National Institute for Health and Care Excellence

Final

Chronic kidney disease

[H] Evidence reviews for interventions to lower proteinuria

NICE guideline NG203

Evidence reviews underpinning recommendations 1.6.5 to 1.6.10 and research recommendations in the NICE guideline

August 2021

Final

These evidence reviews were developed by Guideline Updates Team

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Update information

November 2021: We reviewed the evidence on SGLT2 inhibitors for adults with type 2 diabetes and chronic kidney disease. We made new recommendations, and removed the original recommendation 1.6.7 from this guideline. See the new recommendations on chronic kidney disease in the NICE guideline on type 2 diabetes in adults. We also clarified the use of the term `male' in the 4-variable Kidney Failure Risk Equation.

See www.nice.org.uk/guidance/NG28 for more information.

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ISBN: 978-1-4731-4233-6

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Interventions to lower proteinuria

1.1 Review question

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

1.1.1 Introduction

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

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

1.1.2 Summary of the protocol

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

	○ cardiovascular impact, ○ anaemia • Health-related quality of life • Adverse outcome: ○ AKI, ○ 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. None of these references were included based on their 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 N=81	**Diabetes** Type 2 around 85% **CKD** diabetic nephropathy **Proteinuria** Urinary albumin/creatinine ratio ≥30 mg/mmol (300 mg/g)[a] **Age** 20 to 65 years	11 months	Spironolactone (aldosterone antagonist)	Placebo	• Reduction in albuminuria • Mortality: cardiovascular • Adverse outcome: hospitalisation
van den Meiracker, 2006 N=59	**Diabetes** Type 2 **CKD** Diabetic nephropathy **Proteinuria**	12 months	Spironolactone (aldosterone antagonist)	Placebo	• Reduction in proteinuria • 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 **Age** 20 to 80 years				
ARB compared to placebo					
Brenner, 2001 N=1513	**Diabetes** Type 2 **CKD** Nephropathy **Proteinuria** Urinary protein excretion ≥0.5 g/24 h **Age** 31 to 70 years	3.4 years (range 2.3 to 4.6)	Losartan (ARB)	Placebo	• Reduction in albuminuria • CKD progression: occurrence of end stage kidney disease • Mortality: all cause • Morbidity: non-fatal CV events • Adverse outcome: hospitalisation
Lewis, 2001 N=1715	**Diabetes** Type 2 **CKD** Diabetic nephropathy **Proteinuria** Urinary protein excretion at least 900 mg/24 h **Age** 30 to 70 years	2 years	Irbesartan (ARB)	Placebo	• Reduction in proteinuria • CKD progression: occurrence of end stage kidney disease • Mortality: all cause
Mehdi, 2009 N=81	See above	11 months	Losartan (ARB)	Placebo	See above
CCB compared to placebo					
Lewis, 2001 N=1715	See above	2 years	Amlodipine (CCB)	Placebo	See above
ACE-I compared to ARB					
Krairittichai, 2009 N=80	**Diabetes** Type 2 **CKD** Diabetic nephropathy **Proteinuria** Urinary protein/creatinine ratio >50 mg/mmol (0.5 g/g)[a] **Age**	6 months	Enalapril (ACE-I)	Telmisartan (ARB)	• Reduction in proteinuria

Author, year, sample size	Population	Follow-up	Intervention	Comparator	Outcome
	Adults				
Saglimbene, 2018 N=1287	**Diabetes** Type 2 around 95% **CKD** **Proteinuria** 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] **Age** ≥18 years	2.7 years	ACE inhibitor	ARB	• CKD progression: occurrence of end stage kidney disease • Mortality: all cause • Mortality: cardiovascular • Morbidity: non-fatal CV events • Adverse outcome: hospitalisation ; hypotension
ARB compared to aldosterone antagonist					
Mehdi, 2009 N=81	See above	11 months	Losartan (ARB)	Spironolactone (aldosterone antagonist)	See above
ARB compared to CCB					
Lewis, 2001 N=1715	See above	2 years	Irbesartan (ARB)	Amlodipine (CCB)	See above
Gliptin compared to placebo					
Groop, 2017 N=360	**Diabetes** Type 2 **CKD** eGFR ≥30 mL/min/1.73 m² **Proteinuria** Urinary albumin/creatinine ratio 3 to 300 mg/mmol (30 to 3000 mg/g)[a] **Age** 18 to 80 years	6 months	Linagliptin (gliptin)	Placebo	• Reduction in albuminuria • Mortality: all cause • Adverse outcome: hypoglycaemia
Thiazolidinedione compared to placebo					
Kanjanabuch, 2009 N=41	**Diabetes** Type 2 **CKD** Biopsy-proven immunoglobulin A nephropathy **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 **Age** Adults				
SGLT2 inhibitor compared to placebo					
Neuen, 2019 N=3026	**Diabetes** Type 2 **CKD** Microalbuminuria, macroalbuminuria **Proteinuria** 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] **Age** ≥30 years	6 years	Canagliflozin (SGLT2 inhibitor)	Placebo	• Mortality: all cause
Perkovic, 2019 N=4401	**Diabetes** Type 2 **CKD** eGFR 30 to <90 ml per minute per 1.73 m² **Proteinuria** Urinary albumin/creatinine ratio >30 to 500 mg/mmol (300 to 5000 mg/g)[a] **Age** ≥30 years	2.6 years (range 0.02 to 4.53)	Canagliflozin (SGLT2 inhibitor)	Placebo	• CKD progression: occurrence of end stage kidney disease • Mortality: all cause • Mortality: cardiovascular • Adverse outcome: hospitalisation; acute kidney injury
Pollock, 2019 N=461	**Diabetes** Type 2 **CKD** eGFR 20 to 80 mL/min/1.73 m² **Proteinuria** Urinary albumin/creatinine ratio 3 to 350 mg/mmol (30 to 3500 mg/g)[a] **Age** ≥18 years	6 months	Dapagliflozin (SGLT2 inhibitor)	Placebo	• Reduction in albuminuria • Mortality: all cause • Adverse outcome: hypoglycaemia

Author, year, sample size	Population	Follow-up	Intervention	Comparator	Outcome
SGLT2 inhibitor + gliptin compared to SGLT2 inhibitor					
Pollock, 2019 N=461	See above	6 months	Dapagliflozin (SGLT2 inhibitor) plus Saxagliptin (gliptin)	Dapagliflozin (SGLT2 inhibitor)	See above
Exercise compared to no intervention					
Leehey, 2009 N=13	**Diabetes** Type 2 **CKD** stage 2-4 CKD (eGFR 15-90 mL/min/1.73 m²) **Proteinuria** Urinary protein/creatinine ratio >20 mg/mmol (200 mg/g)[a] **Age** Adults	6 months	Exercise	No intervention (patients did not participate in any exercise training)	• Reduction in proteinuria • Reduction in albuminuria
Exercise compared to diet					
Leehey, 2016 N=36	**Diabetes** Type 2 **CKD** CKD stages 2–4 (eGFR 15 to 90 ml/min/ 1.73 m²) **Proteinuria** Urinary protein/creatinine ratio >20 mg/mmol (200 mg/g)[a] **Age** Adults	12 months	Exercise plus Diet	Diet-Alone	• Health-related quality of life
ACE-I + ARB compared to ARB					
Fried, 2013 N=1448	**Diabetes** Type 2 **CKD** eGFR 30.0 to 89.9 ml/min/1.73 m² **Proteinuria** Urinary albumin/creatinine ratio ≥30 mg/mmol (300 mg/g)[a] **Age** Adults	2.2 years	Losartan (ARB) plus Lisinopril (ACE-I)	Losartan (ARB) plus Placebo	• Reduction in albuminuria • CKD progression: occurrence of end stage kidney disease • Mortality: all cause • Morbidity: non-fatal CV events • Adverse outcome: acute kidney injury

Author, year, sample size	Population	Follow-up	Intervention	Comparator	Outcome
Saglimbene, 2018 N=1287	See above	2.7 years	ACE inhibitor plus ARB	ARB	See above
ACE-I + ARB compared to ACE-I					
Saglimbene, 2018 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 N=166	**CKD** creatinine clearance 20-70 mL/min per 1.73m² **Proteinuria** Urinary protein excretion >1 g/24 h **Age** 18 to 70 years	3 years	Ramipril (ACE-I)	Placebo	• Reduction in proteinuria • CKD progression: occurrence of end stage kidney disease • Mortality: all cause • Mortality: cardiovascular • Morbidity: non-fatal CV events
Lewis, 1993 N=409	**Diabetes** Type 1 **CKD** Diabetic nephropathy **Proteinuria** Urinary protein excretion ≥500 mg/24 h **Age** 18 to 49 years	3 years	Captopril (ACE-I)	Placebo	• CKD progression: occurrence of end stage kidney disease • Mortality: all cause
Ruggenenti, 1999 N=186	**CKD** chronic nephropathy **Proteinuria** Urinary protein excretion ≥1 g/24 h **Age** 18 to 70 years	6 years	Ramipril (ACE-I)	Placebo	• CKD progression: occurrence of end stage kidney disease • Mortality: cardiovascular
Aldosterone antagonist compared to placebo					
Ando, 2014b N=336	**CKD** eGFR ≥50 mL/min per 1.73 m² **Proteinuria** Urinary albumin/creatinine ratio 3 to 59	12 months	Eplerenone (aldosterone antagonist)	Placebo	• Reduction in albuminuria • Mortality: all cause • Morbidity: non-fatal CV events

Author, year, sample size	Population	Follow-up	Intervention	Comparator	Outcome
	mg/mmol (30–599 mg/g)[a] **Age** 20 to 79 years				
ARB compared to placebo					
Li, 2006 N=109	**CKD** Biopsy-confirmed immunoglobulin A nephropathy **Proteinuria** Urinary protein excretion ≥1 g/24 h **Age** ≥18 years	2 years	Valsartan (ARB)	Placebo	• Reduction in proteinuria • Morbidity: non-fatal CV events
ARB compared to control					
Lee, 2011 N=32	**CKD** Chronic non-diabetic CKD **Proteinuria** Urinary protein/creatinine ratio 40 to 200 mg/mmol (0.4 to 2.0 g/g)[a] **Age** 20 to 65 years	24 months	Losartan (ARB)	Control (usual antihypertensive therapy except ACE inhibitors and ARBs)	• Reduction in proteinuria • Reduction in albuminuria
ACE-I compared to ARB					
Luño, 2002 N=46	**CKD** eGFR >50 mL/min/1.73m² **Proteinuria** Urinary protein excretion >2 g/24 h **Age** 18 to 80 years	6 months	Lisinopril (ACE-I)	Candesartan (ARB)	• Reduction in proteinuria
Matsuda, 2003a N=52	**CKD** Immunoglobulin A nephropathy; membranous nephropathy; focal segmental glomerulosclerosis; and proliferative glomerulonephritis **Proteinuria** Urinary protein excretion >0.3 g/24 h **Age** Adults	11 months	ACE-I	ARB	• Reduction in proteinuria
Matsuda, 2003b	**CKD** Underlying renal diseases:	22 months	Perindopril (ACE-I)	Candesartan (ARB)	• Reduction in proteinuria

Author, year, sample size	Population	Follow-up	Intervention	Comparator	Outcome
N=62	proliferative glomerulonephritis, membranous nephropathy, or focal segmental glomerulosclerosis **Proteinuria** Urinary protein excretion >0.5 g/24 h **Age** Adults		Or Trandolapril (ACE-I)	Or Losartan (ARB)	
ARB compared to CCB					
Iino, 2003 N=93	**CKD** 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 **Proteinuria** Urinary protein excretion ≥0.5 g/24 h **Age** 20 to 75 years	12 months	Losartan (ARB)	Amlodipine (CCB)	• Reduction in proteinuria • Morbidity: non-fatal CV events
Praga, 2003 N=97	**CKD** chronic proteinuric nephropathy of non-diabetic cause **Proteinuria** Urinary protein excretion >1.5 g/24 h **Age** ≥18 years	4.5 months	Losartan (ARB)	Amlodipine (CCB)	• Reduction in proteinuria
Subcutaneous insulin infusion compared to conventional insulin					
Ciavarella, 1985 N=10	**Diabetes** Type 1 **CKD** Diabetic nephropathy **Proteinuria** Urinary protein excretion >0.5 g/24 h **Age** Adults	12 months	Subcutaneous insulin infusion	Conventional insulin	• Reduction in albuminuria
ACE-I + ARB compared to ARB					

Author, year, sample size	Population	Follow-up	Intervention	Comparator	Outcome
Luño, 2002 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 N=90	**CKD** chronic renal insufficiency **Proteinuria** Urinary protein excretion >1.0 g/24 h **Age** 35 to 79 years	3 years	Candesartan (ARB) plus ACE Inhibitor	ACE Inhibitors	• Reduction in proteinuria
Luño, 2002 N=46	See above	6 months	Candesartan (ARB) plus Lisinopril (ACE-I)	Lisinopril (ACE-I)	See above
ARB + CCB compared to ARB					
Ameen, 2016 N=140	**CKD** No details of CKD stage **Proteinuria** Urinary albumin/creatinine ratio >3.5 mg/mmol **Age** 20 to 70 years	6 months	Valsartan (ARB) and Amlodipine (ACE-I)	Valsartan (ARB)	• Reduction in albuminuria
ARB + diuretic compared to ARB					
Fujisaki, 2014 N=102	**CKD** eGFR ≥15 ml/min/1.73m² **Proteinuria** Urinary protein/creatinine ratio 30 mg/mmol (300 mg/g)[a] **Age** 20 to 74 years	12 months	Losartan plus Hydrochlorothiazide	Losartan	• Reduction in proteinuria
Spironolactone + conventional therapy compared to conventional therapy					
Bianchi, 2006 N=165	**CKD** 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	12 months	Conventional therapy plus spironolactone	Conventional therapy	• Reduction in proteinuria

Author, year, sample size	Population	Follow-up	Intervention	Comparator	Outcome
	no evidence of systemic diseases **Proteinuria** Urinary protein/creatinine ratio 100 to 390 mg/mmol (1.0 to 3.9 g/g)[a] **Age** Adults				

(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)				
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

ARB	Placebo	Effect size (95% CI)	Quality	Interpretation of effect
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)				
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 - Canagliflozin vs Placebo (type 2 diabetes)				
116/2202 (5.3%)	165/2199 (7.5%)	HR 0.68 (0.54 to 0.86)	MODERATE	Effect

SGLT2 inhibitor	Placebo	Effect size (95% CI)	Quality	Interpretation of effect
All-cause mortality				
169/2347 (7.2%)	201/2347 (8.6%)	RR 0.84 (0.69 to 1.02)	MODERATE	Effect
All-cause mortality - Dapagliflozin vs Placebo (type 2 diabetes)				
1/145 (0.69%)	0/148 (0%)	RR 3.06 (0.13 to 74.55)	MODERATE	Could not differentiate
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 - Canagliflozin vs Placebo (type 2 diabetes)				
110/2202 (5%)	140/2199 (6.4%)	HR 0.78 (0.61 to 1)	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%)	HR 0.85 (0.64 to 1.13)	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
Hospitalisation - Canagliflozin vs Placebo (type 2 diabetes)				
89/2202 (4%)	141/2199 (6.4%)	HR 0.61 (0.47 to 0.80)	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 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
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)				

Exercise	Diet	Effect size (95% CI)	Quality	Interpretation of effect
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
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
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

ACE-I	Placebo	Effect size (95% CI)	Quality	Interpretation of effect
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				

ARB	Placebo	Effect size (95% CI)	Quality	Interpretation of effect
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

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

ACE-I	ARB	Effect size (95% CI)	Quality	Interpretation of 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
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)				
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

ARB + Diuretic	ARB	Effect size (95% CI)	Quality	Interpretation of 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. A further paper was identified during consultation resulting in 15 studies included in the evidence review.

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.

One cost effectiveness study analysed the effect of canagliflozin (an SGLT2) on patients with both CKD and Type 2 diabetes. This study found that canagliflozin was cost saving from an NHS healthcare perspective.

Timing of antihypertensive therapy

Farmer 2014

Study	Comparators[1]	Costs differences[2]	QALY differences	ICER	Uncertainty	Applicability	Limitations
Farmer 2014 Systematic review and cost utility analysis NHS perspective Individual patient simulation 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. In both models, the results were sensitive to ACR progression, producing ICERs in excess of £40,000/QALY. <u>Type 1 diabetes</u> 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. <u>Type 2 diabetes</u> 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.

Adarkwah 2011a

Study	Comparators[1]	Costs[2]	Effects	ICER	Uncertainty	Applicability	Limitations
Adarkwah 2011 People aged 50 with diabetes mellitus Cost utility analysis Dutch health system perspective 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. When assuming a lower baseline risk of having macroalbuminuria, intervention 2 becomes dominant. 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			

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

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

Adarkwah 2011b

Study	Comparators	Costs[1]	Effects	ICER	Uncertainty	Applicability	Limitations
Adarkwah 2011 People aged 44 with advanced renal insufficiency, proteinuria and hypertension Cost utility analysis 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 Cost utility analysis People aged >30 years US health system 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). 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 Cost utility analysis People aged >25 years with sub-optimally managed diabetes, hypertension and proteinuria Australian healthcare provider perspective 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 People with type 1 diabetes Cost utility analysis 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 Individual patient simulation	+ ACE inhibitor (Standard)				administration of ACE inhibitors was priced at $32,972 (£34,513)/QALY. 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. The results were overall robust to one-way sensitivity 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	Comparators	Costs[2]	QALYs	ICER[3]	Uncertainty	Applicability	Limitations
Boulware 2003 Cost utility analysis US adults aged 50 Societal perspective	**People without hypertension or diabetes**				Results were not sensitive to starting age for screening. 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. 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. The screening strategy remained cost-effective with less frequent screening produced lower ICERs. 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 Cost utility analysis 50-year-old people with type 2 diabetes Lifetime horizon 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. 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 People with type 1 diabetes US third party 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. 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 People with advanced renal disease Cost utility analysis 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. 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) People with type 2 diabetes and microalbuminuria Cost utility analysis US health system 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. 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 Cost utility analysis People with type 2 diabetes US third party perspective 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 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 Cost utility analysis People with CKD stage 4[1] Taiwanese health system 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. 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 Cost utility analysis People with CKD stage 4 or 5 Italian NHS 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. 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.

SGLT2

Willis 2020

Study	Comparators	Costs[2]	QALYs	ICER	Uncertainty	Applicability	Limitations
Willis 2020 Cost effectiveness analysis People with CKD and Type 2 diabetes England NHS 10-year time horizon	Canagliflozin and Standard of Care[1]	£32,950	3.73	Dominates	The analysis was robust to differing time horizons, differing hazard ratios. However, if the eGFR evolves at the same rate then the ICER is £20,921. In probabilistic sensitivity analysis found that at a £0 threshold it is 96% likely that canagliflozin is cost effective which rises to 99% at a £30,000 threshold.	Directly applicable	Potentially serious limitations
	Standard of Care[1]	£37,656	3.45	Dominated			

[1]*Standard of Care includes the maximum tolerated dose of a renin-angiotensin-aladosterone system inhibitor.*

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 2014 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).

