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Insulin and glucose-lowering agents for treating people with diabetes and chronic kidney disease (Review)

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[Intervention Review]

Insulin and glucose-lowering agents for treating people with diabetes and chronic kidney disease

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ABSTRACT

Background

Diabetes is the commonest cause of chronic kidney disease (CKD). Both conditions commonly co-exist. Glucometabolic changes and concurrent dialysis in diabetes and CKD make glucose-lowering challenging, increasing the risk of hypoglycaemia. Glucose-lowering agents have been mainly studied in people with near-normal kidney function. It is important to characterise existing knowledge of glucose-lowering agents in CKD to guide treatment.

Objectives

To examine the efficacy and safety of insulin and other pharmacological interventions for lowering glucose levels in people with diabetes and CKD.

Search methods

We searched the Cochrane Kidney and Transplant Register of Studies up to 12 February 2018 through contact with the Information Specialist using search terms relevant to this review. Studies in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE, conference proceedings, the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Selection criteria

All randomised controlled trials (RCTs) and quasi-RCTs looking at head-to-head comparisons of active regimens of glucose-lowering therapy or active regimen compared with placebo/standard care in people with diabetes and CKD (estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2) were eligible.

Data collection and analysis

Four authors independently assessed study eligibility, risk of bias, and quality of data and performed data extraction. Continuous outcomes were expressed as post-treatment mean differences (MD). Adverse events were expressed as post-treatment absolute risk differences (RD). Dichotomous clinical outcomes were presented as risk ratios (RR) with 95% confidence intervals (CI).

Main results

Forty-four studies (128 records, 13,036 participants) were included. Nine studies compared sodium glucose co-transporter-2 (SGLT2) inhibitors to placebo; 13 studies compared dipeptidyl peptidase-4 (DPP-4) inhibitors to placebo; 2 studies compared glucagon-like peptide-1 (GLP-1) agonists to placebo; 8 studies compared glitazones to no glitazone treatment; 1 study compared glinide to no glinide treatment; and 4 studies compared different types, doses or modes of administration of insulin. In addition, 2 studies compared sitagliptin to glipizide; and 1 study compared each of sitagliptin to insulin, glitazars to pioglitazone, vildagliptin to sitagliptin, linagliptin to voglibose, and albiglutide to sitagliptin. Most studies had a high risk of bias due to funding and attrition bias, and an unclear risk of detection bias.

Compared to placebo, SGLT2 inhibitors probably reduce HbA1c (7 studies, 1092 participants: MD -0.29%, -0.38 to -0.19 (-3.2 mmol/mol, -4.2 to -2.2); I^2 = 0%), fasting blood glucose (FBG) (5 studies, 855 participants: MD -0.48 mmol/L, -0.78 to -0.19; I^2 = 0%), systolic blood pressure (BP) (7 studies, 1198 participants: MD -4.68 mmHg, -6.69 to -2.68; I^2 = 40%), diastolic BP (6 studies, 1142 participants: MD -1.72 mmHg, -2.77 to -0.66; I^2 = 0%), heart failure (3 studies, 2519 participants: RR 0.59, 0.41 to 0.87; I^2 = 0%), and hyperkalaemia (4 studies, 2788 participants: RR 0.58, 0.42 to 0.81; I^2 = 0%); but probably increase genital infections (7 studies, 3086 participants: RR 2.50, 1.52 to 4.11; I^2 = 0%), and creatinine (4 studies, 848 participants: MD 3.82 µmol/L, 1.45 to 6.19; I^2 = 16%) (all effects of moderate certainty evidence). SGLT2 inhibitors may reduce weight (5 studies, 1029 participants: MD -1.41 kg, -1.8 to -1.02; I^2 = 28%) and albuminuria (MD -8.14 mg/mmol creatinine, -14.51 to -1.77; I^2 = 11%; low certainty evidence). SGLT2 inhibitors may have little or no effect on the risk of cardiovascular death, hypoglycaemia, acute kidney injury (AKI), and urinary tract infection (low certainty evidence). It is uncertain whether SGLT2 inhibitors have any effect on death, end-stage kidney disease (ESKD), hypovolaemia, fractures, diabetic ketoacidosis, or discontinuation due to adverse effects (very low certainty evidence).

Compared to placebo, DPP-4 inhibitors may reduce HbA1c (7 studies, 867 participants: MD -0.62%, -0.85 to -0.39 (-6.8 mmol/mol, -9.3 to -4.3); I^2 = 59%) but may have little or no effect on FBG (low certainty evidence). DPP-4 inhibitors probably have little or no effect on cardiovascular death (2 studies, 5897 participants: RR 0.93, 0.77 to 1.11; I^2 = 0%) and weight (2 studies, 210 participants: MD 0.16 kg, -0.58 to 0.90; I^2 = 29%; moderate certainty evidence). Compared to placebo, DPP-4 inhibitors may have little or no effect on heart failure, upper respiratory tract infections, and liver impairment (low certainty evidence). Compared to placebo, it is uncertain whether DPP-4 inhibitors have any effect on eGFR, hypoglycaemia, pancreatitis, pancreatic cancer, or discontinuation due to adverse effects (very low certainty evidence).

Compared to placebo, GLP-1 agonists probably reduce HbA1c (7 studies, 867 participants: MD -0.53%, -1.01 to -0.06 (-5.8 mmol/mol, -11.0 to -0.7); I^2 = 41%; moderate certainty evidence) and may reduce weight (low certainty evidence). GLP-1 agonists may have little or no effect on eGFR, hypoglycaemia, or discontinuation due to adverse effects (low certainty evidence). It is uncertain whether GLP-1 agonists reduce FBG, increase gastrointestinal symptoms, or affect the risk of pancreatitis (very low certainty evidence).

Compared to placebo, it is uncertain whether glitazones have any effect on HbA1c, FBG, death, weight, and risk of hypoglycaemia (very low certainty evidence).

