standard antihypertension medications excluding ACE inhibitors, other angiotensin-2 receptor antagonists, and dihydropyridine calcium channel blockers) or late irbesartan treatment in patients with Type 2 diabetes, hypertension, and renal disease | Cost consequences analysis |
| Palmer 2007 | Health economic implications of irbesartan treatment versus standard blood pressure control in patients with type 2 diabetes, hypertension and renal disease: a Hungarian analysis | Cost consequences analysis |
| Rodby 1996 | An economic analysis of captopril in the treatment of diabetic nephropathy | Cost benefit analysis |
| Saito 2007 | Renoprotective effect and cost-effectiveness of using benidipine, a calcium channel blocker, to lower the dose of angiotensin receptor blocker in hypertensive patients with albuminuria | Cost consequences analysis |
| Saito 2005 | Pharmacoeconomical evaluation of combination therapy for lifetime hypertension treatment in Japan | Not a cost utility analysis, outcomes reported and life-years |
| Sakthong 2001 | Cost-effectiveness of using angiotensin-converting enzyme inhibitors to slow nephropathy in normotensive patients with diabetes type II and microalbuminuria | Not a cost-utility analysis, outcomes reported as life-years |
| Schadlich 2001 | Cost effectiveness of ramipril in patients with non-diabetic nephropathy and hypertension: economic evaluation of ramipril efficacy in nephropathy (REIN) study for Germany from the perspective of statutory health insurance | Not a cost-utility analysis, outcomes reported as life-years |
| Van Hout 1997 | Economic evaluation of benazepril in chronic renal insufficiency | Cost benefit analysis |
| Yang 2007 | Irbesartan and amlodipine in the treatment of patients with microalbuminuria, hypertension and type 2 diabetes in Taiwan: A modelling projection over 25 years | Not a cost-utility analysis, outcomes reported as life-years, non-OECD country |

1

# Appendix M – Research recommendations – full details

## M.1 Research recommendation

For adults, children and young people with suspected or diagnosed CKD and proteinuria or albuminuria, what is the effect of ACE-I compared to ARB for lowering proteinuria?

## M.2 Why this is important

ACE inhibitors and ARBs are currently recommended for adults with type 2 diabetes and an ACR of 3 mg/mmol or more; for adults with hypertension and an ACR of 30 mg/mmol or more; and for adults with an ACR of 70 mg/mmol or more (irrespective of hypertension or cardiovascular disease). However, there are few data on head to head RCTs comparing the effectiveness of these 2 classes of medications. Future research on head to head RCTs could inform decisions to recommend ACE inhibitors and ARBs as first- or second-line options.

## M.3 Rationale for research recommendation

| | |
|---|---|
| Importance to patients | Little is known about the long-term outcomes of using ACE inhibitors compared to ARBs for the treatment of proteinuria in adults, children and young people with CKD. There might be a benefit for patients in the management of their proteinuria if further evidence shows that there is a larger effect with either ACE inhibitors or ARBs. |
| Relevance to NICE guidance | ACE inhibitors and ARBs have been considered in this guideline and there is a lack of data on long-term outcomes. Further evidence might fill in the gap in this area during future updates of the guideline. |
| Relevance to the NHS | The outcome could affect the type of treatment to lower proteinuria or albuminuria in adults, children and young people with suspected or diagnosed CKD and proteinuria or albuminuria. If new recommendations are made in future, this may change the cost of proteinuria treatment provided by the NHS. |
| National priorities | High |
| Current evidence base | Minimal long-term data from 1 RCT of very low quality in adults with type 2 diabetes reporting on end stage renal disease, all-cause mortality, cardiovascular mortality, non-fatal cardiovascular events |
| Equality considerations | None known |

## M.1.4 Modified PICO table

2

| | |
|---|---|
| Population | Adults, children and young people with suspected or diagnosed CKD and proteinuria or albuminuria |
| Intervention | ACE inhibitors |
| Comparator | ARBs |
| Outcome | • Reduction in proteinuria<br>• CKD progression: occurrence of end stage kidney disease (ESRD or ESKD as reported by the study)<br>• Mortality (all-cause and cardiovascular)<br>• Specific morbidity:<br>  ○ fractures,<br>  ○ advancement of renal bone disease,<br>  ○ vascular calcification,<br>  ○ cardiovascular impact,<br>  ○ anaemia<br>• Health-related quality of life<br>• Adverse outcome:<br>  ○ AKI,<br>  ○ drug specific (hypotension/falls, hypoglycaemia, hospitalisation) |
| Study design | Randomised controlled trial sufficiently powered |
| Timeframe | Long term |
| Additional information | Subgroups:<br>• age<br>• with type 2 diabetes<br>• without type 2 diabetes |

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