SGLT2 inhibitors

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 (SGLT2 inhibitor) compared to placebo:

- End stage kidney disease in adults with ACR ≥30 mg/mmol (HR 0.68 [95% CI 0.54, 0.86], 2.6 years follow-up, moderate 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)
- Hospitalisation for heart failure in adults with ACR ≥30 mg/mmol (HR 0.61 [95% CI 0.47, 0.80], median 2.6 years follow-up, moderate quality of evidence

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 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:

- Neuen, 2019 (n=2266, canagliflozin, CANVAS trial): 3 to 30 mg/mmol
- Neuen, 2019 (n=760, canagliflozin, CANVAS trial): ≥30 mg/mmol
- Perkovic, 2019 (n=4401, canagliflozin, CREDENCE trial): >30 to 500 mg/mmol
- Pollock, 2019 (n=461, dapagliflozin, DELIGHT trial): 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. The committee discussed the small increases in serum phosphate with the use of SGLT2 inhibitors which is not a significant issue.

The committee cautioned that SGLT2 inhibitors are not suitable for everyone and should only be used within their marketing authorisation. The committee highlighted that people taking these drugs should also have monitoring, in line with the advice in the BNF. Volume depletion was a particular issue of concern for the committee, as this may cause falls for people with frailty.

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 or type 1 diabetes and proteinuria or albuminuria (ACR ≥30 mg/mmol) who have hypertension.

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.

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 was one recently published cost-effectiveness study for SGLT2 inhibitors; the limited amount of evidence is likely due to all the licences until recently containing contraindications for people with CKD. The cost effectiveness analysis found that canagliflozin was cost saving and while the committee noted the limitations with the study, they felt that it was likely to be a cost-effective treatment and a recommendation for SGLT2 inhibitors should be introduced. 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 inhibitors used in people with diabetes and CKD are lower than in people without renal impairment, and the committee would not expect the drugs to have the same benefits for blood glucose control as in people with diabetes but without CKD. However, with benefits on proteinuria and overall kidney outcomes, they were confident that the overall clinical benefit in people with diabetic kidney disease would be as large as the benefits estimated in the technology appraisals for people with diabetes but not CKD. The committee were therefore confident that, with a at least as large a benefit for a similar cost, it is appropriate that these drugs are available earlier 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.

1.1.10 References – included studies

1.1.10.1 Effectiveness

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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: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE

		Searches will be restricted by: • English language • Human studies Searches will not be limited by date. The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion. 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. Exclusion: • people receiving renal replacement therapy (RRT) • people with acute kidney injury combined with rapidly progressive glomerulonephritis • people receiving palliative care.
7.	Intervention/Exposure/Test	Interventions to lower proteinuria • Blood pressure medication • Diabetes medication • Weight loss/Exercise • Dietary interventions (NaCl, protein) • Endothelin antagonists
8.	Comparator/Reference standard/Confounding factors	• No intervention • Placebo • Other intervention in class to lower proteinuria (for diabetes and blood pressure medication) • Other interclass intervention

9.	Types of study to be included	• RCTs • Systematic reviews of RCTs

10.	Other exclusion criteria	• Population:
		  ○ people receiving renal replacement therapy (RRT)
		  ○ people with acute kidney injury combined with rapidly progressive glomerulonephritis
		  ○ pregnant women
		  ○ people receiving palliative care.
		• Abstracts, conference presentations and theses
		• Non-human studies
		• 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
		• CKD progression: occurrence of end stage kidney disease (ESRD or ESKD as reported by the study)
		• Mortality (all-cause and cardiovascular)
		• Specific morbidity:
		  ○ fractures,
		  ○ advancement of renal bone disease,
		  ○ vascular calcification,
		  ○ cardiovascular impact,
		  ○ anaemia
		  ○ health-related quality of life
		• Adverse outcome:
		  ○ AKI,
		  ○ drug specific (hypotension/falls, hypoglycaemia, hospitalisation)
		
		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. 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). 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: • Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. • The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$. Meta-analyses will be performed in Cochrane Review Manager V5.3. 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 ☐ Diagnostic

		☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ 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** NICE Guideline Updates Team **5b Named contact e-mail** GUTprospero@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE)		
25.	Review team members	From the Guideline Updates Team: • Mr Chris Carmona • Dr Yolanda Martinez		

		• Ms Hannah Nicholas • Ms Lynda Ayiku • 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: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • 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 ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued

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

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. 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. 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. 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. 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. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. 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. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels. 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. 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. 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> Search Strategy: --- 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:

---

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:

---

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:

---

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)

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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)

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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

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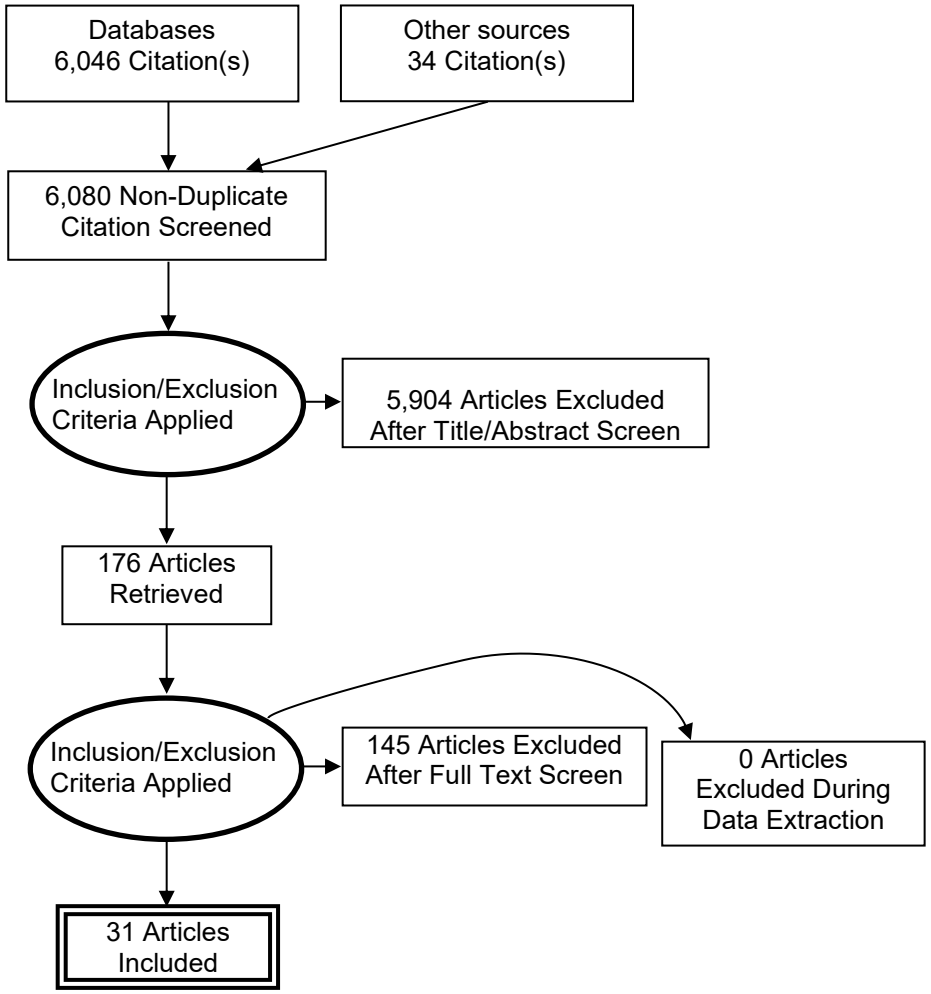
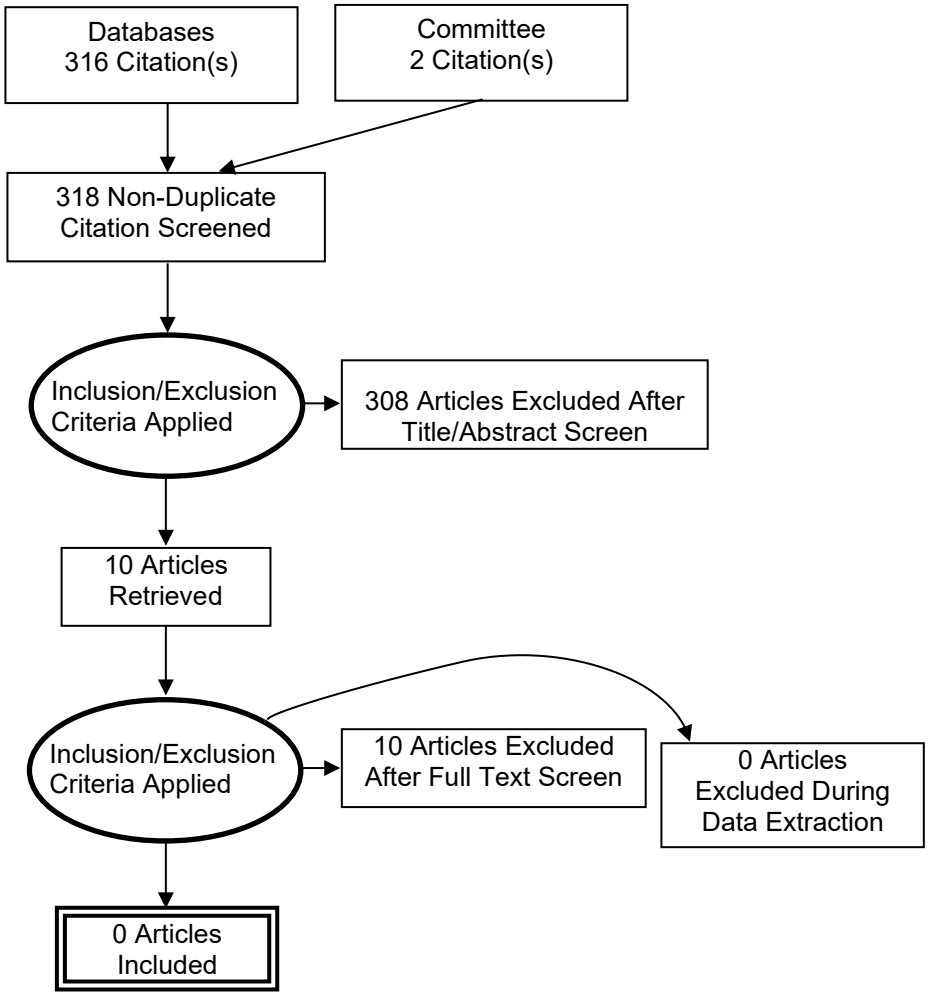
2	((chronic* or progressi*) near1 (renal* or kidney*))	489	Delete
3	((kidney* or renal*) near1 insufficien*)	320	Delete
4	(ckd*)	93	Delete
5	((kidney* or renal*) near1 fail*)	836	Delete
6	((endstage* or end-stage* or "end stage*") near1 (renal* or kidney))	354	Delete
7	(esrd* or eskd*)	150	Delete
8	(MeSH 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

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 No details of CKD stage Albuminuria urinary albumin: creatinine ratio >3.5 mg/mmol Age 20 to 70 years

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

Study arms

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

Loss to follow-up	None
Mean age (SD)	56.3 (8.2)

Condition specific characteristics	Baseline albuminuria 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 to be altered during the study period

Loss to follow-up	None
Mean age (SD)	53.0 (9.8)
Condition specific characteristics	Baseline albuminuria 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 eGFR 50 mL/min per 1.73 m² or more Albuminuria pre-treatment urinary albumin creatinine ratio in the first morning void urine (a mean of three measurements in three consecutive visits) of 30–599 mg/g Age 20 to 79 years Hypertension systolic blood pressures of 130–179 mm Hg or diastolic blood pressures of 80–99 mm Hg Treatment

	Patients had received an angiotensin-converting enzyme inhibitor, an angiotensin receptor blocker, or both, for at least 8 weeks
Exclusion criteria	Diabetes fasting blood glucose concentration ≥126 mg/dL or treatment with anti-diabetic drugs Other conditions 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 flutter 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 effects from mineralocorticoid receptor antagonists, angiotensin converting enzyme inhibitors, or angiotensin-receptor blockers Treatment administration of a mineralocorticoid receptor antagonist less than 8 weeks before registration; taking contraindicated drugs (including adreno corticosteroidal drugs, immunosuppressants, potassium-sparing diuretics, potassium supplementation, itraconazole, ritonavir, and nelfinavir); and treatment for more than 2 weeks with nonsteroidal anti-inflammatory drugs at registration
Sample size	336
Interventions	Blood pressure medication Eplerenone Placebo
Outcome measures	Reduction in albuminuria Mean percentage change from baseline for urinary albumin creatinine ratio Mortality: all cause Morbidity 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 Urinary albumin creatinine ratio (mg/g): mean 163.1 (SD 148.0) eGFR 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 Urinary albumin creatinine ratio (mg/g): mean 156.8 (SD 133.6) eGFR 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) 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 Clinical Research Institute, Frankfurt am Main, Germany
Inclusion criteria	CKD creatinine clearance 20-70 mL/min per 1.73m² with variation of <30% during the previous 3 months Proteinuria

	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) Age 18 to 70 years Hypertension 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 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 Treatment corticosteroids, non-steroidal anti-inflammatory drugs, or immunosuppressive drugs
Sample size	166
Condition specific characteristics	Additional notes This paper reports stratum 2 which contains participants with proteinuria ≥3 g/24 h
Interventions	Blood pressure medication Ramipril Placebo Additional notes 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

	Median percentage change from baseline for urinary protein excretion (g/24 h) at 1, 3, 6, 12, 24, 36 months CKD progression: occurrence of end stage kidney disease Requirement of dialysis or renal transplantation Mortality: all cause Mortality: cardiovascular Morbidity 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 Urinary protein excretion (g/24 h): mean 5.6 (SD 2.8) eGFR 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 Urinary protein excretion (g/24 h): mean 5.1 (SD 2.0) eGFR 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 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 Proteinuria Urinary protein/creatinine ratio (g/g) ranging from 1.0 to 3.9
Exclusion criteria	Diabetes Other conditions 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 Treatment steroids, nonsteroidal anti-inflammatory drugs, or immunosuppressive agents
Sample size	165
Interventions	Blood pressure medication Conventional therapy plus spironolactone vs Conventional therapy Additional notes

	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 hyperkalaemia 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 counselled 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 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 Urinary protein/creatinine ratio (g/g): mean 2.1 (SEM 0.08) eGFR 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 Urinary protein/creatinine ratio (g/g): mean 2.0 (SEM 0.07) eGFR 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 centres 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 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 decilitre (115 and 265 µmol per litre), with a lower limit of 1.5 mg per decilitre (133 µmol per litre) for male patients weighing more than 60 kg Proteinuria rate of urinary protein excretion of at least 0.5 g per day Albuminuria urinary albumin/creatinine ratio (mg/g) of at least 300 Age 31 to 70 years Diabetes type 2 diabetes
Exclusion criteria	Diabetes type 1 diabetes Other conditions

	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 Losartan Placebo Additional notes 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 Percentage reduction reported only for losartan in text and for both arms in graph CKD progression: occurrence of end stage kidney disease defined by the need for long-term dialysis or renal transplantation Mortality: all cause Morbidity Myocardial infarction Adverse outcome 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 urinary albumin/creatinine ratio (mg/g): median 1237 % Diabetes 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 urinary albumin/creatinine ratio (mg/g): median 1261 % Diabetes 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 Diabetic nephropathy Proteinuria Urinary protein excretion >0.5 g/24 h

	Diabetes Type 1 diabetes with poor glycaemic control
Interventions	Diabetes medication Subcutaneous insulin infusion vs Conventional insulin
Outcome measures	Reduction in albuminuria 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 Albumin excretion rate (mcg/min): mean 1161 (SD 803) % Diabetes 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 Albumin excretion rate (mcg/min): mean 1115 (SD 904) % Diabetes 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 eGFR 30.0 to 89.9 ml per minute per 1.73 m² Albuminuria urinary albumin/creatinine ratio at least 300 (mg/g) in a random sample Diabetes type 2 diabetes
Exclusion criteria	Other conditions non-diabetic kidney disease, a serum potassium level of more than 5.5 mmol per litre Treatment current treatment with sodium polystyrene sulfonate, or an inability to stop proscribed medications that increase the risk of hyperkalaemia
Sample size	1448
Interventions	Blood pressure medication Losartan plus Lisinopril

	Placebo Losartan plus Placebo Additional notes 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 hyperkalaemia, elevations in the potassium level (5.0 to 6.0 mmol per litre) were managed by means of dietary modification and adjustment in diuretics and other medications
Outcome measures	Reduction in albuminuria urinary albumin/creatinine ratio only reported as median CKD progression: occurrence of end stage kidney disease defined by the initiation of maintenance dialysis or an eGFR of <15 ml per minute per 1.73 m² Mortality: all cause Morbidity Myocardial infarction; Congestive heart failure; Stroke Adverse outcome 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 urinary protein/creatinine ratio (g/g): median 2.1 (interquartile range 1.1, 3.2) Baseline albuminuria urinary albumin/creatinine ratio (mg/g): median 842 (interquartile range 495, 1698) % Diabetes 100 (type 2 diabetes) eGFR mean 53.6 (SD 15.5) mL/min/1.73m² Additional notes 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 urinary protein/creatinine ratio (g/g): median 1.6 (interquartile range 0.9, 3.0) Baseline albuminuria urinary albumin/creatinine ratio (mg/g): median 862 (interquartile range 488, 1789) % Diabetes 100 (type 2 diabetes) eGFR mean 53.7 (SD 16.2) mL/min/1.73m²

	Additional notes 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 eGFR was 15 ml/min/1.73m² or more Proteinuria urinary protein/creatinine ratio (mg dl-1/mg dl-1): for the 8 weeks before the study commencing exceeded 300 mg/g Age 20 to 74 years Hypertension 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 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; hyperkalaemia (5.5mEq l-1 or more) Treatment undergoing thiazide diuretics or thiazide-like diuretics administration
Interventions	Blood pressure medication Losartan vs Losartan plus Hydrochlorothiazide Additional notes Antihypertensive drugs other than diuretics, ACEI and ARB, were added when blood pressure did not decline to <130/80mmHg
Outcome measures	Reduction in proteinuria 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 urinary protein/creatinine ratio (mg/g): mean 1800 (SD 1630) eGFR 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 urinary protein/creatinine ratio (mg/g): mean 1740 (SD 1400) eGFR 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 eGFR ≥30 mL/min/1.73 m² Albuminuria 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 Age 18 to 80 years Diabetes type 2 diabetes, HbA1c 6.5% to 10.0% (48-86 mmol/mol) Treatment 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 Other body-mass index ≤40 kg/m²,
Exclusion criteria	Other conditions 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 Linagliptin Placebo