Compared to glipizide, sitagliptin probably reduces hypoglycaemia (2 studies, 551 participants: RR 0.40, 0.23 to 0.69; I^2 = 0%; moderate certainty evidence). Compared to glipizide, sitagliptin may have had little or no effect on HbA1c, FBG, weight, and eGFR (low certainty evidence). Compared to glipizide, it is uncertain if sitagliptin has any effect on death or discontinuation due to adverse effects (very low certainty).

For types, dosages or modes of administration of insulin and other head-to-head comparisons only individual studies were available so no conclusions could be made.

Authors' conclusions

Evidence concerning the efficacy and safety of glucose-lowering agents in diabetes and CKD is limited. SGLT2 inhibitors and GLP-1 agonists are probably efficacious for glucose-lowering and DPP-4 inhibitors may be efficacious for glucose-lowering. Additionally, SGLT2 inhibitors probably reduce BP, heart failure, and hyperkalaemia but increase genital infections, and slightly increase creatinine. The safety profile for GLP-1 agonists is uncertain. No further conclusions could be made for the other classes of glucose-lowering agents including insulin. More high quality studies are required to help guide therapeutic choice for glucose-lowering in diabetes and CKD.

PLAIN LANGUAGE SUMMARY

Glucose-lowering medications to treat diabetes and chronic kidney disease

What is the issue?

Diabetes is the commonest cause of chronic kidney disease (CKD). Due to decreased kidney function and changes in the clearance of medications and glucose, treating people with diabetes and CKD is challenging. There is an increased risk of hypoglycaemia (low blood sugar). However, most glucose-lowering medications have been studied in people with near normal kidney function. The aim of this review is to determine the effectiveness and safety of glucose-lowering medication in people with diabetes and CKD.

What did we do?
We looked at studies comparing different medications with each other or to no medications in people with diabetes and CKD.

What did we find?

We included 44 studies involving 13,036 people. Most studies compared different medication types - sodium glucose co-transporter-2 (SGLT2) inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) agonists, and glitazones to no treatment. Two studies compared the medications sitagliptin to glipizide.

SGLT2 inhibitors probably reduce glucose levels, blood pressure, heart failure and high potassium levels but increase genital infections and slightly reduce kidney function. SGLT2 inhibitors may reduce weight. Their effect on the risk of death, hypoglycaemia, acute kidney injury, urinary tract infection, end-stage kidney disease, low blood volume, bone fractures, diabetic ketoacidosis is uncertain.

DPP-4 inhibitors may reduce glucose levels. Their effect on the risk of death due to heart attacks and strokes, heart failure, upper respiratory tract infections, liver problems, kidney function, hypoglycaemia, pancreatitis and pancreatic cancer is uncertain.

GLP-1 agonists probably reduce glucose levels and may reduce weight. Their effect on kidney function, hypoglycaemia, gastrointestinal symptoms and pancreatitis is uncertain.

Compared to glipizide, sitagliptin probably has a lower risk of hypoglycaemia.

No conclusions could be made regarding other glucose-lowering medications when compared to another medication or no treatment because of the lack of studies.

Conclusions

Evidence concerning the efficacy and safety of glucose-lowering agents for people with diabetes and CKD is limited. SGLT2 inhibitors and GLP-1 agonists are probably efficacious for lowering glucose levels. Other potential effects of SGLT2 inhibitors include lower BP, lower potassium levels and a reduced risk of heart failure but an increased risk of genital infections. The safety of GLP-1 agonists is uncertain.

The benefits and safety of other classes of glucose-lowering agents are uncertain.

More studies are required to help guide which glucose-lowering medications are most suitable in people with both diabetes and CKD.

Summary of findings for the main comparison. SGLT2 inhibitors versus placebo for treating people with diabetes and chronic kidney disease (CKD)

SGLT2 inhibitors versus placebo for treating people with diabetes and CKD

Patient or population: people with diabetes and CKD
Intervention: SGLT2 inhibitors
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Effect estimate (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with SGLT2 inhibitors			
HbA1c (%) HbA1c (mmol/mol)	The mean HbA1c was 0.29% lower (0.19 to 0.38 lower) with SGLT2 inhibitors compared to placebo The mean HbA1c was 3.2 mmol/mol lower (2.2 to 4.2 lower) with SGLT2 inhibitors compared to placebo		MD -0.29 (-0.38 to -0.19) MD -3.2 (-4.2 to -2.2)	1092 (7)	⊕⊕⊕⊖ MODERATE [1]
FBG (mmol/L)	The mean FBG was 0.48 mmol/L lower (0.19 to 0.78 lower) with SGLT2 inhibitors compared to placebo		MD -0.48 (-0.78 to -0.19)	855 (5)	⊕⊕⊕⊖ MODERATE [1]
Death (all causes)	78 per 1,000	61 per 1,000 (47 to 79)	RR 0.78 (0.60 to 1.02)	2933 (5)	⊕⊖⊖⊖ VERY LOW [1 2]
All cardiovascular death	52 per 1,000	40 per 1,000 (29 to 57)	RR 0.78 (0.56 to 1.10)	2788 (4)	⊕⊕⊖⊖ LOW [1 2]
Weight (kg)	Weight was 1.41 kg lower (1.02 to 1.8 lower) with SGLT2 inhibitor compared to placebo		MD -1.41 (-1.8 to -1.02)	1029 (5)	⊕⊕⊖⊖ LOW [1]
eGFR (mL/min/1.73 m^2)	The mean eGFR was 1.85 mL/min/1.73 m^2 lower (0.94 to 2.76 lower) with SGLT2 inhibitors compared to placebo		MD -1.85 (-2.76 to -0.94)	848 (4)	⊕⊕⊕⊖ MODERATE [1]
Hypoglycaemia	118 per 1,000	104 per 1,000 (86 to 126)	RR 0.88 (0.73 to 1.07)	3086 (7)	⊕⊕⊖⊖ LOW [1 2]
Discontinuation of medication due to adverse events	105 per 1,000	90 per 1,000 (59 to 138)	RR 0.86 (0.56 to 1.32)	917 (4)	⊕⊖⊖⊖ VERY LOW [1 3 4]