Outcome measures	Reduction in albuminuria urinary albumin/creatinine ratio at baseline and adjusted geometric mean for time-weighted average of percentage change from baseline with 95% confidence interval Mortality: all cause Adverse outcome 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 urinary albumin/creatinine ratio (mg/g): geometric mean 120.8 (geometric coefficient of variation ±152.9) % Diabetes 100 (type 2 diabetes) eGFR 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 urinary albumin/creatinine ratio (mg/g): geometric mean 131.9 (geometric coefficient of variation ±166.6) % Diabetes 100 (type 2 diabetes) eGFR 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

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 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 Proteinuria Urinary protein excretion ≥0.5 g/day Age 20 to 75 years Hypertension 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 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 Treatment 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 Losartan vs Amlodipine

	Additional notes 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 Urinary protein excretion (g/day) at baseline, 3 months and percentage change at 3 months Morbidity 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 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 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 Biopsy-proven immunoglobulin A nephropathy Proteinuria Urinary protein excretion ≥0.5 g/24 h despite receiving ACEI or ARB therapy Other 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 Receiving immunosuppressive agents or steroid (>10 mg/day of prednisolone)
Sample size	41
Interventions	Diabetes medication Pioglitazone Placebo Additional notes

	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 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 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 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 chronic renal insufficiency Proteinuria urinary protein excretion of >1.0 g/day Age 35 to 79 years Hypertension systolic blood pressure >130 and <180 mmHg, diastolic blood pressure >80 and <120 mmHg Other serum creatinine concentration of between 1.2 and 5.0 mg/dl
Exclusion criteria	Other conditions 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 Candesartan plus ACE Inhibitor vs ACE Inhibitors Additional notes 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

	Urinary protein excretion (g/day) at baseline and 3 years

Study arms

Candesartan plus ACE Inhibitor (N = 45)
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 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 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 Diabetic nephropathy Proteinuria Urinary protein/creatinine ratio >0.5 (g/g) Diabetes Type 2 diabetes Hypertension Treatment maximal recommended dose of ACE inhibitor (Enalapril 40 mg daily) over three months Other absence of any other clinical or laboratory evidence of other kidney disease
Exclusion criteria	Age <18 years Other conditions 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 Telmisartan vs Enalapril
Outcome measures	Reduction in proteinuria 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 Urinary protein/creatinine ratio (g/g): mean 2.64 (SD 1.81) % Diabetes 100 (type 2 diabetes) eGFR 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 Urinary protein/creatinine ratio (g/g): mean 1.96 (SD 1.57) % Diabetes 100 (type 2 diabetes) eGFR 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 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) Proteinuria 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 Age 20 to 65 years
Exclusion criteria	Diabetes Evidence or suspicion of diabetes mellitus Other conditions 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 Treatment Hypersensitivity or intolerance to ARBs
Interventions	Blood pressure medication Losartan vs control (usual antihypertensive therapy except ACE inhibitors and ARBs)
Outcome measures	Reduction in proteinuria 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 Mean urinary protein to creatinine ratio 0.13 g/mmol (SD 0.04) Baseline albuminuria Mean urinary albumin to creatinine ratio 0.10 g/mmol (SD 0.05) eGFR 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 Mean urinary protein to creatinine ratio 0.13 g/mmol (SD 0.04) Baseline albuminuria Mean urinary albumin to creatinine ratio 0.10 g/mmol (SD 0.05) eGFR 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 *(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 *(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 *(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

Section	Question	Answer
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 Centre
Study dates	Not reported
Duration of follow-up	52 weeks

Sources of funding	Department of Veterans Affairs
Inclusion criteria	CKD CKD stages 2–4 (eGFR 15 to 90 ml/min/ 1.73 m²) Proteinuria Urinary protein/creatinine ratio >200 mg/g for at least 3 months Diabetes Type 2 diabetes Other Body mass index >30 kg/m²
Exclusion criteria	Other conditions 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 Exercise plus Diet Dietary interventions (NaCl, protein) Diet alone
Outcome measures	Reduction in proteinuria Urinary protein/creatinine ratio reported as median and interquartile range Reduction in albuminuria Urinary albumin/creatinine ratio reported as median and interquartile range Health-related quality of life Centre 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 counselling, 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 Urinary protein/creatinine ratio (mg/g): median 625 (interquartile range 275, 1619) Baseline albuminuria Urinary albumin/creatinine ratio (mg/g): median 329 (interquartile range 94, 1307) % Diabetes 100 (type 2 diabetes) eGFR mean 40.9 (SD 18.1) mL/min/1.73m²

Diet-Alone (N = 18)
A nutritional counselling 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 Urinary protein/creatinine ratio (mg/g): median 626 (interquartile range 414, 1563)

	Baseline albuminuria Urinary albumin/creatinine ratio (mg/g): median 428 (interquartile range 161, 1191) % Diabetes 100 (type 2 diabetes) eGFR 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 stage 2-4 CKD (eGFR 15-90 mL/min/1.73 m²) Proteinuria Urinary protein/creatinine ratio (mg/g) >200 for ≥3 months Diabetes Type 2 diabetes Treatment ACE inhibitor or ARB, aspirin, and statin (if LDL >100) Other obesity (body mass index >30 kg/m²)
Exclusion criteria	Other conditions 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 Exercise No intervention
Outcome measures	Reduction in proteinuria Urinary protein/creatinine ratio (mg/g) and urinary protein excretion (mg/24 h) at baseline, 6 and 24 weeks Reduction in albuminuria 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 Urinary protein/creatinine ratio (mg/g): mean 565 (SD 600); Urinary protein excretion (mg/24 h): mean 1020 (SD 1081) Baseline albuminuria Urinary albumin/creatinine ratio (mg/g): mean 327 (SD 385) % Diabetes 100 (type 2 diabetes) eGFR 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 Urinary protein/creatinine ratio (mg/g): mean 347 (SD 178); Urinary protein excretion (mg/24 h): mean 542 (SD 258) Baseline albuminuria Urinary albumin/creatinine ratio (mg/g): mean 156 (SD 148) % Diabetes 100 (type 2 diabetes) eGFR 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 Diabetic nephropathy Proteinuria Urinary protein excretion ≥500 mg/24 h Age 18 to 49 years Diabetes Insulin-dependent diabetes mellitus for at least 7 years, with an onset before the age of 30 years Other Diabetic retinopathy, serum creatinine concentration ≤2.5 mg/dL (221 mmol/l)

Exclusion criteria	Other conditions 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 Captopril Placebo Additional notes 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 Reduction in proteinuria was only reported for the captopril arm CKD progression: occurrence of end stage kidney disease Dialysis or transplantation Mortality: all cause

Study arms

Captopril (N = 207)
25 mg 3 times daily

Loss to follow-up	27
% Female	38
Mean age (SD)	35 (7)

Condition specific characteristics	Baseline proteinuria Urinary protein excretion (mg/day): mean 2500 (SD 2500) % Diabetes 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 Urinary protein excretion (mg/day): mean 3000 (SD 2600) % Diabetes 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 Diabetic nephropathy Proteinuria Urinary protein excretion at least 900 mg/24 h Age 30 to 70 years Diabetes

	Documented diagnosis of type 2 diabetes mellitus Hypertension 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 Other serum creatinine concentration was required to be between 1.0 and 3.0 mg per decilitre (88 and 265 µmol per litre) in women and 1.2 and 3.0 mg per decilitre (106 and 265 µmol per litre) in men
Sample size	1715
Interventions	Blood pressure medication Irbesartan vs amlodipine Placebo Additional notes Antihypertensive agents other than ACE inhibitors, angiotensin-receptor blockers, and calcium channel 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 Percentage reduction in proteinuria (g/24 h) CKD progression: occurrence of end stage kidney disease indicated by the initiation of dialysis, renal transplantation, or a serum creatinine concentration of at least 6.0 mg per decilitre (530 µmol per litre) 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 Urinary protein excretion (g/24 h): median 2.9 (interquartile range 1.6, 5.4) Baseline albuminuria Urinary albumin excretion (g/24 h): median 1.9 (interquartile range 1.0, 3.8) % Diabetes 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 Urinary protein excretion (g/24 h): median 2.9 (interquartile range 1.6, 5.2) Baseline albuminuria Urinary albumin excretion (g/24 h): median 1.9 (interquartile range 1.0, 3.5) % Diabetes 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 Urinary protein excretion (g/24 h): median 2.9 (interquartile range 1.8, 5.2) Baseline albuminuria Urinary albumin excretion (g/24 h): median 1.9 (interquartile range 1.1, 3.5) % Diabetes 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 Biopsy-confirmed immunoglobulin A nephropathy (defined using standard morphological and immunohistochemical criteria) Proteinuria Urinary protein excretion at least 1 g/day Age at least 18 years Other 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 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 Treatment recent treatment (within 4 weeks of enrollment) with ACE inhibitors or ARBs
Sample size	109
Interventions	Blood pressure medication Valsartan

	Placebo Additional notes 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 Urinary protein excretion (g/day) at baseline, 12, 24, 52, 76 and 104 weeks, absolute changes and percentage of change Morbidity 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 Urinary protein excretion (g/day): mean 1.8 (SD 1.2) eGFR 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 Urinary protein excretion (g/day): mean 2.3 (SD 1.7) eGFR 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 eGFR >50 mL/min/1.73m² Proteinuria Urinary protein excretion >2 g/24 h in at least 2 collections Age 18 to 80 years Other 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 Other conditions 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), hyperkalaemia (>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 Treatment

	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 Additional notes 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 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 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 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 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 Immunoglobulin A nephropathy (n=8); membranous nephropathy (n=5); focal segmental glomerulosclerosis (n=1); and proliferative glomerulonephritis (n=38) Proteinuria Urinary protein excretion >0.3 g/24 h Hypertension >140 and/or 90 mmHg

	Other 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 Diabetic nephropathy, polycystic kidney disease, and chronic pyelonephritis
Sample size	52
Interventions	Blood pressure medication ACE-I vs ARB Additional notes 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 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 ACE-I-H 35.7
Mean age (SD)	ACE-I-L 50 (3) ACE-I-H 50 (4)
Condition specific characteristics	Baseline proteinuria

	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 ARB-H 33.3
Mean age (SD)	ARB-L 55 (2) ARB-H 53 (4)
Condition specific characteristics	Baseline proteinuria 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 Underlying renal diseases: proliferative glomerulonephritis (n＝58), membranous nephropathy (n＝ 2), or focal segmental glomerulosclerosis (n＝2) Proteinuria Urinary protein excretion >0.5 g/day Hypertension ＞140 and/or 90 mmHg Other Serum creatinine level ＜265 μmol/l or creatinine clearance ＞30 ml/min/1.72m²

Exclusion criteria	Other conditions diabetic nephropathy, polycystic kidney disease, or chronic pyelonephritis
Sample size	62
Interventions	Blood pressure medication Perindopril vs Trandolapril vs Candesartan vs Losartan 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 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 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 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 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 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 Centre for Research Resources General Clinical Research Centre
Inclusion criteria	Proteinuria 24 h urinary albumin/creatinine ratio ≥300 mg/g despite treatment with an ACEi or an ARB for at least 3 months Age 20 to 65 years Diabetes type 1 or type 2 diabetes mellitus Hypertension seated systolic blood pressure >130 mmHg
Exclusion criteria	Other conditions 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, haemoglobin 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 Losartan vs Spironolactone Placebo Additional notes A research dietitian counselled 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 Urinary albumin/creatinine ratio reported as percentage change at 48 weeks

	Mortality: cardiovascular stroke, heart failure, myocardial infarction Adverse outcome 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 Urinary albumin/creatinine ratio (mg/g): geometric mean 897 (95% confidence interval [CI] 611, 1316) % Diabetes 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 Urinary albumin/creatinine ratio (mg/g): geometric mean 1094 (95% CI 758, 1579) % Diabetes 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 Urinary albumin/creatinine ratio (mg/g): geometric mean 917 (95% CI 633, 1329) % Diabetes 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% (spironolactone), 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 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 Albuminuria Subgroups with microalbuminuria (urinary albumin/creatinine ratio 30 to <300 mg/g) and macroalbuminuria (urinary albumin/creatinine ratio ≥300 mg/g) Age 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) Diabetes

	Type 2 diabetes Other HbA1c levels ≥7.0% and ≤10.5%
Exclusion criteria	Other conditions eGFR <30 mL/min/1.73 m²
Sample size	3026
Interventions	Diabetes medication Canagliflozin 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 Macroalbuminuria: 30.0
Mean age (SD)	Microalbuminuria: 63.8 (8.3) Macroalbuminuria: 63.4 (8.3)
Condition specific characteristics	Baseline albuminuria 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) % Diabetes

	100 (type 2 diabetes) eGFR 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 Macroalbuminuria: 29.9
Mean age (SD)	Microalbuminuria: 64.2 (8.3) Macroalbuminuria: 64.0 (8.2)
Condition specific characteristics	Baseline albuminuria 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) % Diabetes 100 (type 2 diabetes) eGFR 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	Median 2.6 years (range 0.02 to 4.53)
Sources of funding	Janssen Research and Development
Inclusion criteria	CKD defined as an eGFR 30 to <90 ml per minute per 1.73 m² Albuminuria Urinary albumin/creatinine ratio >300 to 5000 mg/g Age ≥30 years Diabetes Type 2 diabetes

	Treatment 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 labelled dose or a dose not associated with unacceptable side effects Other glycated haemoglobin level of 6.5 to 12.0% (6.5 to 10.5% in Germany, according to a country amendment)
Exclusion criteria	Other conditions 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 Treatment 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 Canagliflozin Placebo Additional notes The use of other background therapy for glycaemic management and control of cardiovascular risk factors was recommended in accordance with local guidelines
Outcome measures	CKD progression: occurrence of end stage kidney disease eGFR <15 ml/min/1.73 m² or dialysis initiated/kidney transplantation Mortality: all cause Mortality: cardiovascular Adverse outcome 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 Urinary albumin/creatinine ratio (mg/g): median 923 (interquartile range 459, 1794) % Diabetes 100 (type 2 diabetes) eGFR 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 Urinary albumin/creatinine ratio (mg/g): median 931 (interquartile range 473, 1868) % Diabetes 100 (type 2 diabetes) eGFR

	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) 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 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) Albuminuria Urinary albumin/creatinine ratio 30 to 3500 mg/g Age 18 years or older Diabetes type 2 diabetes for more than 12 months Treatment 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 Other HbA1c of 7.0 to 11.0% (53 to 97 mmol/mol) at screening
Exclusion criteria	Other conditions 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) Treatment 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 Dapagliflozin plus Saxagliptin vs Dapagliflozin Placebo Additional notes

	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 24-h urinary albumin excretion (g/day) reported as median at baseline and 24 weeks and adjusted mean change from baseline Mortality: all cause Adverse outcome 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 Urinary albumin/creatinine ratio (mg/g): median 218.4 (interquartile range 74, 936) % Diabetes 100 (type 2 diabetes) eGFR 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 Urinary albumin/creatinine ratio (mg/g): median 270.0 (interquartile range 69, 751) % Diabetes 100 (type 2 diabetes) eGFR 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 Urinary albumin/creatinine ratio (mg/g): median 257.5 (interquartile range 80, 949) % Diabetes 100 (type 2 diabetes) eGFR 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

	chronic proteinuric nephropathy of non-diabetic cause Proteinuria Urinary protein excretion >1.5 g/24 h Age >18 years Hypertension systolic blood pressure >140 mm Hg while sitting and/or a diastolic blood pressure >90 mm Hg while sitting Other Serum creatinine ≤2.5 mg/dl
Exclusion criteria	Diabetes type 1 or type 2 diabetes Other conditions 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 Treatment patients who required diuretics because of oedema,
Sample size	97
Interventions	Blood pressure medication Losartan vs Amlodipine
Outcome measures	Reduction in proteinuria 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 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 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) 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

	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 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) Age 18 to 70 years Hypertension normotensive (defined as systolic <140 and diastolic <90 mm Hg without antihypertensive therapy) or hypertensive Treatment 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 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 Treatment corticosteroids, non-steroidal anti-inflammatory drugs, or immunosuppressive drugs
Sample size	186
Condition specific characteristics	Additional notes This paper reports stratum 2 which contains participants with proteinuria >1 to 2.9 g/24 h
Interventions	Blood pressure medication Ramipril Placebo Additional notes 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 Mortality: cardiovascular 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 Urinary protein excretion (g/day): mean 1.7 (SE 0.1) eGFR 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 Urinary protein excretion (g/day): mean 1.7 (SE 0.1) eGFR 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 moderate albuminuria (urinary albumin/creatinine ratio 30–299 mg/g) or severe albuminuria (urinary albumin/creatinine ratio ≥300 mg/g) Age ≥18 years Diabetes Type 1 or type 2 diabetes Hypertension systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or antihypertensive treatment Other one or more cardiovascular risk factors: current or recent smoking, hypertension, abdominal obesity, dyslipidaemia, or family history of premature cardiovascular events
Exclusion criteria	Other conditions pregnant, intended to become pregnant, had active malignancy (except basal cell carcinoma), r had substantially reduced life expectancy Treatment contraindication to ACE inhibitor or ARB
Sample size	1287
Interventions	Blood pressure medication

	ACE inhibitor vs ARB vs ACE inhibitor plus ARB
Outcome measures	CKD progression: occurrence of end stage kidney disease Mortality: all cause Mortality: cardiovascular Morbidity Non-fatal myocardial infarction, non-fatal stroke, Adverse outcome 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 Urinary albumin/creatinine ratio (mg/g): median 108 (interquartile range 55, 302) % Diabetes Type 2 diabetes 96.8 eGFR 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 Urinary albumin/creatinine ratio (mg/g): median 110 (interquartile range 52, 316) % Diabetes Type 2 diabetes 96.8 eGFR 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 Urinary albumin/creatinine ratio (mg/g): median 128 (interquartile range 57, 325) % Diabetes Type 2 diabetes 97.1 eGFR 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 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 Albuminuria 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 Age 20 to 80 years Diabetes Type 2 diabetes
Exclusion criteria	Other conditions 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 study if their serum potassium concentration remained >5.5 mmol/l with one tablet of study medication
Sample size	59
Interventions	Blood pressure medication Spironolactone Placebo Additional notes Apart from antidiabetic medication, antihypertensive medications were kept constant throughout the course of the study
Outcome measures	Reduction in proteinuria Urinary protein/creatinine ratio reported as percentage reduction with 95% confidence interval Reduction in albuminuria 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 Urinary protein/creatinine ratio (mg/mmol): geometric mean 111 (interquartile range 69, 173) Baseline albuminuria Urinary albumin/creatinine ratio (mg/mmol): geometric mean 64.6 (interquartile range 33.1, 107.7) % Diabetes 100 (type 2 diabetes) eGFR 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 Urinary protein/creatinine ratio (mg/mmol): geometric mean 145 (interquartile range 63, 262)

	Baseline albuminuria Urinary albumin/creatinine ratio (mg/mmol): geometric mean 101.6 (interquartile range 43.7, 285) % Diabetes 100 (type 2 diabetes) eGFR 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)