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

CI: Confidence interval; **RR:** Risk ratio; **MD**: mean difference

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

[1] All studies had funding bias and/or attrition bias
[2] Effect is beneficial or harmful but confidence interval is wide and crosses 1
[3] Moderate heterogeneity in effect
[4] Wide CI and the effect shows appreciable benefit and harm

Summary of findings 2. DPP-4 inhibitors versus placebo for treating people with diabetes and chronic kidney disease (CKD)

DPP-4 inhibitors versus placebo for treating people with diabetes and CKD

Patient or population: people with diabetes and CKD
Intervention: DPP-4 inhibitors
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Effect estimate (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with DPP-4 inhibitors			
HbA1c (%) HbA1c (mmol/mol)	The mean HbA1c was 0.62% lower (0.39 to 0.62 lower) with DPP-4 inhibitors compared to placebo The mean HbA1c was 6.8 mmol/mol lower (4.3 to 9.3 lower) with DPP-4 inhibitors compared to placebo		MD -0.62 (-0.85 to -0.39) MD -6.8 (-9.3 to -4.3)	867 (7)	⊕⊕⊖⊖ LOW [1 2]
FBG (mmol/L)	The mean FBG was 0.47 mmol/L lower (1.08 lower to 0.15 higher) with DPP-4 inhibitors compared to placebo		MD -0.47 (-1.08 to 0.15)	589 (4)	⊕⊕⊖⊖ LOW [3 4]
Death (all causes)	108 per 1,000	96 per 1,000 (81 to 115)	RR 0.89 (0.75 to 1.07)	4211 (6)	⊕⊕⊖⊖ LOW [1 3]

All cardiovascular death	77 per 1,000	71 per 1,000 (59 to 85)	RR 0.93 (0.77 to 1.11)	5897 (2)	⊕⊕⊕⊖ MODERATE [5]
Weight (kg)	The mean weight was 0.16 kg higher (0.58 lower to 0.9 higher) with DPP-4 inhibitors compared to placebo		MD 0.16 (-0.58 to 0.9)	210 (2)	⊕⊕⊕⊖ MODERATE [5]
eGFR (mL/min/1.73 m^2)	The mean eGFR was 1.99 mL/min/1.73 m^2 lower (0.49 to 3.49 lower) with DPP-4 inhibitors compared to placebo		MD -1.99 (-3.49 to -0.49)	130 (1)	⊕⊖⊖⊖ VERY LOW [5 6]
Hypoglycaemia	229 per 1,000	245 per 1,000 (183 to 325)	RR 1.07 (0.80 to 1.42)	1443 (11)	⊕⊖⊖⊖ VERY LOW [2 3 7]
Discontinuation of medication due to adverse events	65 per 1,000	61 per 1,000 (40 to 94)	RR 0.94 (0.61 to 1.45)	1257 (7)	⊕⊖⊖⊖ VERY LOW [1 8]

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

CI: Confidence interval; **RR:** Risk ratio; **MD**: mean difference; **HbA1c**: haemoglobin A1c (glycated); **FBG**: fasting blood glucose; **eGFR**: estimated glomerular filtration rate

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

[1] All studies had funding bias, and the majority had attrition bias
[2] Moderate heterogeneity in results
[3] Effect had appreciable benefit or harm but the confidence interval crossed 1
[4] All studies had risk of funding bias and attrition bias
[5] All studies had a risk of funding bias
[6] Only 1 study reported this outcome
[7] Majority of studies had funding bias and/or attrition bias
[8] Wide confidence interval with appreciable benefit and harm

Summary of findings 3. GLP-1 agonists versus placebo for treating people with diabetes and chronic kidney disease (CKD)

GLP-1 agonists versus to placebo for treating people with diabetes and CKD

Patient or population: people with diabetes and CKD
Intervention: GLP-1 agonists
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Effect estimate (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with GLP-1 agonists				
HbA1c (%) HbA1c (mmol/mol)	The mean HbA1c was 0.53% lower (0.06 to 1.01 lower) with GLP-1 agonists compared to placebo The mean HbA1c was 5.8 mmol/mol lower (0.7 to 11.0 lower) with GLP-1 agonists compared to placebo		MD -0.53 (-1.01 to -0.06) MD -5.8 (-11.0 to -0.7)	283 (2)	⊕⊕⊕⊖ MODERATE [1]	-
FBG (mmol/L)	The mean FBG was 1.08 mmol/L lower (0.45 to 1.71 lower) with GLP-1 agonists compared to placebo		MD -1.08 (-1.71 to -0.45)	231 (1)	⊕⊖⊖⊖ VERY LOW [1 2]	-
Death (all causes)	7 per 1,000	27 per 1,000 (3 to 235)	RR 3.91 (0.44 to 34.58)	301 (2)	⊕⊖⊖⊖ VERY LOW [1 2]	-
All cardiovascular death	-	-	-	-	-	Not reported.
Weight (kg)	-		-	303 (2)	⊕⊕⊖⊖ LOW [1 3]	On qualitative synthesis of results from two studies (total of 303 participants), liraglutide reduced body weight to a greater extent compared to the control group in people with an eGFR < 60 mL/min/1.73 m^2, including patients receiving HD. In one study in patients with ESKD receiving HD (24 participants), liraglutide resulted in a 2.20 kg loss of weight (-3.87 to 0.53; P = 0.01) compared to placebo. However, weight (mean ± SE) was reduced insignificantly compared to before the treatment (91.1 ± 4.9 to 88.7 ± 5.2 kg, P= 0.22). In another study, in patients with an eGFR 30 to < 60 mL/min/1.73 m^2 both liraglutide and placebo exhibited gradual weight reduction (279 participants). The patients in the liraglutide group had a greater reduction in body weight com-

					pared to placebo (-2.41 and -1.09 kg respectively) with an estimated treatment different of -1.32 kg (95% CI -2.24 to -0.4; P = 0.0052).
eGFR (mL/min/1.73 m^2)	-	-	279 (1)	⊕⊕⊖⊖ LOW [1 4]	Only one study reported eGFR. In this study, the mean observed changes in eGFR (MDRD) from baseline to week 26 was -0.35 mL/min/1.73 m^2 in the GLP-1 group and +0.37 mL/min/1.73 m^2 in the placebo group; the estimated treatment effect was not significant (P = 0.36). The other study occurred in HD.
Hypoglycaemia	-	-	303 (2)	⊕⊕⊖⊖ LOW [1 3]	In one study in patients with an eGFR of 30 to < 60 mL/min/1.73 m^2 (279 participants) liraglutide resulted in an equivalent risk of hypoglycaemia to placebo (0.79; 0.51 to 1.21; P = 0.28). In the other study (24 participants) with ESKD on HD, the number of episodes of hypoglycaemia did not differ between those receiving liraglutide and those receiving placebo.
Discontinuation of medication due to adverse events	-	-	303 (2)	⊕⊕⊖⊖ LOW [1 2]	In one study in patients with ESKD comparing liraglutide to placebo, there were no discontinuations due to adverse events in the liraglutide or placebo group (24 participants). In another study, in patients with an eGFR 30 to < 60 mL/min/1.73 m^2, (279 participants) liraglutide resulted in a 4.65 times higher risk of discontinuation due to adverse events compared to placebo (4.65; 1.62 to 13.31; P = 0.004)

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

CI: Confidence interval; **RR:** Risk ratio; **MD**: mean difference; ; **HbA1c**: haemoglobin A1c (glycated); **FBG**: fasting blood glucose; **eGFR**: estimated glomerular filtration rate; **ESKD**: end-stage kidney disease; **HD**: haemodialysis

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

[1] All had risk of attrition bias and funding bias
[2] Effect had appreciable benefit or harm but the confidence interval crossed 1
[3] Narrative/qualitative synthesis was conducted. Estimates were not precise
[4]Downgraded one point because only one study reported eGFR, and therefore there is a likelihood of publication bias

Summary of findings 4. Glitazone versus placebo for treating people with diabetes and chronic kidney disease (CKD)

Glitazone versus placebo for treating people with diabetes and CKD

Patient or population: people with diabetes and CKD
Intervention: glitazone
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Effect estimate (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with glitazone				
HbA1c (%) HbA1c (mmol/mol)	The mean HbA1c was 0.41% lower (1.15 lower to 0.32 higher) with glitazone agonists compared to placebo The mean HbA1c was 4.5 mmol/mol lower (12.6 lower to 3.5 higher) with glitazone agonists compared to placebo		MD -0.41 (-1.15 to 0.32) MD -4.5 (-12.6 to 3.5)	88 (2)	⊕⊖⊖⊖ VERY LOW [1 2 3]	-
FBG (mmol/L)	-	-	-	233 (5)	⊕⊖⊖⊖ VERY LOW [5 6]	Qualitative synthesis of studies showed that glitazones, particularly pioglitazone lowered FBG compared to placebo in patients with an eGFR < 60 mL/min/1.73 m^2, including patients on HD. Two studies (total of 71 participants) in people with HD reported that pioglitazone lowered FBG at the end of the study compared to the start, and also lower than in placebo group (both P < 0.05). Similarly another study (39 participants) in HD patients reported that pioglitazone reduced the FBG by 2.91 mmol/L (-5.44 to -0.38 mmol/L); P = 0.02 compared to placebo. Conversely another study in HD patients (63 participants) reported that pioglitazone resulted in a lower FBG (mean ± SD) at the end of the study compared to the start (7.72 ± 2.50 versus 6.89 ± 2.67 mmol/L P < 0.05), but this was not statistically lower than placebo (6.89 ± 2.67 versus 7.33 ± 2.56 mmol/L, P > 0.05). One study of people with earlier stages of CKD (60 participants) showed that in people with stage 3 CKD who were treated with pioglitazone-losartan, there were higher rates of decline in blood glucose values compared with people treated with losartan only. This difference was significant after 12 months (change (mean ± SD) after 12 months –22.7 ± 6.9% for pioglitazone-losartan ther-

						apy as compared with −15.1 ± 6.3% for losartan alone; P < 0.01). Larger reductions in FBG concentrations were observed for people in this study with stage 4 CKD after 12 months of the combined as compared with the single-drug treatment (i.e. −22.9 ± 8.9% versus −17.6 ± 5.9%; P = 0.07), but the difference was not significant.
Death (all causes)	77 per 1,000	38 per 1,000 (4 to 398)	RR 0.50 (0.05 to 5.18)	52 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1 4]	-
All cardiovascular death	-	-	-	-	-	Not reported.
Weight (kg)	-	-	-	222 (5)	⊕⊖⊖⊖ VERY LOW[5 6]	From qualitative synthesis of data from 3 studies (total of 110 participants), pioglitazone did not result in a significant increase of dry weight compared to placebo in patients receiving HD (Abe 2007; Abe 2008a; Pfutzner 2011) or a significant increase of body weight compared to placebo in patients with an eGFR 15 to < 60 mL/min/1.73 m^2 (Jin 2007: 60 participants). Conversely, in patients receiving PD (Wong 2005: 52 participants), rosiglitazone resulted in more weight gain (mean ± SD) compared to placebo (2.0% ± 5.6% versus control, -0.8% ± 4.4%; P = 0.049).
eGFR (mL/min/1.73 m^2)	-	-	-	-	-	Not reported.
Hypoglycaemia	59 per 1,000	56 per 1,000 (9 to 358)	RR 0.95 (0.15 to 6.08)	70 (2 RCTs)	⊕⊖⊖⊖ VERY LOW [1 4]	-
Discontinuation of medication due to adverse events	0 per 1,000	0 per 1,000 (0 to 0)	not estimable	63 (1 RCT)	⊕⊖⊖⊖ VERY LOW [4 5]	-

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

__CI:__ Confidence interval; __RR:__ Risk ratio; __MD__: mean difference; __HbA1c__: haemoglobin A1c (glycated); __FBG__: fasting blood glucose; __eGFR__: estimated glomerular filtration rate; __HD__: haemodialysis; __CKD__: chronic kidney disease