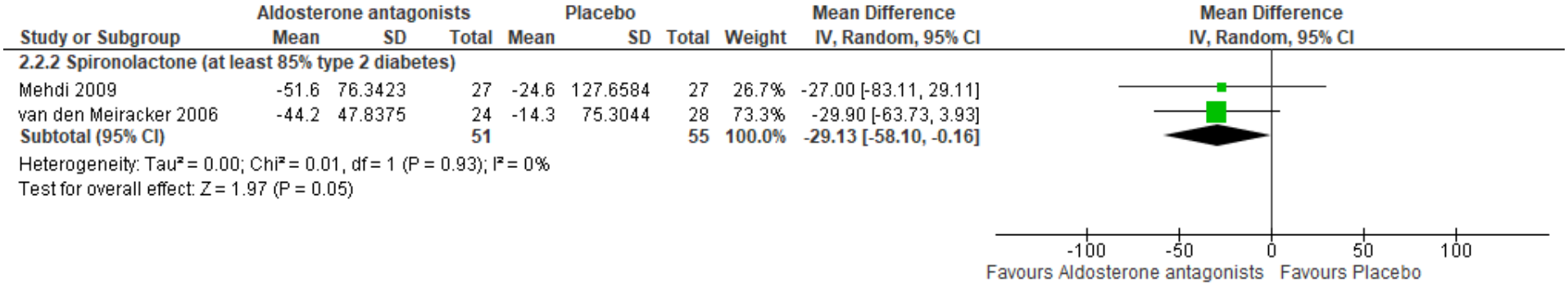


Figure 2 ARB vs Placebo; outcome: End stage kidney disease

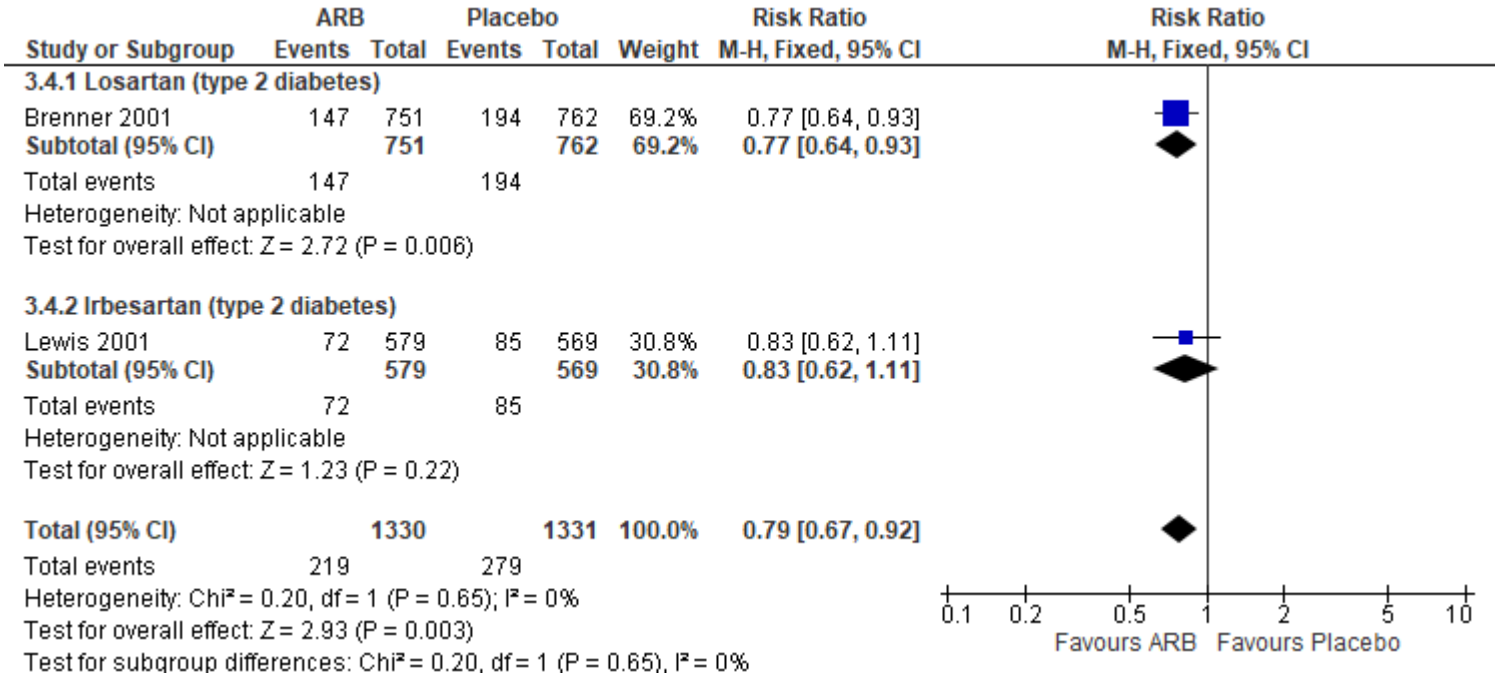


Figure 3 ARB vs Placebo; outcome: All-cause mortality

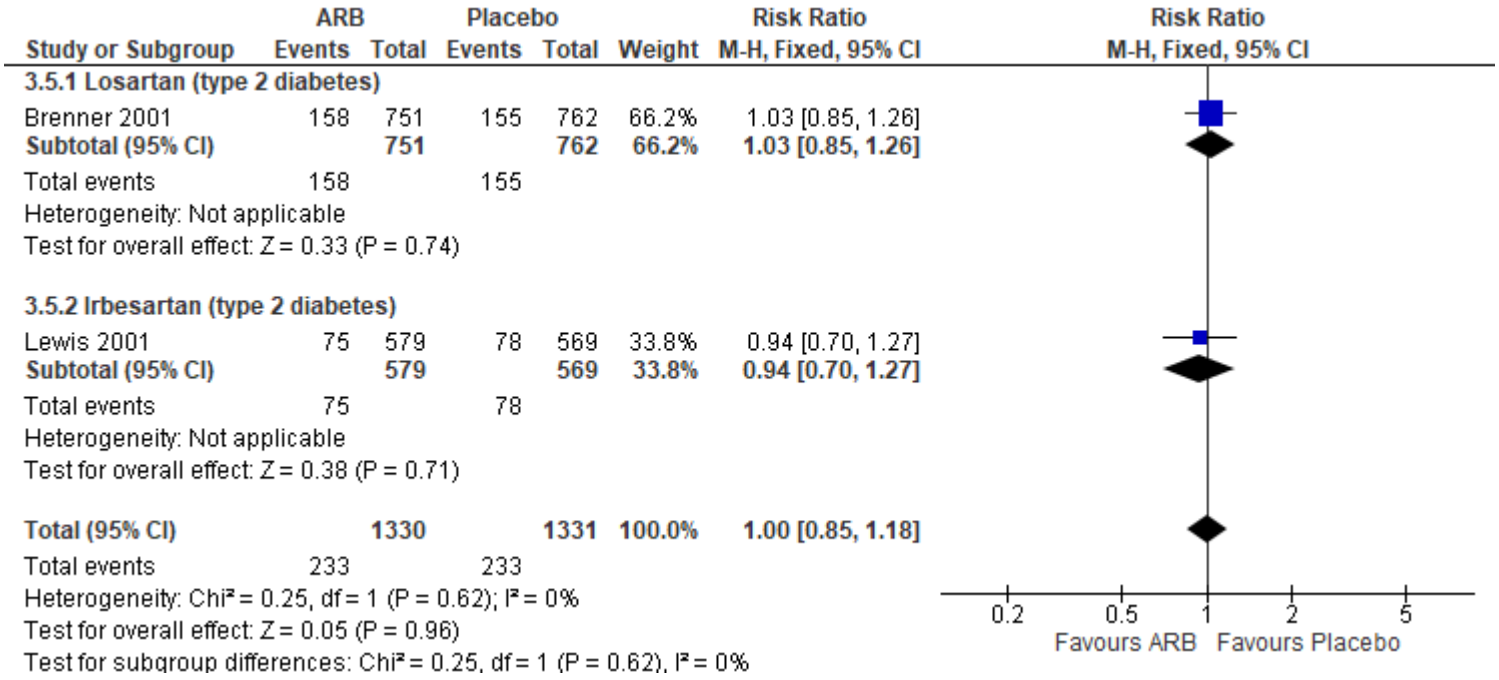


Figure 4 ARB vs Placebo; outcome: Non-fatal CV events

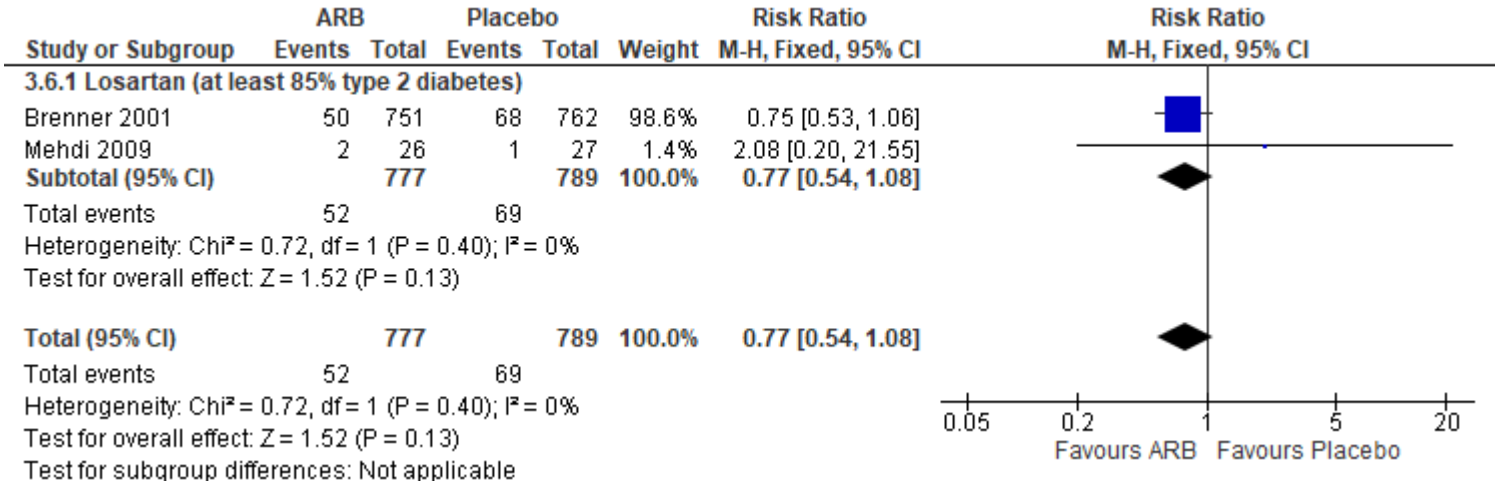


Figure 5 ARB vs Placebo; outcome: Hospitalisation

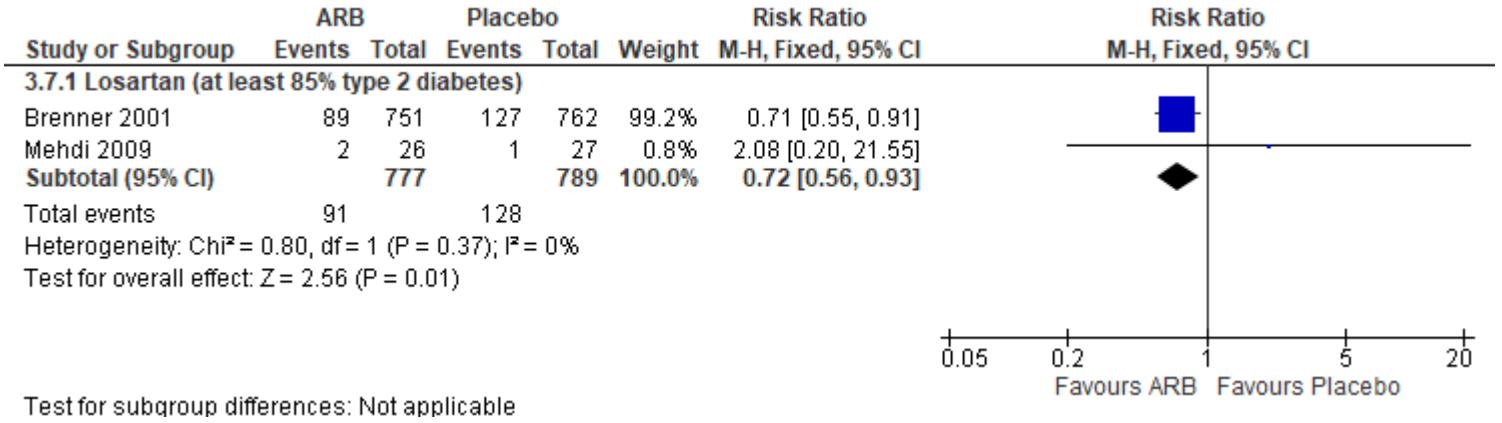
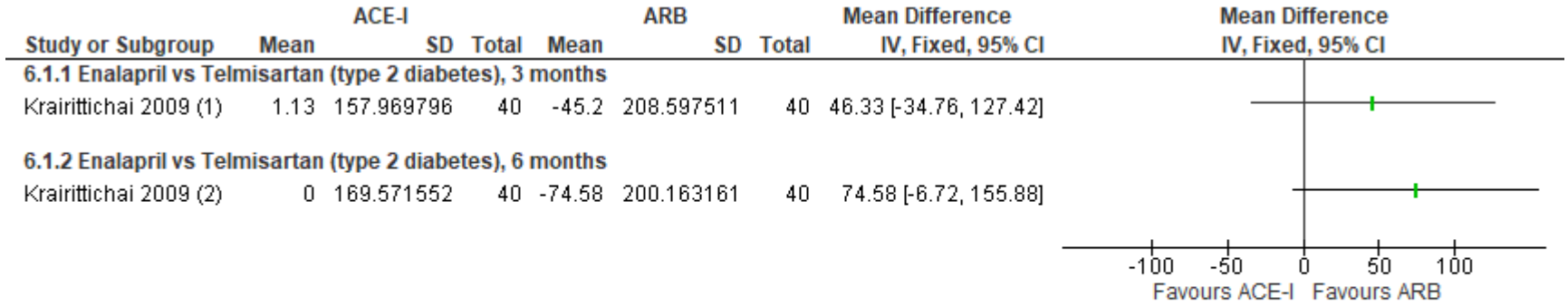


Figure 6 ACE-I vs ARB; outcome: Urinary protein/creatinine ratio (mg/mmol)