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Risk of attrition and funding bias
[2] Substantial heterogeneity
[3] CI is wide and effect shows appreciable benefit and harm
[4] Only 1 study had data for this outcome
[5] Risk of selection, performance and detection bias
[6] Narrative/qualitative synthesis was conducted. Estimates were not precise

Summary of findings 5. Sitagliptin versus glipizide for treating people with diabetes and chronic kidney disease (CKD)

Sitagliptin versus glipizide for treating people with diabetes and CKD

Patient or population: people with diabetes and CKD
Intervention: sitagliptin
Comparison: glipizide

Outcomes	Anticipated absolute effects* (95% CI)		Effect estimate (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with glipizide	Risk with sitagliptin				
HbA1c (%) HbA1c (mmol/mol)	The mean HbA1c was 0.05% lower (0.39 lower to 0.29 higher) with glipizide compared to sitagliptin The mean HbA1c was 0.6 mmol/mol lower (4.3 lower to 3.2 higher) with glipizide compared to sitagliptin		MD -0.05 (-0.39 to 0.29) MD -0.6 (-4.3 to 3.2)	398 (2)	⊕⊕⊖⊖ LOW [1,2]	-
FBG (mmol/L)	Mean FBG was 0.36 mmol/L higher (0.1 lower to 0.82 higher) with glipizide compared to sitagliptin		MD 0.36 (-0.1 to 0.82)	397 (2)	⊕⊕⊖⊖ LOW [1,3]	-
Death (all causes)	47 per 1,000	26 per 1,000 (10 to 64)	RR 0.55 (0.22 to 1.36)	551 (2)	⊕⊖⊖⊖ VERY LOW [1,4]	-
All cardiovascular death	-	-	-	-	-	Not reported.
Weight (kg)	-	-	-	552 (2)	⊕⊕⊖⊖ LOW [1,5]	In one study in people with an eGFR < 50 mL/min/1.73 m^2 but not on dialysis (423 participants) sitagliptin resulted in

						a reduction in body weight (-0.6 kg) compared to glipizide where the body weight increased (1.2 kg), resulting in a statistically significant (P < 0.001) between-group difference of -1.8 kg. Conversely in another study in people with ESKD on dialysis (129 participants), sitagliptin had a similar effect to glipizide on weight -1.00 kg (-2.80 to 0.80) P = 0.28.
eGFR (mL/min/1.73 m^2)	-	-	-	552 (2)	⊕⊕⊖⊖ LOW [1 5]	One study (423 participants) occurred in patients with an eGFR < 50 mL/min/1.73 m^2 and not on dialysis. There were similar reductions from baseline in eGFR observed in the sitagliptin and glipizide groups (sitagliptin, 23.9 mL/min/1.73 m^2; glipizide, 23.3 mL/min/1.73 m^2). Similarly in another study (129 participants) which occurred in patients receiving dialysis, there were no meaningful differences in changes from baseline in eGFR, SCr, UACR between sitagliptin and glipizide.
Hypoglycaemia	155 per 1,000	62 per 1,000 (36 to 107)	RR 0.40 (0.23 to 0.69)	551 (2)	⊕⊕⊕⊖ MODERATE [1]	-
Discontinuation of medication due to adverse events	90 per 1,000	84 per 1,000 (49 to 144)	RR 0.93 (0.54 to 1.60)	551 (2)	⊕⊖⊖⊖ VERY LOW [1 4]	-

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

CI: Confidence interval; **RR:** Risk ratio; **MD**: mean difference; **HbA1c**: haemoglobin A1c (glycated); **FBG**: fasting blood glucose; **eGFR**: estimated glomerular filtration rate; **ESKD**: end-stage kidney disease; **SCr**: serum creatinine; **UACR**: urinary albumin/creatinine ratio

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

[1] Both studies had funding bias and attrition bias
[2] Heterogeneity in results
[3] Effect has either benefit or harm with a confidence interval that crosses 1
[4] Effect has both appreciable benefit and harm with a wide confidence interval that crosses 1

[5] Narrative/Qualitative synthesis was conducted. Estimates were not precise

BACKGROUND

Description of the condition

Diabetes is a highly prevalent condition, affecting 8.2% of adults or 382 million people globally. The incidence is increasing with an estimated global prevalence of 592 million people by 2035 (IDF 2013).

Chronic kidney disease (CKD), defined as the sustained loss of kidney function over an extended period of time or the presence of albuminuria or other markers of kidney damage, has been estimated to affect 16% of the general population in screening studies (Chadban 2003; Coresh 2003; Perkovic 2007). CKD prevalence is increasing in the USA and other countries (Chadban 2003). Progression to end-stage kidney disease (ESKD) leads to significant morbidity and mortality with people requiring permanent renal replacement therapy (RRT) either as dialysis or kidney transplantation. The prognosis of people with ESKD is poor, with a 6% to 20% annual mortality rate for all people on dialysis (Collins 2008).

Diabetes is the commonest cause of CKD, and accounts for up to 50% of people who develop ESKD (Collins 2007; ANZDATA 2008). The increasing incidence of diabetes is a likely contributor to the escalating incidence of CKD, with one third of the increase in ESKD cases from 1978 to 1991 in the USA attributable to diabetes. Diabetes is also a common comorbidity in people with non-diabetic kidney disease (ANZDATA 2008). Both diabetes and CKD are associated with an increased risk of cardiovascular disease, with the risk being additive for people with both conditions, and increasing with CKD progression (Radbill 2008).

Observational studies reporting on the relationship between glucose control and clinical outcomes in diabetes and CKD are conflicting with some showing a clear positive association (Morioka 2001; Oomichi 2006; Wu 1997), others showing no relationship (Shurraw 2010; Williams 2006), and some a U-shaped association (Shurraw 2011). This discrepancy results from inherent limitations of observational studies, differences in the characteristics of study populations, and differences in glucose control measurements. Additionally, most considered glucose control as a single predictor of clinical outcomes rather than a component of a multifaceted treatment regimen including the control of blood pressure (BP), cholesterol and weight (Feldt-Rasmussen 2006).

Description of the intervention

Pharmacological interventions used to improve glucose control include both oral glucose-lowering agents and injectables including glucose-like peptide type 1 analogues (GLP-1) and insulin. In type 2 diabetes, these agents are used as single or combination therapy, with pharmacological agent choice and combination tailored to the patient being treated. Pharmacotherapy is typically introduced in a stepwise fashion beginning with oral agents followed by the introduction of injectables such as GLP-1 analogues and insulin (ADA 2017; Inzucchi 2012). In type 1 diabetes, insulins are the mainstay of therapy (ADA 2017).

Apart from insulins, the choice of available pharmacological interventions to lower high glucose levels has expanded rapidly over the past decade. Commonly prescribed classes of glucose-lowering medications include biguanides, thiazolidinediones (glitazones), second generation sulphonylureas, α-glucosidase inhibitors, glucagon-like peptide-1 analogues, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium glucose co-transporter 2 (SGLT2) inhibitors, and insulins. Newer or emerging classes of glucose-lowering medications are dual peroxisome proliferator-activated receptor (PPAR) agonists, amylin analogues, bromocriptine and GPR40 or free fatty acid receptor 1 (FFAR1) agonists.

To date, the efficacy and safety of these therapies have not been well documented in people with diabetes and CKD.

How the intervention might work

Large scale studies conducted in people with diabetes and preserved kidney function provide evidence that intensive glucose-lowering reduces the incidence and progression of microvascular outcomes (ADVANCE Group 2008; CONTROL Group 2009; DCCT Group 1993; DCCT Group 1995; Duckworth 2009; Holman 2008; Ismail-Beigi 2010 Nathan 2005; UKPDS 33 1998; UKPDS 34 1998). Additionally, several large studies and meta-analysis have shown that intensive glucose-lowering reduces the progression of kidney disease (ADVANCE Group 2008; DCCT Group 1995; Duckworth 2009; Ismail-Beigi 2010; Levin 2000; Ohkubo 1995; UKPDS 33 1998; Zoungas 2017), with both the ADVANCE (ADVANCE Group 2008) and ACCORD (Ismail-Beigi 2010) studies showing that progression of both microalbuminuria and macroalbuminuria were reduced, and the ADVANCE study showing a reduction in the development of ESKD (Perkovic 2013).

Given that diabetes is the leading cause of CKD worldwide, optimal glucose control in people with kidney disease has been proposed to reduce adverse kidney and cardiovascular events. However, existing studies have mainly studied participants without CKD. Consequently, it is unknown whether these benefits would be observed in people with established CKD, especially with more advanced CKD (stages 3 to 5).

Why it is important to do this review

Achieving near normal glucose levels in people with diabetes and CKD poses a challenging task. The development and progression of CKD results in glucometabolic changes (increased hepatic glucose output, reduced glucose disposal and greater insulin resistance), that increase blood glucose levels. Simultaneously, reduced insulin and drug clearance increase the risk of hypoglycaemia (Moen 2009). Moreover, the commencement of dialysis improves insulin sensitivity (Kobayashi 2000) and increases the risk of hypoglycaemia (Jackson 2000; Loipl 2005).

Past studies of intensive glucose control have failed to include meaningful numbers of people with CKD (that is, reduced glomerular filtration rate (GFR)) with much of the evidence coming from studies involving people with diabetes in the general population or those with earlier stages of kidney disease. Based on currently available evidence, international guidelines (Chadban 2010; KDOQI 2012) continue to advocate the achievement of optimal glucose control as part of a comprehensive treatment approach for people with diabetes and CKD.

Given the current uncertainty regarding the effectiveness and safety of contemporary glucose-lowering strategies, a critical review is urgently needed to inform clinical practice and highlight areas requiring further research.

Originally, this review was to be part of a larger review examining glucose-lowering therapies in CKD and kidney transplantation ("Glucose-lowering therapies for chronic kidney disease and kidney transplantation") (Jun 2012). However, as the specific challenges of managing blood glucose levels were deemed different in kidney transplant recipients compared with other people with CKD, we decided to examine the efficacy and safety of contemporary glucose-lowering in these different populations in separate reviews. This review examined glucose-lowering in people with diabetes and CKD. The accompanying review "Glucose-lowering agents for treating pre-existing and new onset diabetes in kidney transplant recipients" (Lo 2017) was published in February 2017.

OBJECTIVES

To examine the efficacy and safety of insulin and other pharmacological interventions for lowering glucose levels in people with diabetes and CKD.

METHODS

Criteria for considering studies for this review

Types of studies

1. All randomised controlled trials (RCTs)
2. Quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods)
3. Cross-over studies (first phase considered only).

Types of participants

Inclusion criteria

Adults and children with diabetes and CKD. The definition of CKD will be limited to an eGFR < 60 mL/min/1.73 m^2 or The Kidney Disease Improving Global Outcomes (KDIGO) GFR stages 3 to 5 (KDIGO 2011; KDOQI 2002).

Exclusion criteria

Transplant recipients (kidney, pancreas and islet cell).

Types of interventions

Head-to-head comparisons of active regimens (including comparisons of monotherapy or combination therapy with two or more pharmacological glucose-lowering interventions, comparisons of different doses and durations of the same intervention) or active regimen compared with placebo, control or standard care.

1. Metformin
2. Insulin
3. Sulphonylurea (excluding first generation)
4. Glinides
5. Glitazones
6. α-glucosidase inhibitors
7. Glucagon-like peptide-1 agonists
8. DPP-4 inhibitors
9. SGLT2 inhibitors
10. Amylin analogues
11. Bromocriptine.

Types of outcome measures

1. Efficacy
2. Safety.

Primary outcomes

1. Glycated haemoglobin A1c (HbA1c)
2. Fasting blood glucose (FBG)

Secondary outcomes

1. Kidney function (creatinine, estimated GFR (eGFR), albuminuria)
2. Systolic and diastolic BP
3. Lipids (total cholesterol, HDL, LDL, triglyceride)
4. Body weight
5. Death (all causes)
6. Macrovascular events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke)
7. Microvascular events (new or worsening kidney disease, or retinopathy)
8. Safety
   a. Hypoglycaemia
   b. Discontinuation of medication due to adverse events
   c. Other adverse events as described by the authors.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Specialised Register to 12 February 2018 through contact with the Information Specialist using search terms relevant to this review. The Specialised Register contains studies identified from the following sources.