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: All-cause mortality

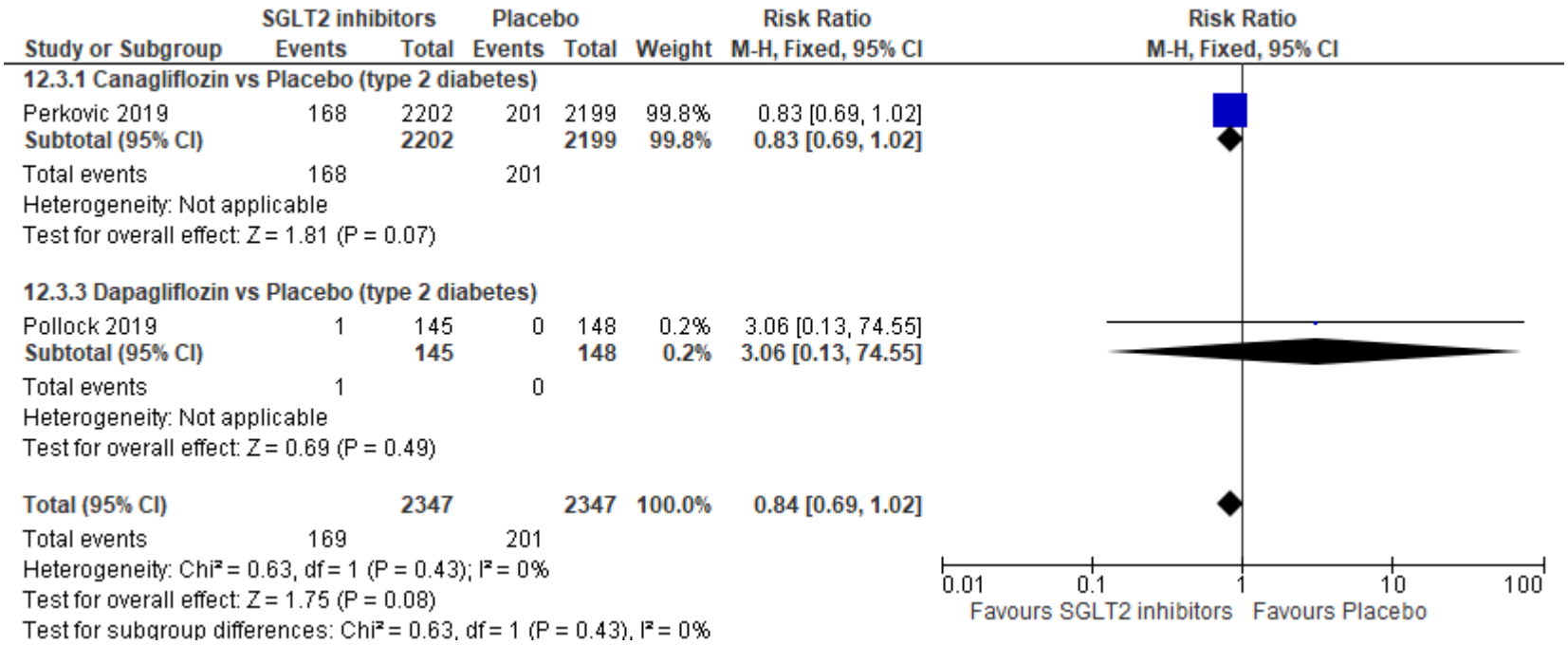


Figure 8 ACE-I + ARB vs ARB; outcome: End stage kidney disease

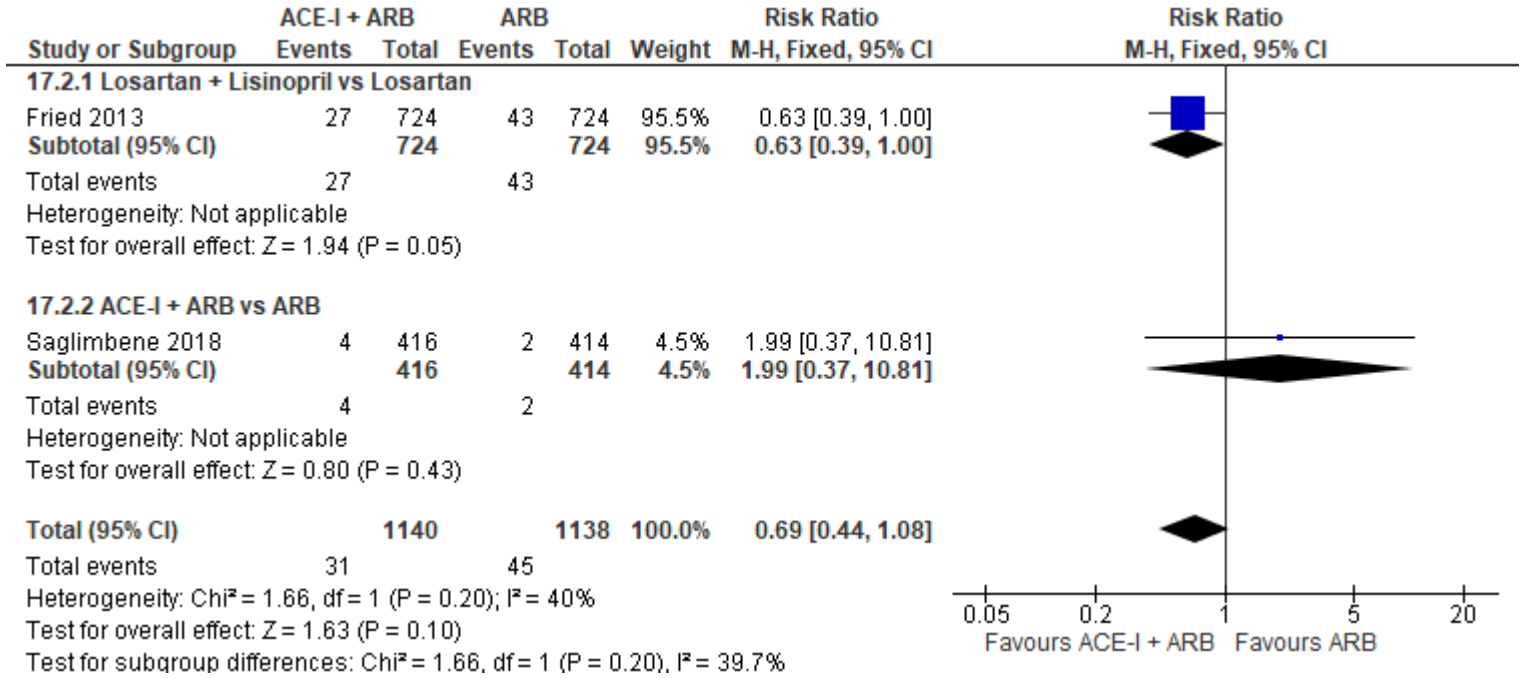


Figure 9 ACE-I + ARB vs ARB; outcome: All-cause mortality

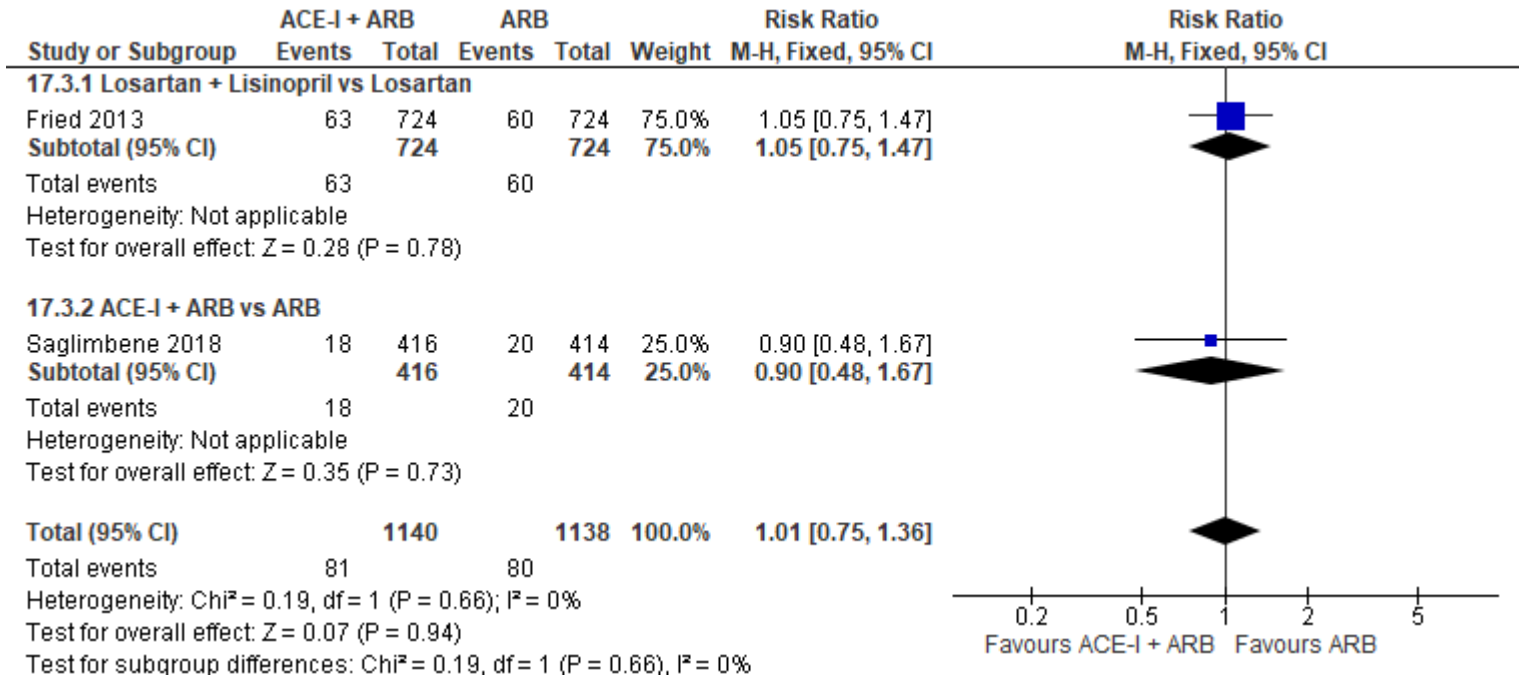
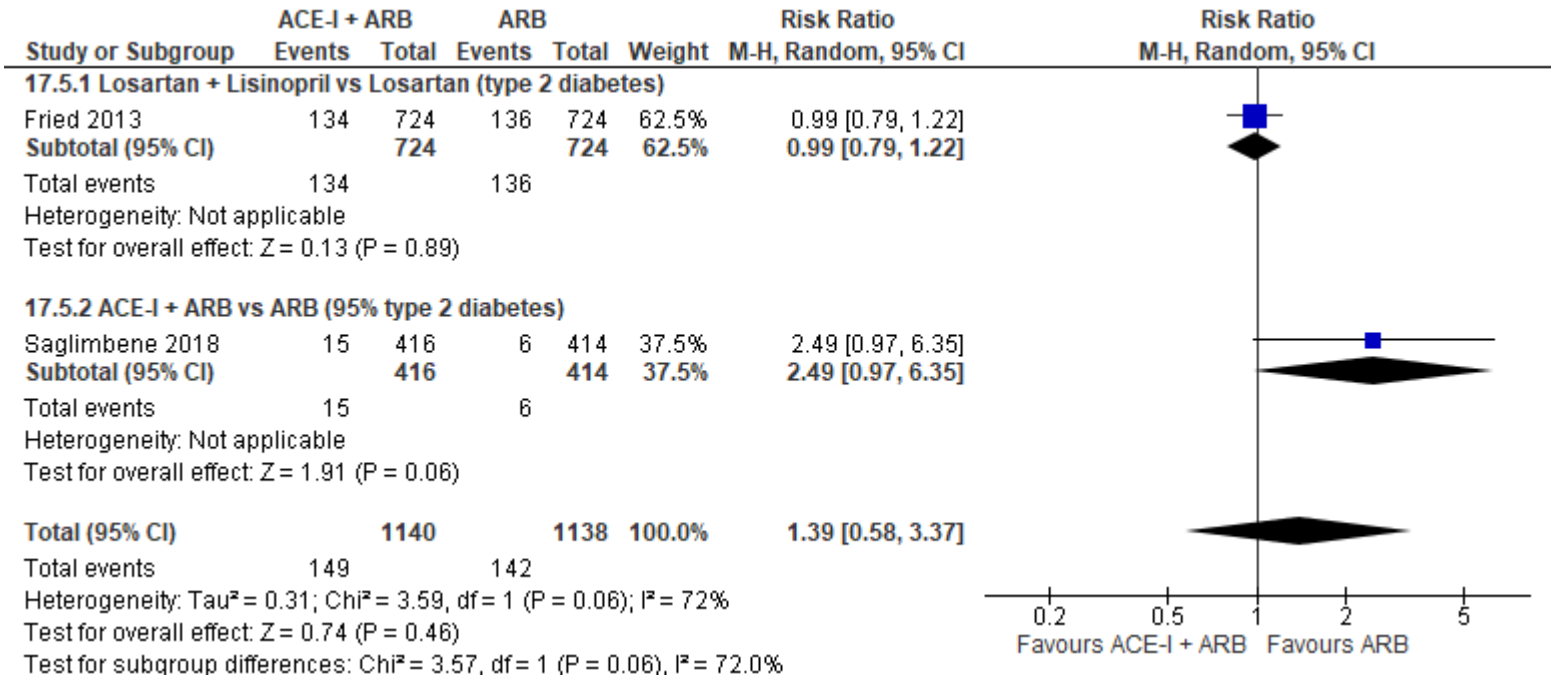


Figure 10 ACE-I + ARB vs ARB; outcome: Non-fatal CV events



Adults without type 2 diabetes

Figure 11 ACE-I vs Placebo; outcome: End stage kidney disease

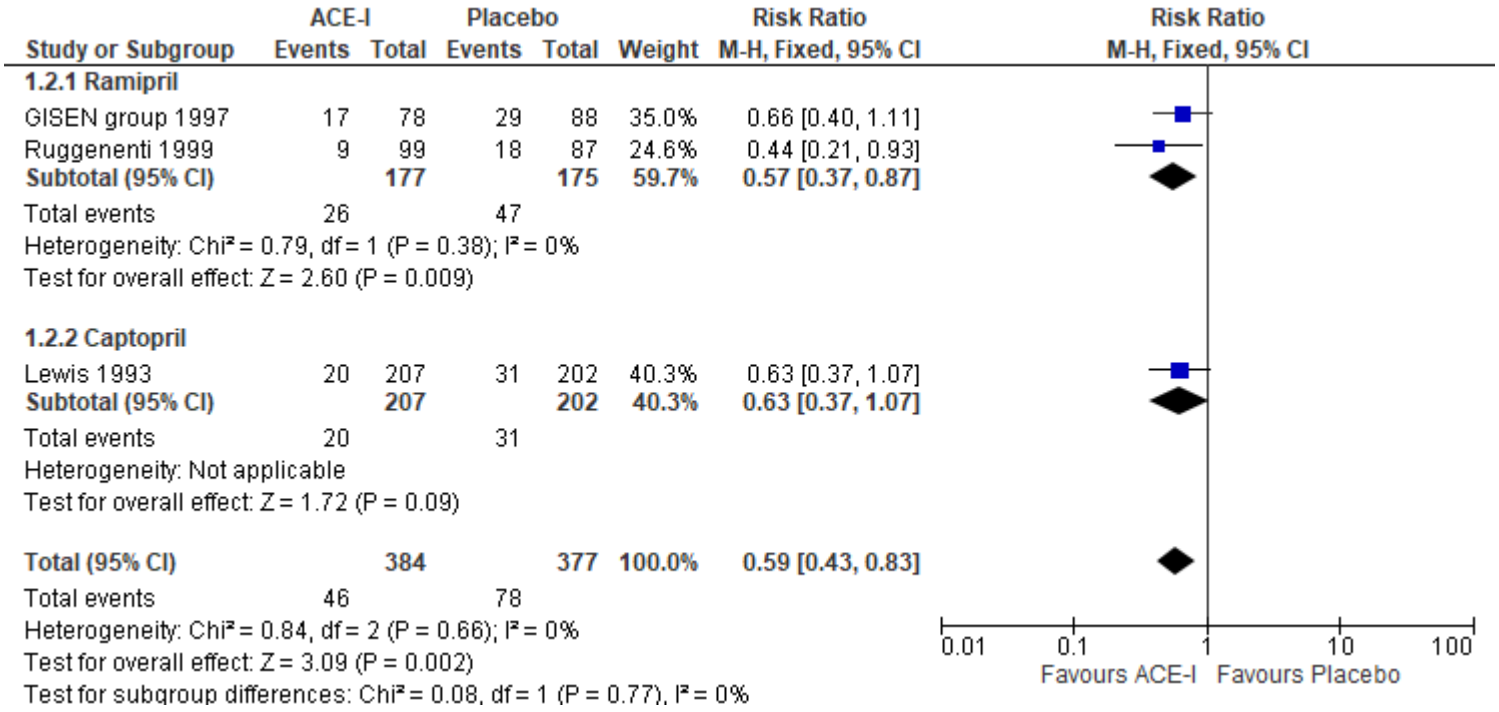


Figure 12 ACE-I vs Placebo; outcome: All-cause mortality

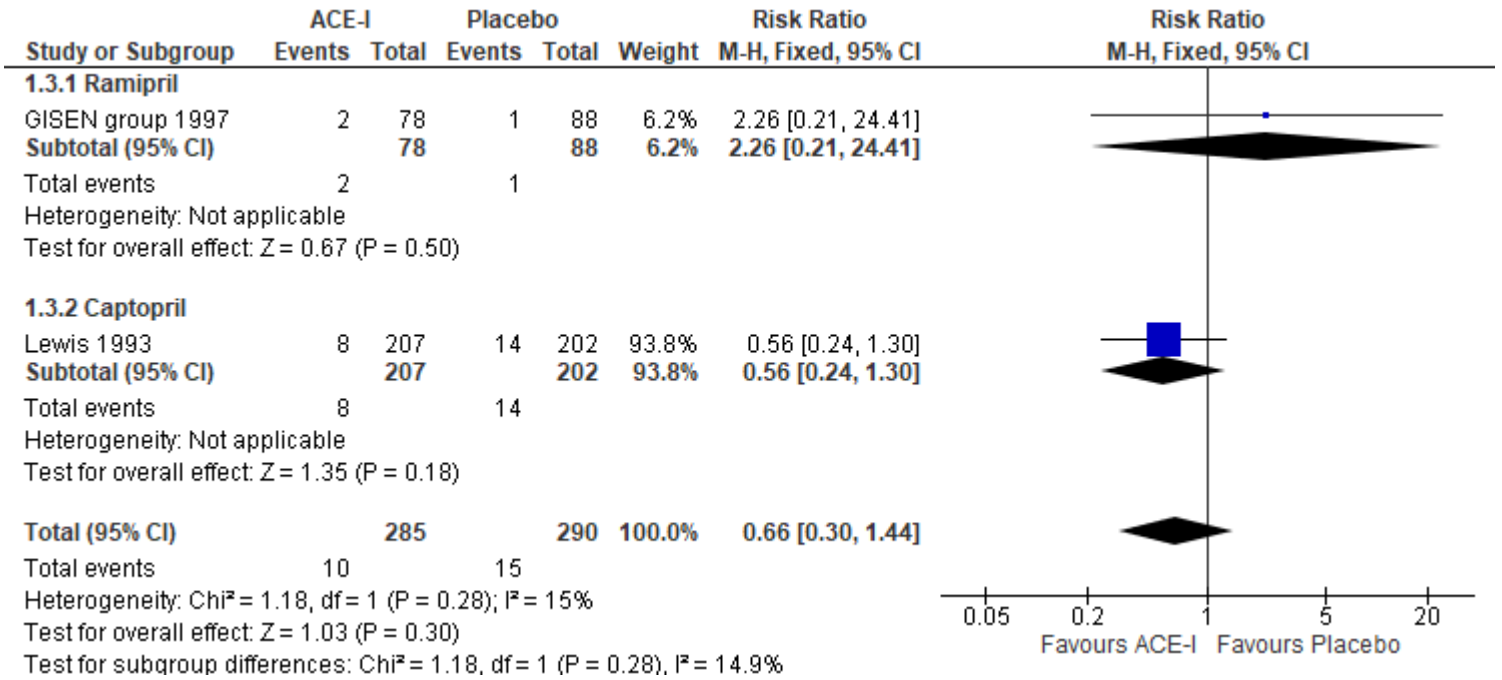


Figure 13 ACE-I vs Placebo; outcome: CV mortality

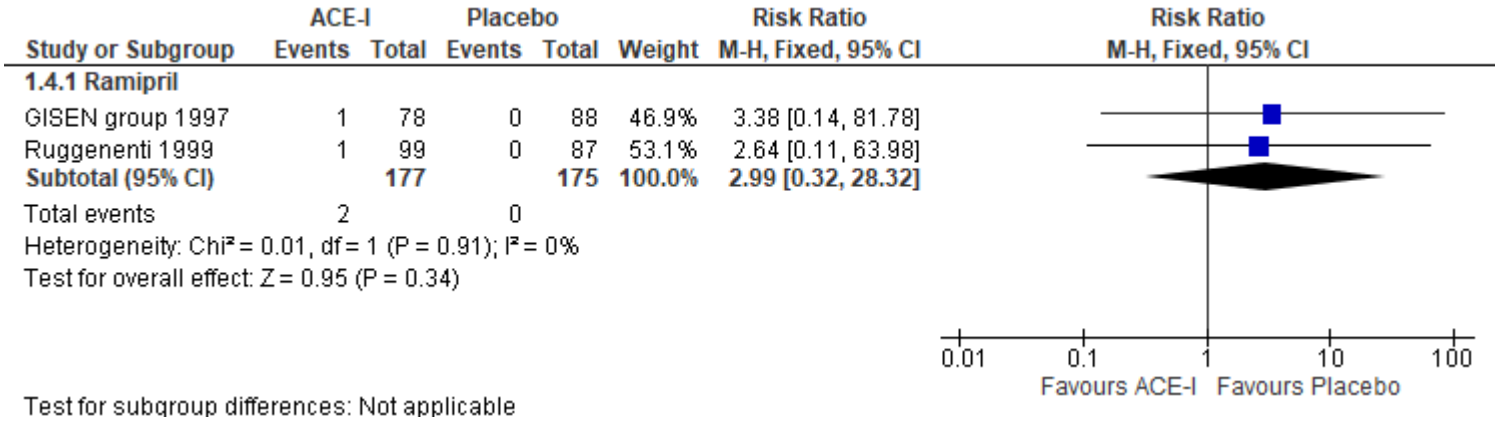


Figure 14 ACE-I vs Placebo; outcome: Non-fatal CV events

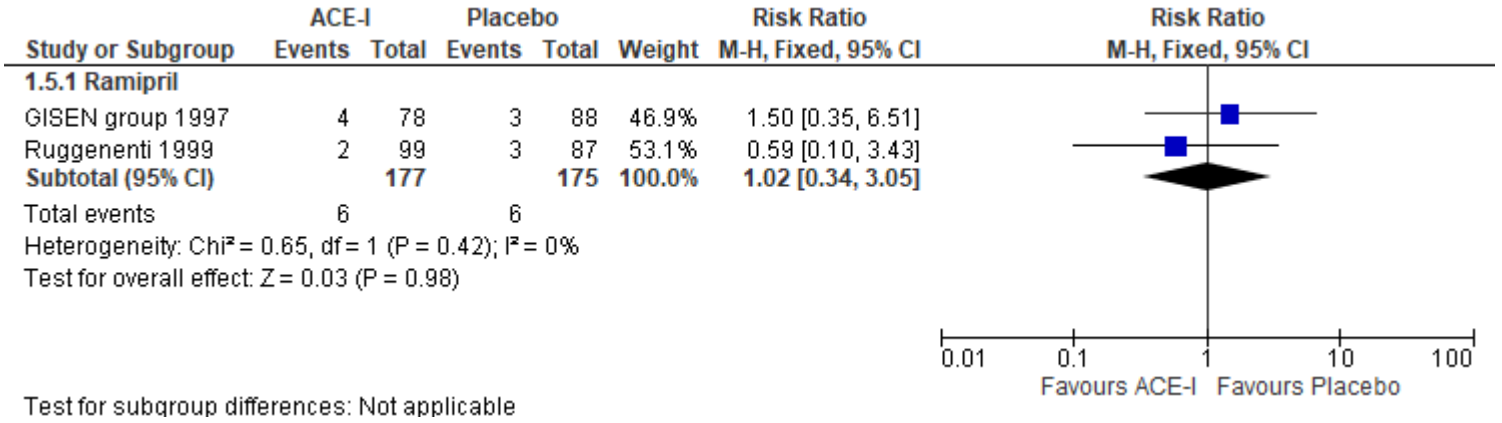


Figure 15 ARB vs Placebo; outcome: Urinary albumin excretion (g/24 h)