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

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

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

Searching other resources

1. Reference lists of review articles, relevant studies and clinical practice guidelines.

2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

The search strategy described was used to obtain titles and abstracts of all possible studies relevant to the review. The titles and abstracts were screened independently by two authors, who discarded studies that were not applicable. However, studies and reviews that might include relevant data or information on studies were retained initially. Two authors independently assessed retrieved abstracts, and if necessary the full text, of these studies to determine which satisfied the inclusion criteria. Two other independent authors assessed studies written in Chinese.

Data extraction and management

Data extraction was carried out independently by two authors using standard data extraction forms for English studies, and two other authors independently extracted data for relevant studies in Chinese. Where more than one publication of one study existed, reports were grouped together and relevant data from each report were used in the analyses. Where relevant outcomes were only published in earlier versions these data were used. Any discrepancies between published versions were highlighted. The following data were extracted - participant characteristics (including demographic information and comorbidities), interventions (including concomitant medications and interventions), and the previously specified primary and secondary outcomes (Types of outcome measures). Any disagreements were resolved by a fifth author.

Assessment of risk of bias in included studies

The following items were independently assessed by four authors (two for studies in English and two for studies in Chinese) using the risk of bias assessment tool (Higgins 2011) (see Appendix 2).

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

Any disagreements were resolved by a fifth author.

Measures of treatment effect

For dichotomous outcomes (all-cause mortality, macrovascular events, microvascular events) results were expressed as risk ratios (RR) with 95% confidence intervals (CI). Where continuous scales of measurement were used to assess the effects of treatment (HbA1c, FBG, BP, lipids, body weight), the mean difference (MD) was expressed, or the standardised mean difference (SMD) if different scales had been used.

For adverse events, results were expressed as post treatment absolute risk differences.

Unit of analysis issues

All units for analysis were converted to SI units and % for HbA1c.

Dealing with missing data

Any additional information required from the original authors were requested by written correspondence (e.g. emailing corresponding author) and any relevant information obtained was included in the review. Evaluation of important numerical data such as screened and randomised people as well as intention-to-treat, as-treated and per-protocol populations were carefully performed. Attrition rates, for example drop-outs, losses to follow-up and withdrawals were investigated. Issues of missing data and imputation methods (for example, last-observation-carried-forward) were critically appraised (Higgins 2011).

Assessment of heterogeneity

Heterogeneity was first assessed by visual inspection of the forest plot before being analysed using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test (Higgins 2003).

The interpretation of I^2 values is as follows:

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

The importance of the observed value of I^2 depends on the magnitude and direction of treatment effects and the strength of evidence for heterogeneity (e.g. P-value from the Chi^2 test, or a confidence interval for I^2; Higgins 2011).

Assessment of reporting biases

If sufficient RCTs were identified, funnel plots were used to assess for the potential existence of small study bias (Higgins 2011).

Data synthesis

Data were pooled using the random-effects model but the fixed-effect model was also used to ensure robustness of the model chosen and susceptibility to outliers. Where data were reported in insufficient detail to allow meta-analysis and further information was not forthcoming from trialists, these outcomes were tabulated and assessed with descriptive techniques and where possible the risk difference (RD) with 95% CI was calculated. If adequate data were available then the number of persons needed to treat to avoid one cardiovascular death was calculated.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was used to explore possible sources of heterogeneity according to the following characteristics:

- Sex
- Age

- History of cardiac disease
- Glucose-lowering agent and dose of glucose-lowering agent
- Concomitant glucose-lowering agents (such as insulin)
- Dose and duration of concomitant glucose-lowering agent used (such as insulin)
- Concomitant medications (such as aspirin or BP medications)
- Baseline HbA1c level
- Type 1 diabetes versus type 2 diabetes
- CKD stages (3, 4 and 5)
- Primary cause of kidney disease (diabetes versus others).

Adverse effects were tabulated and assessed with descriptive techniques. Where possible, the risk difference with 95% CI was calculated for each adverse effect, either compared to no treatment or to another agent.

Sensitivity analysis

Sensitivity analyses explored the influence of the following factors on effect size:

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

'Summary of findings' tables

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

- HbA1c
- Fasting glucose
- eGFR
- Weight
- Death (all causes)
- All cardiovascular death
- Hypoglycaemia
- Discontinuation of medications due to adverse events.