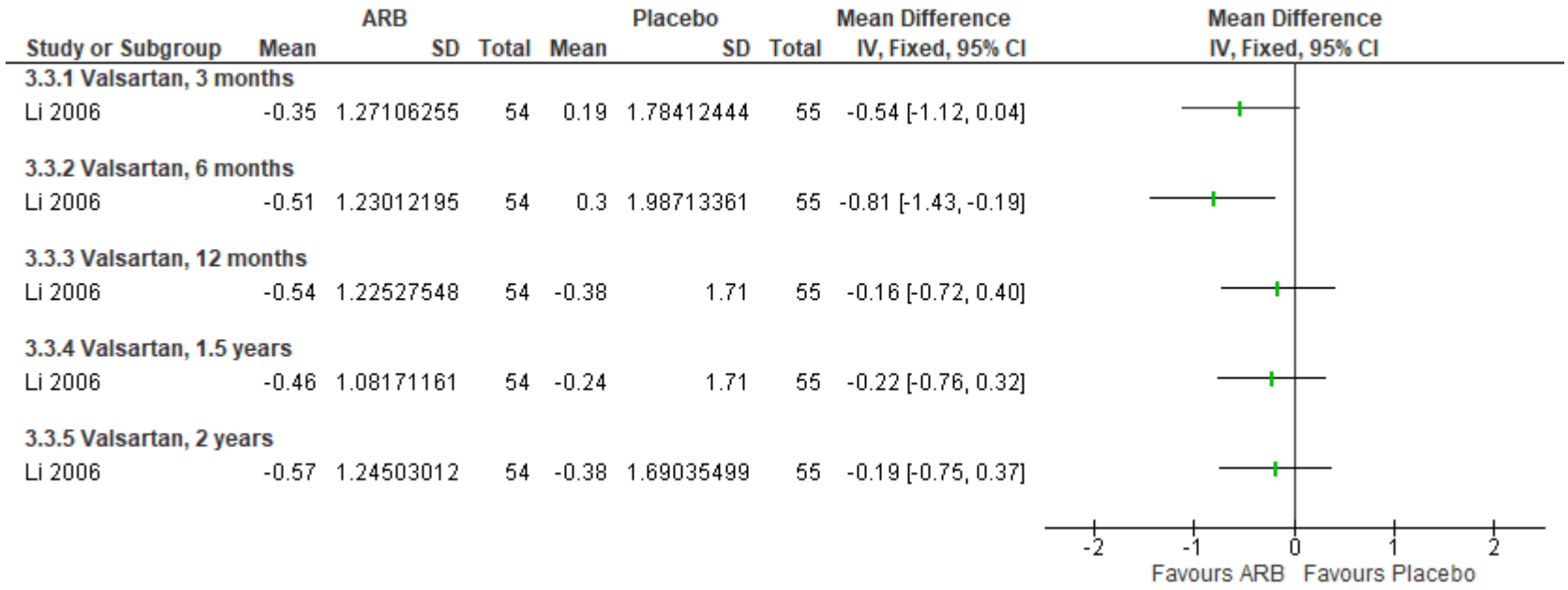
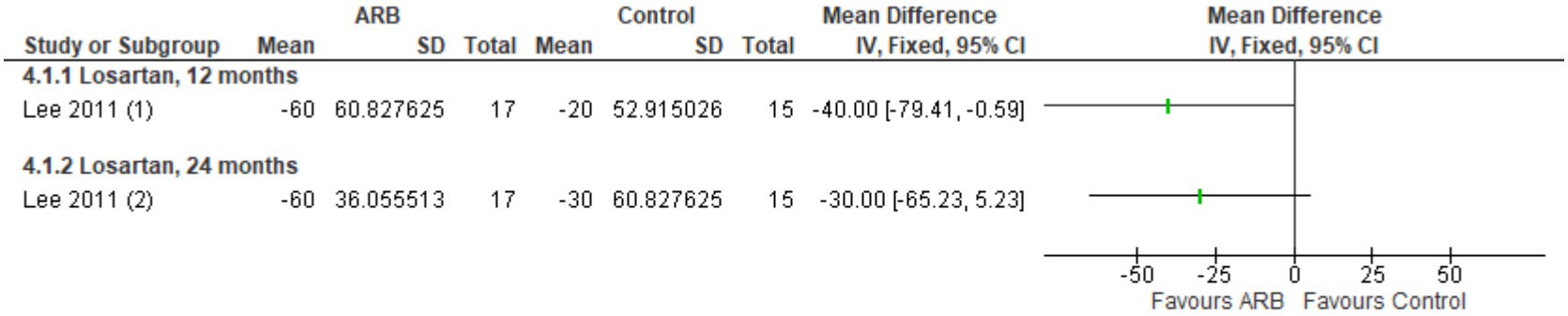
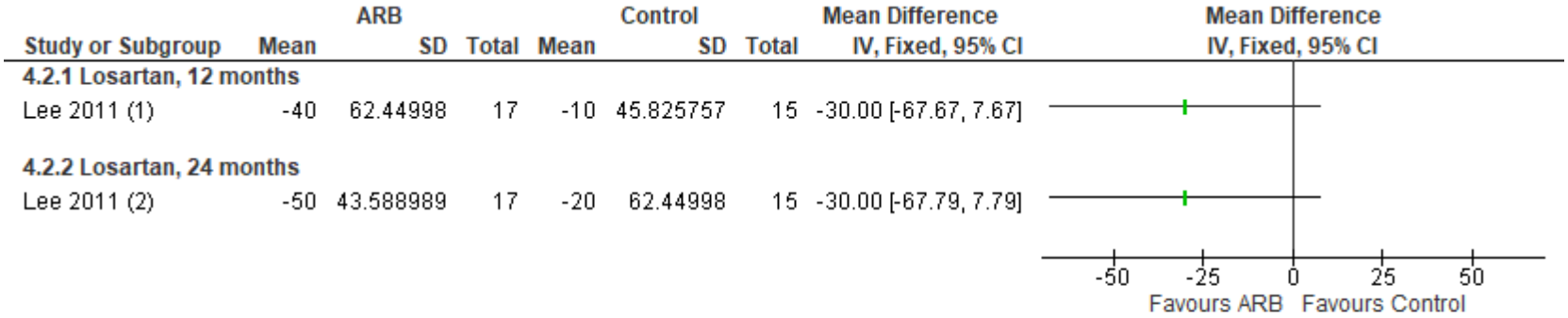


Figure 16 ARB vs Control (usual antihypertensive therapy except ACE inhibitors and ARBs); outcome: Urinary protein creatinine ratio (mg/mmol)



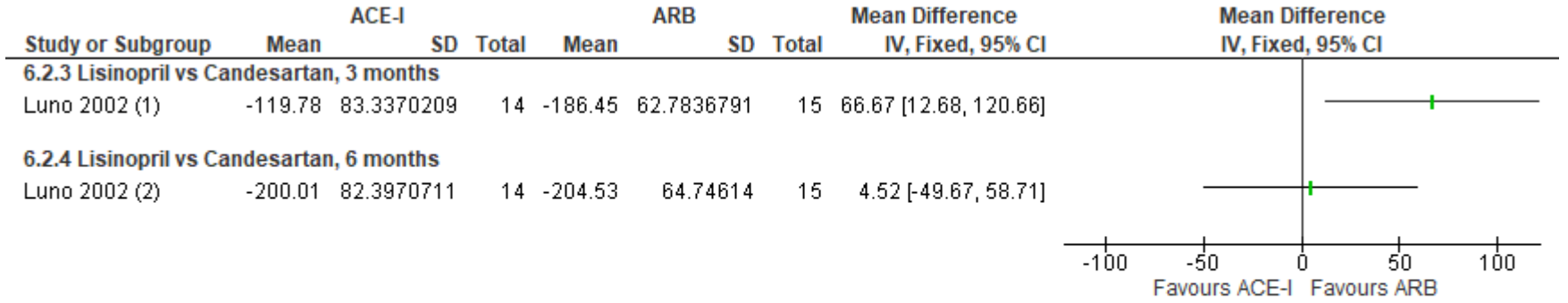
Footnotes
(1) g/mmol converted to mg/mmol multiplying g/mmol by 1000
(2) g/mmol converted to mg/mmol multiplying g/mmol by 1000

Figure 17 ARB vs Control (usual antihypertensive therapy except ACE inhibitors and ARBs); outcome: Urinary albumin creatinine ratio (mg/mmol)



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 18 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 19 ACE-I vs ARB; outcome: Urinary protein excretion (g/24h), Mean percentage reduction from baseline in adults with moderate proteinuria

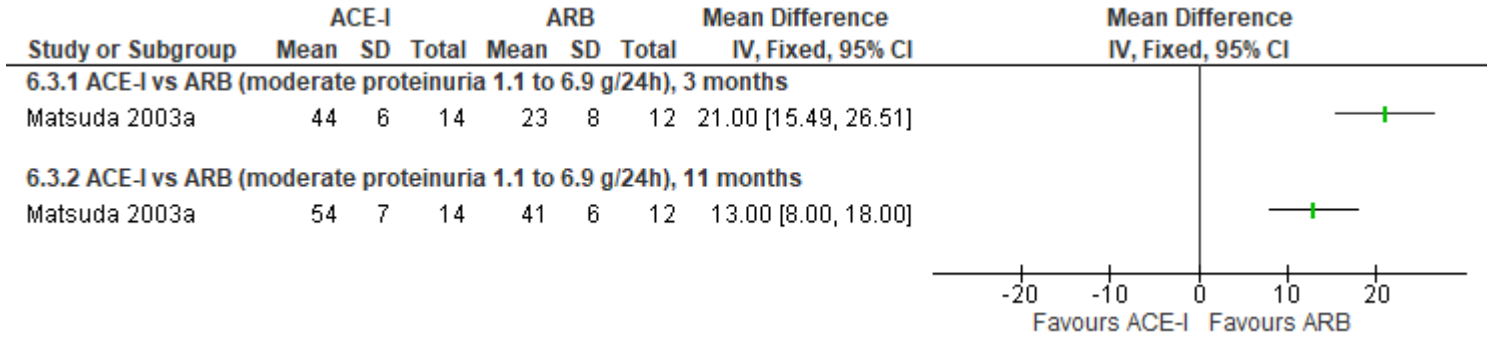


Figure 20 ACE-I vs ARB; outcome: Urinary protein excretion (g/24h), Mean percentage reduction from baseline to 3 months

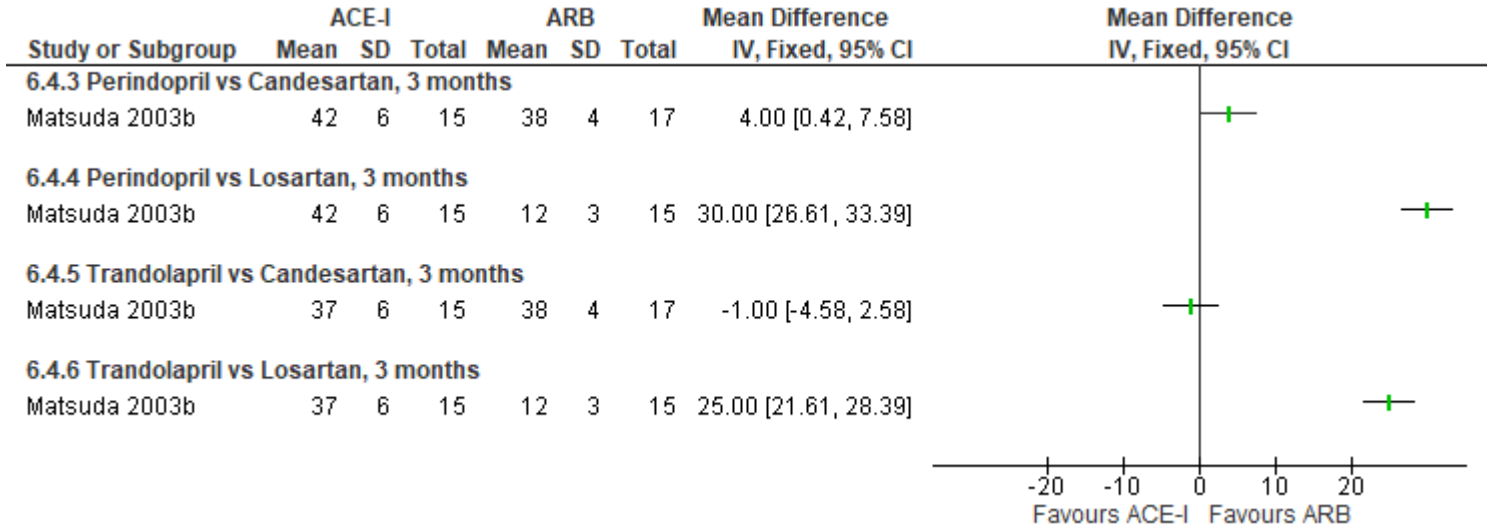


Figure 21 ACE-I vs ARB; outcome: Urinary protein excretion (g/24h), Mean percentage reduction from baseline to 22 months

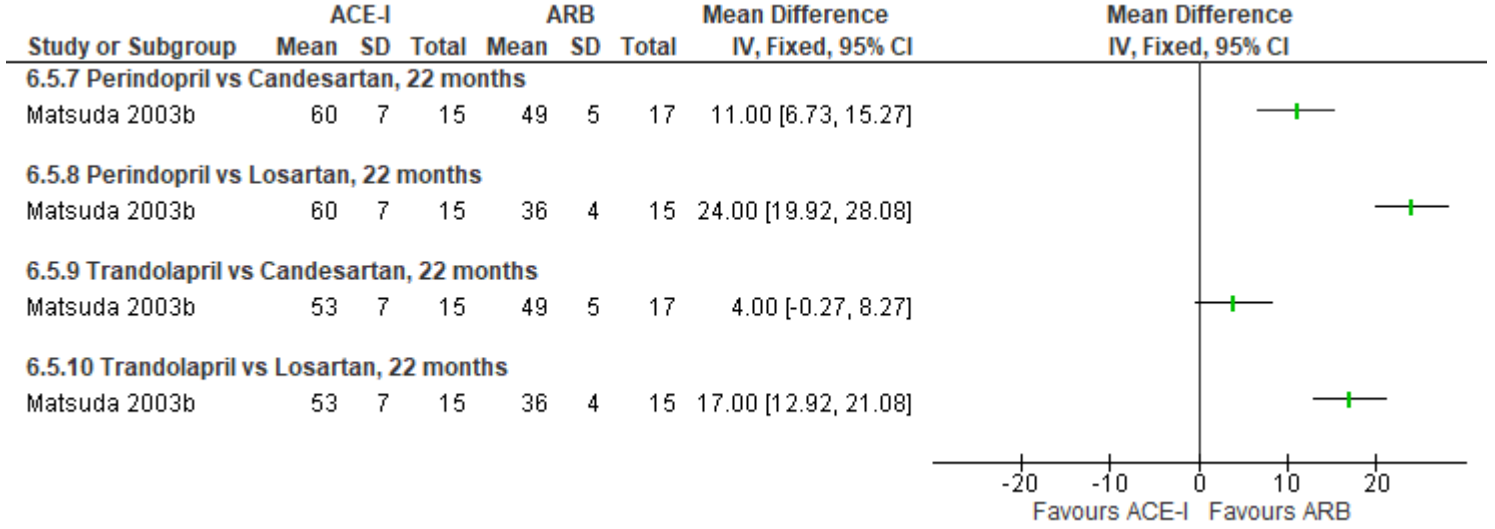
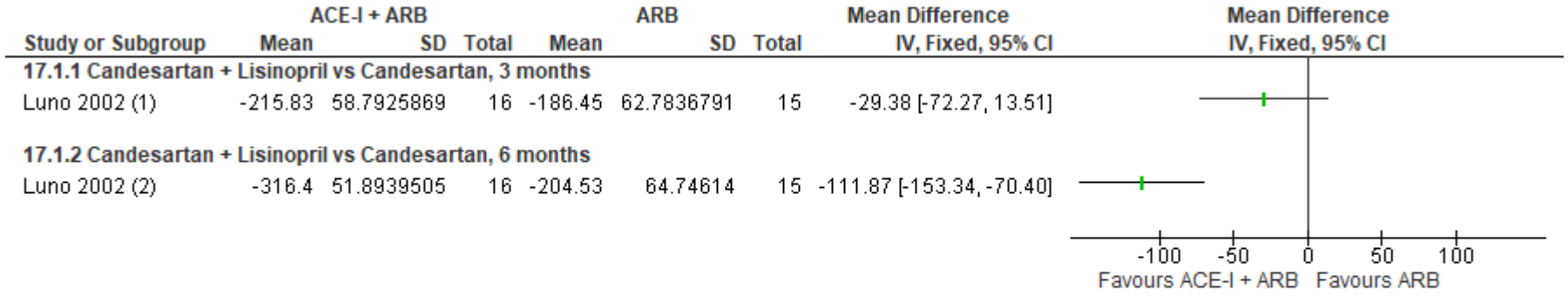


Figure 22 ACE-I + ARB vs ARB; outcome: Urinary protein/creatinine ratio (mg/mmol)

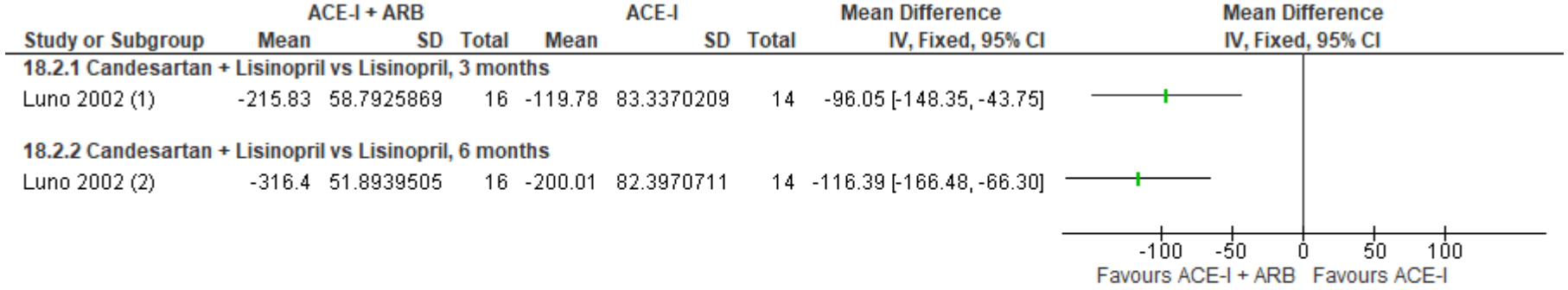


Footnotes

(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

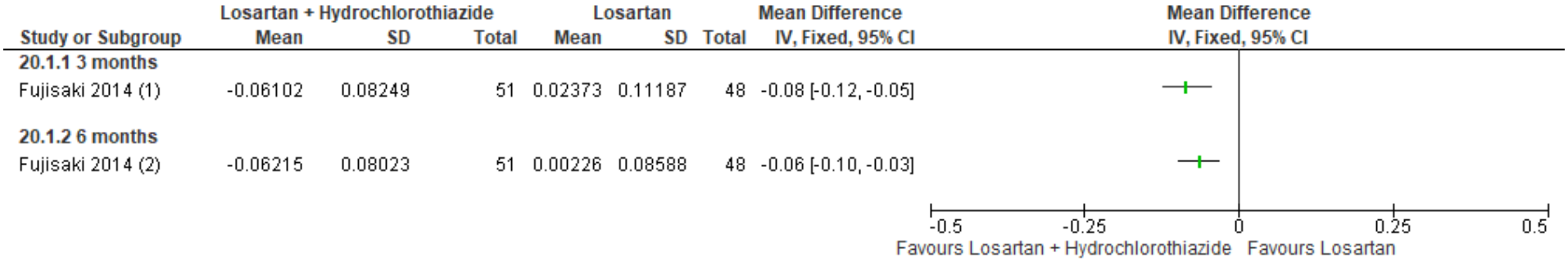
(2) Mean change from baseline, g/g converted to mg/g (g/g multiplied by 1000), mg/g converted to mg/mmol multiplying mg/g by 0.113

Figure 23 ACE-I + ARB vs ACE-I; outcome: Urinary protein/creatinine ratio (mg/mmolg/g)



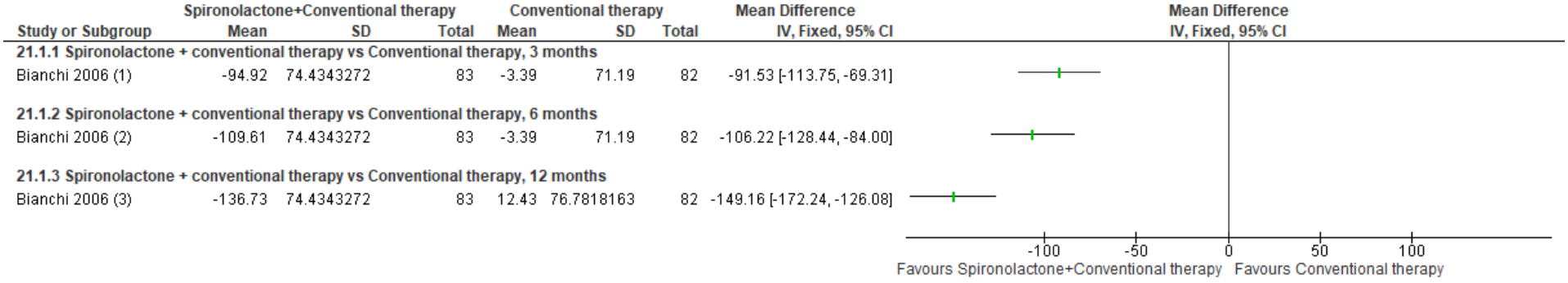
Footnotes
(1) Mean change from baseline, g/g converted to mg/g (g/g multiplied by 1000), mg/g converted to mg/mmol multiplying mg/g by 0.113
(2) Mean change from baseline, g/g converted to mg/g (g/g multiplied by 1000), mg/g converted to mg/mmol multiplying mg/g by 0.113

Figure 24 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 25 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	no serious inconsistency	no serious indirectness	no serious imprecision	none	108	99	-	MD 19.7 lower (56.39	HIGH

		risk of bias								lower to 16.99 higher)	
End stage kidney disease - Canagliflozin vs Placebo (type 2 diabetes)											
1	randomised trials[2]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	116/2202 (5.3%)	165/2199 (7.5%)	HR 0.68 (0.54 to 0.86)	2 fewer per 100 (from 1 fewer to 3 fewer)	MODERATE
All-cause mortality											
2	randomised trials[4]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	169/2347 (7.2%)	201/2347 (8.6%)	RR 0.84 (0.69 to 1.02)	1 fewer per 100 (from 3 fewer to 0 more)	MODERATE
All-cause mortality - Dapagliflozin vs Placebo (type 2 diabetes)											
1	randomised trials[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	1/145 (0.69%)	0/148 (0%)	RR 3.06 (0.13 to 74.55)	-	MODERATE
All-cause mortality - Canagliflozin vs Placebo (type 2 diabetes)											
1	randomised trials[2]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	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[6]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	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)	-[7]	MODERATE
All-cause mortality - Canagliflozin vs Placebo, macroalbuminuria: urinary albumin/creatinine ratio >30 mg/mmol											
1	randomised trials[6]	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)	-[7]	HIGH
CV mortality - Canagliflozin vs Placebo (type 2 diabetes)											

1	randomised trials[2]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	110/2202 (5%)	140/2199 (6.4%)	HR 0.78 (0.61 to 1)	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[6]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	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)	-[7]	MODERATE
CV mortality - Canagliflozin vs Placebo, macroalbuminuria: urinary albumin/creatinine ratio >30 mg/mmol											
1	randomised trials[6]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	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)	-[7]	MODERATE
Acute kidney injury - Canagliflozin vs Placebo (type 2 diabetes)											
1	randomised trials[2]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	86/2200 (3.9%)	98/2197 (4.5%)	HR 0.85 (0.64 to 1.13)	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[8]	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
Hospitalisation for heart failure - Canagliflozin vs Placebo (type 2 diabetes)											
1	randomised trials[2]	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	89/2202 (4%)	141/2199 (6.4%)	HR 0.61 (0.47 to 0.80)	2 fewer per 100 (from 1 fewer to 3 fewer)	MODERATE

[1] Pollock 2019
[2] Perkovic 2019
[3] 95% confidence interval crosses one end of a defined MID interval
[4] Perkovic 2019; Pollock 2019
[5] 95% confidence interval crosses line of no effect
[6] Neuen 2019

[7] Outcome reported as patients with an event per 1000 patient-years
[8] 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	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

		risk of bias									

[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
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

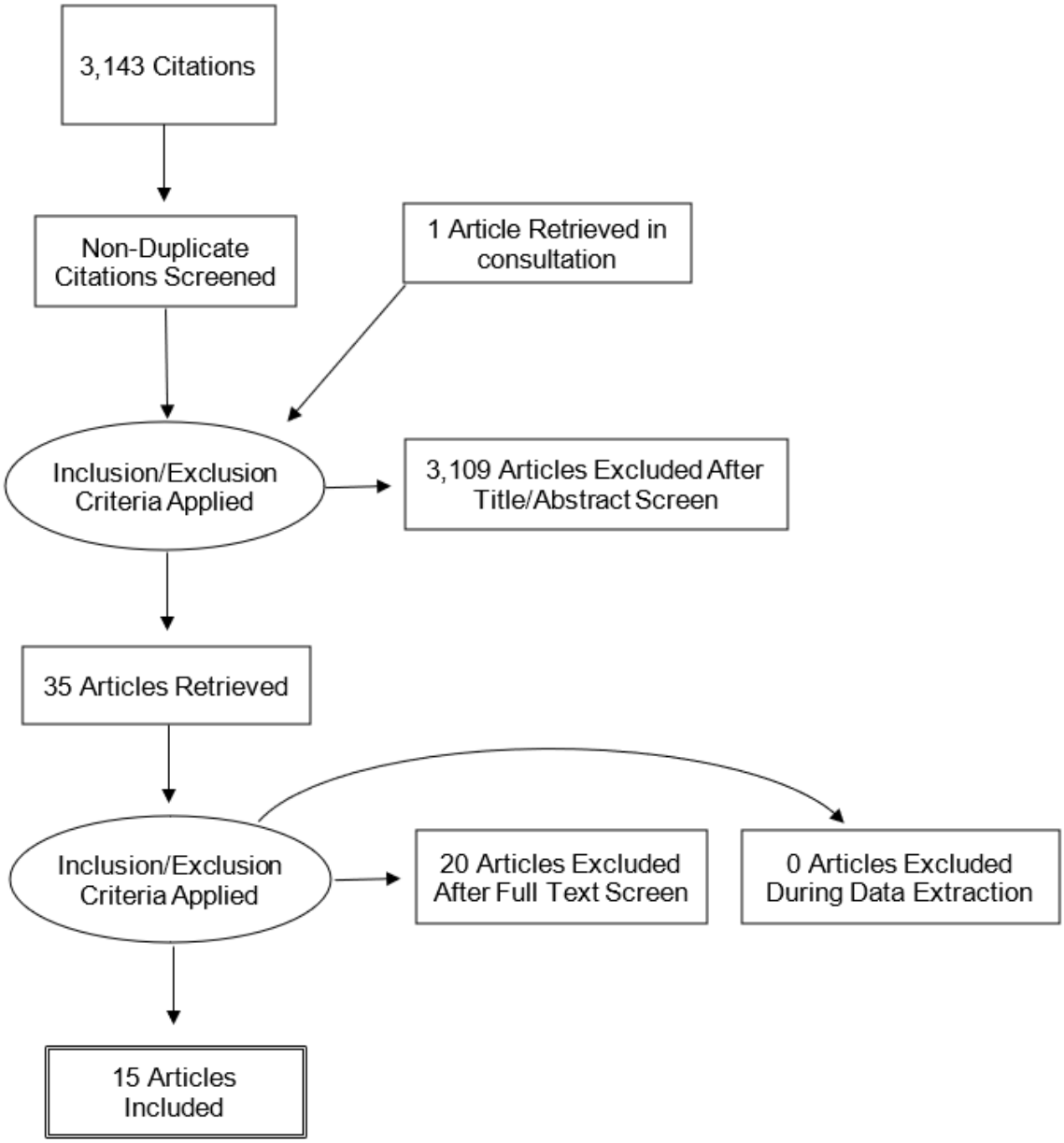
[1] Fujisaki 2014
[2] Study at moderate risk of bias
[3] 95% confidence interval crosses one end of a defined MID interval

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 **Study design:** Systematic review and decision analytic model **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. 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:** Type 1 diabetes People with type 1 diabetes aged 12 years and over[1] Type 2 diabetes People with type 2 diabetes aged 40 to 75 years[2] **Cohort settings** The base case compared biennial to annual screening **Interventions** Annual **s**creening + ACE inhibitor if progression to micro or macroalbuminuria. Alternative frequencies	**Cost differences:** Type 1 diabetes **1-year vs 2-year:** £2,837 **2-year vs 3-year:** £2,222 **3-year vs 4-year:** £672 **4-year vs 5-year:** £337 Type 2 diabetes **1-year vs 2-year:** £244 **2-year vs 3-year:** £131 **3-year vs 4-year:** £82 **4-year vs 5-year:** £83 **Currency & cost year:** Sterling 2011	**QALY differences:** Type 1 diabetes **1-year vs 2-year:** 0.26 **2-year vs 3-year:** 0.39 **3-year vs 4-year:** 0.15 **4-year vs 5-year:** 0.08 Type 2 diabetes **1-year vs 2-year:** 0.42 **2-year vs 3-year:** 0.11 **3-year vs 4-year:** 0.24 **4-year vs 5-year:** 0.09	**Full incremental analysis:** Type 1 diabetes **1-year vs 2-year:** £11,203/QALY **2-year vs 3-year:** £5,766/QALY **3-year vs 4-year:** £2,943/QALY **4-year vs 5-year:** £4,215/QALY Type 2 diabetes **1-year vs 2-year:** £707/QALY **2-year vs 3-year:** £575/QALY **3-year vs 4-year:** £386/QALY **4-year vs 5-year:** £890/QALY In both models, annual screening was more expensive and produced more QALYs **Analysis of uncertainty:** Univariate sensitivity analyses were conducted using the upper and lower levels of the confidence intervals for test cost, ACR progression, CVD and utility. In both models, the results were sensitive to ACR progression,

between 1 and 10 years using 1 and 5-year increments. Model results are the average of 1,000 simulations used to stabilise individual Monte Carlo simulations. **Perspective:** NHS perspective **Time horizon:** Lifetime **Intervention effect duration:** Lifetime **Discounting:** costs and effects were discounted at 3.5% annually for the initial 30 years and at 3% thereafter	of screening were compared: **1-year versus 2-year** **2-year versus 3-year** **3-year versus 4-year** **4-year versus 5-year**	**Cost components incorporated:** Type 1 diabetes monitoring, further investigations, treating diagnosed kidney disease (appointments, ESRD) and costs of complications (CVD)		producing ICERs in excess of £40,000/QALY. Type 1 diabetes 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. Type 2 diabetes 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 **Study design:** Decision analytic model **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 **Cohort settings*** **Intervention 1:** ACE inhibitor at time of DM diagnosis (treat all) **Intervention 2:** ACE inhibitor if microalbuminuria **Intervention 3:** ACE inhibitor if macroalbuminuria *If cough was developed as side-effect, an angiotensin II receptor blocker was used	**Total costs (mean per individual)[3]:** **Int1:** €98,421 (£94,742) **Int2:** €101,140 (£97,359) **Int3:** €110,777 (£106,636) **Currency & cost year:** Euro, 2010 **Cost components incorporated:** direct healthcare costs	**QALYs (mean per individual):** **Int1:** 19.63 **Int2:** 19.54 **Int3:** 19.15	**Full incremental analysis:** The strategy of treating all patients at the time of diagnosis of DM dominates as it is cheaper and produces more QALYs. **Analysis of uncertainty:** 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. When assuming a lower baseline risk of having macroalbuminuria, intervention 2 becomes dominant.

used 1,000 Monte Carlo simulations. **Perspective:** Dutch health system **Time horizon:** 50 years (>99% of cohort dead), 1-year cycle with half-cycle correction **Intervention effect duration:** duration of the analysis **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 **Study design:** Decision analytic model **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. **Perspective:** German health system **Time horizon:** 57 years (>99% of cohort dead), 1-year cycle with half-cycle correction **Intervention effect duration:** duration of the analysis **Discounting:** 3% costs, 3% QALYs	**Population:** People aged 44 with advanced renal insufficiency, proteinuria and hypertension **Cohort settings** **Intervention 1:** ACE inhibitor (treat all) **Intervention 2:** No ACE inhibitor	**Total costs (mean per individual)[1]:** **Int1:** €172,676 (£177,233.60) **Int2:** €205,200 (£210,616.03) **Currency & cost year:** Euro, 2011 **Cost components incorporated:** direct healthcare costs (drugs, cost dialysis and transplant)	**QALYs (mean per individual):** **Int1:** 8.26 **Int2:** 6.77	**Full incremental analysis:** The strategy of treating all patients dominates as it is cheaper and produces more QALYs. **Analysis of uncertainty:** 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. **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. **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. 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]*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 **Study design:** Decision analytic model **Approach to analysis:** Microsimulation modelling the	**Population:** People with 30 years old **Intervention 1:** Usual care[1] **Intervention 2:** Universal 1y* **Intervention 3:** Universal 2y* **Intervention 4:** Universal 5y* **Intervention 5:** Universal 10y*	**Total costs (mean per individual):** **Int1**: $146,500 (£130,029) **Int2**: $147,900 (£131,271) **Int3**: $147,900 (£130,650)	**QALYs (mean per individual):** **Int1**: 17.685 **Int2**: 17.695 **Int3**: 17.693 **Int4**: 17.691 **Int5**: 17.690 **Int6**: 17.682	**Full incremental analysis**[3]**:** (Each strategy compared to usual care) Full population **Int2 vs Int1:** $145,000 (£128,697) **Int3 vs Int1:** $91,000 (£80,769) **Int4 vs Int 1:** $52,000 (£46,153) **Int5 vs Int 1:** $34,000 (£30,177) **Int6 vs Int 1:** $29,000 (£25,739)

progression of renal disease through the stages of no-CKD, CKD stages 1 to 5 and death. **Perspective:** US Health system **Time horizon:** lifetime **Intervention effect duration:** lifetime **Discounting:** Costs and effect at 3% annually	**Intervention 6:** Universal at age 50y only *all from age 50	**Int4**: $146,800 (£130,295) **Int5**: $146,700 (£130,206) **Int6**: $146,400 (£129,940) **Currency & cost year**:** US dollars 2006 **Cost components incorporated:** annual medical management of CKD, direct screening and treatment costs. **Author rounded costs to the nearest $100 and ICERS to the nearest $1000		<u>People with DM</u> 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. <u>People with HTN</u> 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. <u>People without diabetes or hypertension</u> 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) **Analysis of uncertainty:** 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). 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 **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. **Perspective:** Australian health system **Time horizon:** lifetime, 1-year cycle **Intervention effect duration:** lifetime **Discounting:** costs and effects at 5% annually	**Population:** People aged >25 years with sub-optimally managed type 2 diabetes or hypertension and **Intervention 1**. Intensive glycaemic control in people with known type 2 diabetes **Intervention 2** Addition of ACE inhibitor in people with known type 2 diabetes **Intervention 3:** Intensive blood pressure control in people with known hypertension Screening model (unknown risk factors) **Population:** Entire people over 25 years **Intervention 4:** Screening for diabetes and intensive glycaemic control in know and screen-detected people with type 2 diabetes **Intervention 5:** Screening for hypertension and intensive hypertension control in known and screen-detected people with hypertension **Intervention 6:** Screening for proteinuria and addition of ACE inhibitor in people with known diabetes and screen-detected proteinuria	Treatment model **Int1:** $40,144 (£23,530) **SC:** $40,277 (£23,608) **Int2:** $37,781 (£22,145) **SC:** $38,606 (£22,629) **Int3:** $39,716 (£23,279) **SC:** $39,364 (£23,073) Screening model: **Int4:** $17,832 (£10,452) **SC:** $16,487 (£9,664) **Int5:** $14,061 (£8,242) **SC:** $14,004 (8,208) **Int6:** $16,974 (£9,949) **SC:** $16,821 (£9,860) **Currency & cost year:** Australian dollars 2008 **Cost components incorporated:** costs of treatment, screening, diabetes, hypertension and coronary care, dialysis, renal transplantation and graft failure.	Treatment model **Int1:** 9.942 **SC:** 9.867 **Int2:** 10.111 **SC:** 9.987 **Int3:** 10.070 **SC:** 9.934 Screening model: **Int4:** 12.798 **SC:** 12.701 **Int5:** 12.947 **SC:** 12.831 **Int6:** 12.763 **SC:** 12.731	**Int1:** Dominates SC **Int2:** Dominates SC **Int3:** $2,588/QALY (£1,517/QALY Screening model: **Int4:** $13,866/QALY (£8,128/QALY) **Int5:** $491/QALY (£288/QALY) **Int6:** $4,781/QALY (£2,803/QALY) **Analysis of uncertainty:** 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. **Probabilistic sensitivity analysis** Probability cost effective at $50,000/QALY (£29,307/QALY) threshold: Treatment model **Int1:** 85% **Int2:** 88% **Int3:** 82% Screening model: **Int4:** 57% **Int5:** 55% **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

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 **Study design:** Decision analytic model **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. **Perspective:** US healthcare payer **Time horizon:** 70 years or death **Intervention effect duration:** lifetime **Discounting:** costs and effects at 3% annually	**Population:** People with type 1 diabetes aged 20 or older **Cohort settings** **Intervention 1:** ACE inhibitor 1 year after diagnosis of type 1 diabetes (Early) **Intervention 2**: Annual screening for microalbuminuria [1] **+** ACE inhibitor (Standard)	**Total costs (mean per individual):** **Int1:** $130,460 (£136,558) **Int2:** $127,768 (£133,740) **Currency & cost year:** US dollars 1999 **Cost components incorporated:** screening for microalbuminuria, ACE inhibitor, management of diabetes and routine medical costs	**QALYs (mean per individual):** **Int1:** 20.456 **Int2:** 20.357	**Full incremental analysis:** 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 **Analysis of uncertainty:** 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. 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. The results were overall robust to one-way sensitivity analysis. 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			
Study details	**Population & interventions**	**Costs[2]**	**Outcomes**	**Cost effectiveness**

Economic analysis: Cost utility analysis **Study design:** Decision analytical model **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. **Perspective:** Societal perspective **Time horizon:** lifetime **Intervention effect duration:** lifetime **Discounting:** 3% annually for costs and effects	**Population:** US adults aged 50 without hypertension or diabetes or with hypertension **Cohort settings** **Intervention 1:** Annual screening for proteinuria[1] + treatment with ACE inhibitor or ARB therapy **Intervention 2:** No screening (standard care)	**Total costs (mean per individual):** Neither hypertension nor diabetes **Int1:** $13,745 (£14,192) **Int2:** $13,129 (£13,556) Hypertension **Int1:** $23,927 (£24,706) **Int2:** $23,451 (£24,214) **Currency & cost year:** US dollars 2002 **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):** Neither hypertension nor diabetes **Int1:** 19.461 **Int2:** 19.459 Hypertension **Int1:** 17.241 **Int2:** 17.215	**Full incremental analysis:** Neither hypertension nor diabetes The screening strategy was more expensive and produced more QALYs at $280,000 (£289,114)/QALY Hypertension The screening strategy was more expensive and produced more QALYs at $18,594 (£19,999)/QALY **Analysis of uncertainty:** Neither hypertension nor diabetes The screening strategy was not cost-effective when screening started between the ages of 30 to 50 years. 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. Screening was associated with a 1.5% probability of being cost-effective at a threshold less than $50,000 (£51,628) per QALY. Hypertension 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. The screening strategy remained cost-effective with less frequent screening produced lower ICERs. 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. 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			
Study details	**Population & interventions**	**Costs**	**Outcomes**	**Cost effectiveness**
Economic analysis: Cost utility analysis **Study design:** Decision analytic model **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. **Perspective:** US societal **Time horizon:** Lifetime horizon, 1-year cycle **Intervention effect duration:** **Discounting:** 3% annually for costs and QALYs	**Population:** 50-year-old people with type 2 diabetes **Cohort settings** **Intervention 1:** Treat all with ACE inhibitor (no screening) **Intervention 2:** ACE inhibitor if microalbuminuria **Intervention 3:** ACE inhibitor if gross proteinuria	**Total costs (mean per individual):** **Int1:** $15,240 (£15,874) **Int2:** $14,940 (£15,562) **Int3:** $19,520 (£20,333) **Currency & cost year:** US dollars 1998 **Cost components incorporated:** Direct medical cost (ACE inhibitor therapy, monitoring, screening, treatment of ESRD)	**QALYs (mean per individual):** **Int1:** 11.82 **Int2:** 11.78 **Int3:** 11.59	**Full incremental analysis:** 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. **Analysis of uncertainty:** 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. 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				

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. **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). **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. Analysis took a societal perspective of costs. The analysis does not consider standard practice as one of the comparators. 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. 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. 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			
Study details	**Population & interventions**	**Costs[4]**	**Outcomes**	**Cost effectiveness**

Economic analysis: Cost utility analysis **Study design:** Decision analytic model simulating CKD progression through the stages of normoalbuminuria, microalbuminuria, macroalbuminuria, ESRD and death. **Approach to analysis:** Markov model[1] **Perspective:** US, third party **Time horizon:** 60 years **Intervention effect duration:** **Discounting:** Costs and effects at 3% annually	**Population:** People with type 1 diabetes 43 years of age **Intervention 1:** Current recommendations (annual screening for microalbuminuria plus ACE inhibitor)[2] **Intervention 2:** Routine treatment of all people 5 years after diagnosis of diabetes **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):** **Int1:** $29,350 (£32,646) **Int2:** $29,180 (£32,457) **Int3:** $29,236 (£32,520) **Currency & cost year:** US dollars 1995 **Cost components incorporated:** Costs of screening, ACE inhibitor and ESRD	**QALYs (mean per individual):** **Int1:** 19.15 **Int2:** 19.34 **Int3:** 19.17	**Full incremental analysis:** The routine treatment strategy dominated Int1 and Int3, being cheaper and producing more QALYs **Analysis of uncertainty:** The results were robust to univariate sensitivity analyses. 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). **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. **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. 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
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			
Study details	**Population & interventions**	**Costs**	**Outcomes**	**Cost effectiveness**
Economic analysis: Cost utility analysis **Study design:** Decision analytic model **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. **Perspective:** Dutch health system **Time horizon:** Until cohort age of 100 (>99% of cohort dead), 1-year cycle with half-cycle correction **Intervention effect duration:** duration of the analysis **Discounting:** 4% costs, 1.5% QALYs	**Population:** People aged 44 with advanced renal disease[2] **Cohort settings** **Intervention 1:** ACE inhibitor **Intervention 2:** No treatment (Antihypertensives not acting on the renin-angiotensin-system[3])	**Total costs (mean per individual)[4]:** **Int 1:** €183, 535 (£176,674) **Int2**: €220,942 (£212,683) **Currency & cost year:** Euros, 2010 **Cost components incorporated:** direct healthcare costs (ACE inhibitor, chronic kidney disease costs, transplant and dialysis)	**QALYs (mean per individual):** **Int1**: 14.66 **Int 2:** 13.38	**Full incremental analysis:** The ACE inhibitor strategy dominates the no treatment strategy having a lower cost and higher benefit. **Analysis of uncertainty:** 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. The probability of producing savings was 83%.

Data sources
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. **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). **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. 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. 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			
Study details	**Population & interventions**	**Costs**	**Outcomes**	**Cost effectiveness**

Economic analysis: Cost utility analysis **Study design:** Decision analytic model **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. **Perspective:** US health system **Time horizon:** lifetime, 6-month cycles **Intervention effect duration:** lifetime **Discounting:** Cost and QALYs at 3% annually	**Population:** People with type 2 diabetes and microalbuminuria **Cohort settings** **Intervention 1:** Aliskiren 300 mg/day plus losartan 100 mg/day* **Intervention 2:** Losartan 100 mg/day* *Plus optimal antihypertensive therapy	**Total costs (mean per individual)[2]:** **Int1:** $64,746 (£53,849) **Int 2:** $61,794 (£51,394) **Currency & cost year:** US dollars, 2008 **Cost components incorporated:** direct healthcare costs (intervention costs, additional antihypertensive costs,	**QALYs (mean per individual):** **Int1:** 5.9775 **Int2:** 5.8808 **Other:** Incidence of ESRD: **Int1:** 23.43% **Int2:** 20.74% (2.69% reduction, favours intervention 1) Time free of ESRD: Increased by 0.1772 years, favours intervention 1	**Full incremental analysis[3]:** 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). **Analysis of uncertainty:** 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. 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).

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. The analysis was sponsored by the drug manufacturer. 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 **Study design:** Decision analytic model **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 **Cohort settings** **Intervention 1:** Valsartan **Intervention 2:** Amlodipine	**Total costs (mean per individual):** **Int1:** $92,058 (£92,231) **Int2:** $124,470 (£124,703) **Currency & cost year:** US dollars 2001 **Cost components incorporated:** Study drugs, routine healthcare services to manage	**QALYs (mean per individual):** **Int1:** 6.390 **Int2:** 5.835	**Full incremental analysis:** The intervention using valsartan dominated amlodipine being cheaper and producing more QALYs. **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. **Perspective:** US third party perspective **Time horizon:** 8 years, 3-month cycles **Intervention effect duration:** 8 years **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). **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). **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. 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 **Study design:** Decision analytic model **Approach to analysis:** Markov model simulating the progression of CKD to ESRD, dialysis and death. **Perspective:** Taiwanese health system **Time horizon:** 10 years **Intervention effect duration:** **Discounting:** Costs and effects at 3% annually	**Population:** People with CKD stage 4[1] **Cohort settings** **Intervention 1:** Low protein diet[2] + supplementation with ketoanalogues[3] in people with CKD stage 4 **Intervention 2:** Low protein diet and watchful waiting (CKD stage 4) + supplementation with ketoanalogues if CKD stage 5	**Total costs (mean per individual):** **Int1**: $564,637 (£430,741) **Int2**: $914,236 (£697,437) **Currency & cost year:** US dollars 2015 **Cost components incorporated:**	**QALYs (mean per individual):** **Int1**: 3.926 **Int2**: 3.787	**Full incremental analysis**[5]**:** The intervention delivering early low protein diet supplemented with ketoanalogues dominates the watchful waiting strategy, being both cheaper and producing more QALYs. **Analysis of uncertainty:** The analysis was robust to univariate sensitivity analysis of the treatment efficacy parameter. 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). **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). **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. 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. The study was funded by a manufacturer of ketoanalogues. 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 **Study design:** Decision analytic model **Approach to analysis:** Markov model simulating CKD (state 4 and 5) progression to ESRD (dialysis) and death. **Perspective:** Italian National Health Service **Time horizon:** 2, 3,5 or 10 years	**Population:** People with CKD stage 4 and 5 **Cohort settings** **Intervention 1:** Very low protein diet[1] **Intervention 2:** Moderately low protein diet[2]	**Total costs (mean per individual):** **Int1:** € 55,109 (£56,391) **Int2:** € 65,483 (£67,007) **Currency & cost year:** Euros 2014 **Cost components incorporated:** medical and non-medical direct costs of dialysis,	**QALYs (mean per individual):** **Int1:** 5.75 **Int2:** 4.77	**Full incremental analysis:** The very low protein diet strategy dominated the moderately low protein diet being both cheaper and producing more QALYs. **Analysis of uncertainty:** 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 **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) **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). **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. 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. 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. 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.*

SGLT2

Willis 2020

Study	Willis M, Nilsson A, Kellerborg K et al. (2020) Cost-Effectiveness of Canagliflozin Added to Standard of Care for Treating Diabetic Kidney Disease (DKD) in Patients with Type 2 Diabetes Mellitus (T2DM) in England: Estimates Using the CREDEM-DKD Model. Diabetes Therapy 12: 313-28			
Study details	**Population & interventions**	**Costs**	**Outcomes**	**Cost effectiveness**
Economic analysis: Cost effectiveness analysis **Study design:** Microsimulation **Approach to analysis:** Discrete event simulation. **Perspective:** English National Health Service **Time horizon:** 10 years **Intervention effect duration:** up to 10 years **Discounting:** 3.5% for costs and effects	**Population:** People with CKD and Type 2 diabetes **Cohort settings** **Intervention 1:** Canagliflozin and standard of care **Intervention 2:** Standard of care	**Total costs (mean per individual):** **Int1:** £32,950 **Int2:** £37,656 **Currency & cost year:** GBP 2020 **Cost components incorporated:** medicine, adverse events, dialysis and transplant	**QALYs (mean per individual):** **Int1:** 3.73 **Int2:** 3.45	**Full incremental analysis:** Canagliflozin dominated standard of care being both cheaper and producing more QALYs. **Analysis of uncertainty:** The analysis was robust to differing time horizons and differing hazard ratios. However, if the eGFR evolves at the same rate for the two interventions then the ICER is £20,921. In probabilistic sensitivity analysis found that at a £0/QALY threshold it is 96% likely that canagliflozin is cost effective which rises to 99% at a £30,000/QALY threshold.
Data sources				
Outcomes: Baseline characteristics were sourced from the CREDENCE trial **Quality of life weights:** Utility parameters were sourced from a literature review **Costs:** Costs were sourced from the literature				
Comments				
Source of funding: Funded by Mundipharma and Napp Pharmaceuticals**.** Conflict of interest, funded by suppliers of Canagliflozin.				
Overall applicability: Directly applicable				
Study conducted last year from the English NHS perspective.				
Overall quality: Potentially serious limitations				

The analysis included the cost of dialysis even though it is not a cost-effective therapy (even though society has agreed to pay for it). This will affect the ICER as any treatment with the lowest percentage of people on dialysis is likely to appear to be the most cost effective.
The paper funded by the makers and suppliers of canagliflozin.

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**	

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**	

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**	

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**	

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**	

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**	

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**	

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**	

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**	

Comparison of antihypertensive therapies

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**	

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. 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**	

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**	

Diet interventions

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**	

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% 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**	

SGLT2

Willis 2020

Willis M, Nilsson A, Kellerborg K et al. (2020) Cost-Effectiveness of Canagliflozin Added to Standard of Care for Treating Diabetic Kidney Disease (DKD) in Patients with Type 2 Diabetes Mellitus (T2DM) in England: Estimates Using the CREDEM-DKD Model. Diabetes Therapy 12: 313-28		
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?	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	**DIRECTLY 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	The model uses a 10-year time horizon however, in sensitivity analysis a 40 year time horizon was used
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?	Yes	

Willis M, Nilsson A, Kellerborg K et al. (2020) Cost-Effectiveness of Canagliflozin Added to Standard of Care for Treating Diabetic Kidney Disease (DKD) in Patients with Type 2 Diabetes Mellitus (T2DM) in England: Estimates Using the CREDEM-DKD Model. Diabetes Therapy 12: 313-28		
Category	**Rating**	**Comments**
2.6 Are all important and relevant costs included?	Partly	The cost of dialysis is included even though it is not cost effective, this will affect the ICER
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?	No	Sourced from the literature rather than published UK cost statistics eg NHS reference 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?	No	Dialysis is not cost effective (but society has decided to pay for it), this can affect the results of a cost effectiveness analysis. This paper has not explained how they addressed this
2.11 Has no potential financial conflict of interest been declared?	No	
2.12 OVERALL ASSESSMENT	**POTENTIALLY SERIOUS LIMITATIONS**	

Appendix K – Health economic model

No health economic modelling was undertaken for this review question.

Appendix L – Excluded studies

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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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 [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)]
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	- Study will be included in a proposed TA [TA on dapagliflozin for treating chronic kidney disease]
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).	- Does not contain a population of people with CKD or suspected CKD

Reference	Reason for exclusion
Diabetes Research and Clinical Practice 55(2): 113-121	
Kim, M.-J., Song, J.H., Suh, J.H. et al. (2003) Additive antiproteinuric effect of combination 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	- Data not reported in an extractable format [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 [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 [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 [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 [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 [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 [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	- Systematic review used as source of primary studies

Reference	Reason for exclusion
nondiabetic chronic renal disease: a systematic overview of randomized placebo-controlled trials. American journal of kidney diseases : the 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 [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 [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 [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 [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 [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 [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

Reference	Reason for exclusion
Maione, Ausilia, Navaneethan, Sankar D, Graziano, Giusi et al. (2011) Angiotensin-converting enzyme inhibitors, angiotensin 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	- Does not contain a population of people with proteinuria or albuminuria [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 [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 [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 [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 [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 [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 [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 [Albuminuria was not an inclusion criteria]

Reference	Reason for exclusion
McGuire, Darren K., Shih, Weichung J., Cosentino, Francesco et al. (2020) Association of SGLT2 Inhibitors With Cardiovascular and Kidney Outcomes in Patients With Type 2 Diabetes: A Meta-analysis. JAMA Cardiol	- Does not contain a population of people with proteinuria or albuminuria [Proteinuria was not an inclusion criteria]
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 [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 [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 [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 [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 [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 [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 [20% of participants had urinary albumin:creatinine ratio <30 mg/g at baseline]

Reference	Reason for exclusion
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 ACE inhibitor treatment. Diabetes Research and Clinical Practice 70(1): 13-19	- Does not contain a population of people with CKD or suspected CKD
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 [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 [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 [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 [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 [GISEN group 1997]

Reference	Reason for exclusion
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 [GISEN group 1997]
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 [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 [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 [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 [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 [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 [Lowering proteinuria was not the aim of the trials in this pooled analysis]

Reference	Reason for exclusion
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 [Benazepril (not available in the UK)]
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 [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 [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 [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 [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 [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 [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 [Urinary albumin/creatinine ratio reported as geometric means (interquartile range, 25th and 75th percentiles)]

Reference	Reason for exclusion
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 European Dialysis and Transplant Association - European Renal Association	- Does not contain a population of people with proteinuria or albuminuria [Proteinuria/albuminuria was not an inclusion criteria]
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)]

Reference	Reason for exclusion
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
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 [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 [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 [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 [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 [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 [Hou 2007]

Reference	Reason for exclusion
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 [Network meta-analysis also including steroids, urokinase and tonsillectomy]
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 [Fried 2013]

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	Cost consequences analysis

Author (year)	Title	Reason for exclusion
	benefits of irbesartan in patients with type 2 diabetes and hypertension	
Palmer 2004	Health economics studies assessing irbesartan use in patients with hypertension, type 2 diabetes, and microalbuminuria	Cost consequences analysis
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