RESULTS

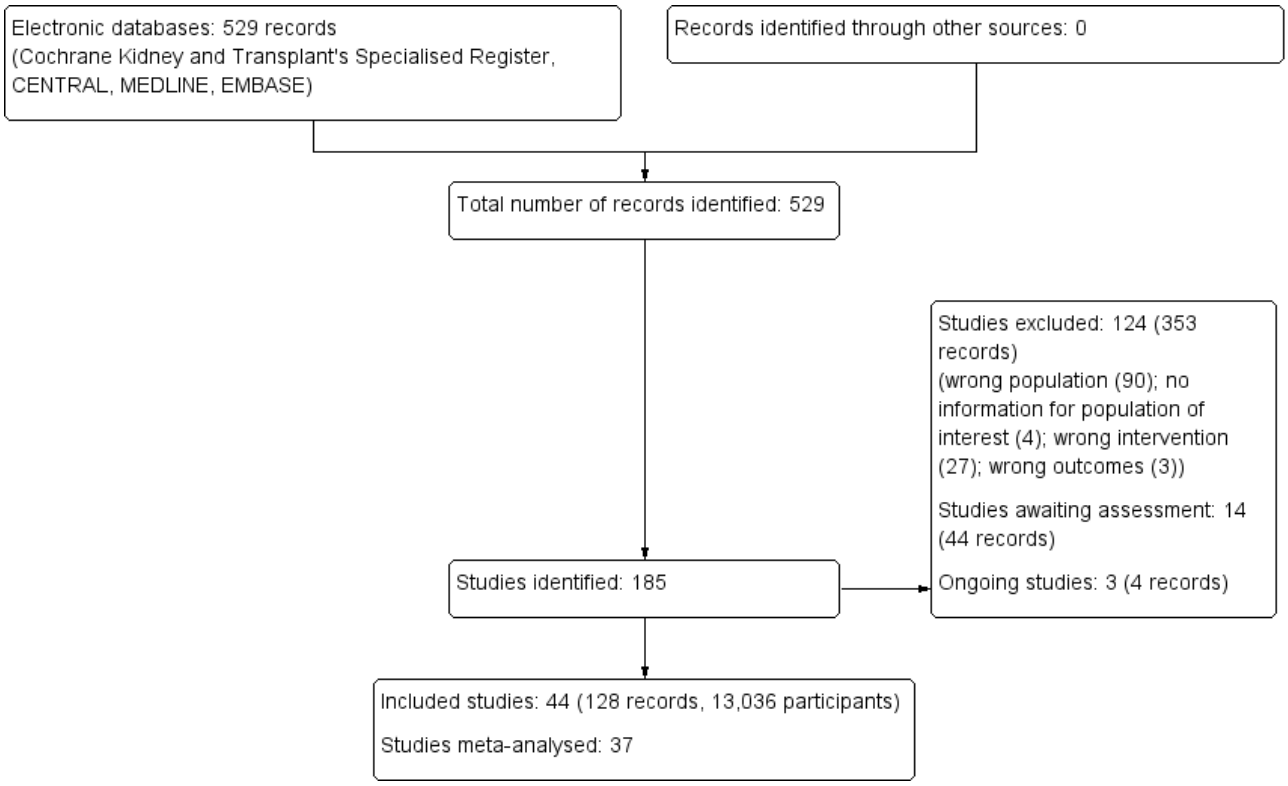
Description of studies

See Characteristics of included studies, Characteristics of excluded studies, Characteristics of studies awaiting classification and Characteristics of ongoing studies.

Results of the search

The search identified 185 studies (529 records). Following assessment of titles, abstracts and full-text articles, we included 44 studies (128 records) and excluded 124 studies (353 records). Fourteen studies are awaiting assessment (mostly awaiting data from the authors), and three studies are ongoing (see Figure 1); these will be included in a future update of this review.

Figure 1. Study flow diagram.



Included studies

We included 44 studies (13,036 participants) for qualitative synthesis, however after contact with authors, only 37 studies had adequate data to be quantitatively synthesised for meta-analyses.

Nine studies compared SGLT2 inhibitors to placebo in people with an eGFR 15 to < 60 mL/min/1.73 m^2. Two studies compared dapagliflozin to placebo (Kaku 2014; Kohan 2014); three studies compared empagliflozin to placebo (EMPA-REG BP 2015; EMPA-REG OUTCOME 2013; EMPA-REG RENAL 2014), one study compared luseogliflozin to placebo (Haneda 2016), one study compared canagliflozin to placebo (Yale 2013), and one study compared ipragliflozin to placebo (LANTERN 2015). Additionally, one study compared a dual SGLT1 and 2 inhibitor, LX4211 or sotagliflozin to placebo (Zambrowicz 2015). All studies could be included in the meta-analysis.

Thirteen studies compared DPP-4 inhibitors to placebo in people with an eGFR < 60 mL/min/1.73 m^2 including those receiving dialysis. Three studies compared saxagliptin to placebo (Abe 2016; Nowicki 2011; SAVOR-TIMI 53 2011), five studies compared linagliptin to placebo (Barnett 2013; Laakso 2015; Lewin 2012; McGill 2013; Yki-Järvinen 2013), two studies compared sitagliptin to placebo (Chan 2008a; TECOS 2013), two studies compared vildagliptin to placebo (Ito 2011a; Lukashevich 2011), and one study compared gemigliptin to placebo (GUARD 2017). All studies could be included in the meta-analysis.

Two studies compared GLP-1 agonists (liraglutide) to placebo (Idorn 2013; LIRA-RENAL 2016) in people with an eGFR < 60 mL/min/1.73 m^2 including those receiving dialysis. All studies were included in the meta-analysis.

Seven parallel studies and 1 cross-over study compared glitazones to placebo. The majority of participants were receiving HD but one study had people with an eGFR 15 to 59 mL/min/1.73 m^2 (Jin 2007). Six studies compared pioglitazone to placebo (Abe 2007; Abe 2008a; Abe 2010a; Jin 2007; Nakamura 2001; Pfutzner 2011), one study compared rosiglitazone to placebo (Wong 2005), and one cross-over study compared troglitazone to placebo (Nakamura 2001). Mohideen 2005 and Nakamura 2001 could not be included in the meta-analysis. It should be noted that troglitazone was withdrawn from the market by the US Food and Drug Administration (FDA) in 2000 due to the risk of liver failure and hepatotoxicity (FDA 2000).

One study compared glinides (mitiglinide) to control (not receiving mitiglinide) in people receiving HD (Abe 2010).

Seven studies compared one glucose-lowering agent to another. Two studies compared sitagliptin to glipizide in people with an eGFR < 50 mL/min/1.73 m^2 including those receiving dialysis (Arjona Ferreira 2013; Arjona Ferreira 2013a), one study compared vildagliptin to sitagliptin in those with an eGFR < 30 mL/min/1.73 m^2 including those receiving HD (Kothny 2015), one study compared albiglutide to sitagliptin in those with an eGFR 15 to <60 mL/min/1.73 m^2 (Leiter 2014), one study compared sitagliptin to insulin in people with an eGFR < 45 mL/min/1.73 m^2 including those on HD (Bellante 2016), and one study compared linagliptin to voglibose in those receiving HD (Mori 2016). Additionally, one study compared glitazars (aleglitazar) to pioglitazone (AleNephro 2014) in people with an eGFR 30 to < 60 mL/min/1.73 m^2. Only Arjona Ferreira 2013 and Arjona Ferreira 2013a could be included in the meta-analyses. One should note that the development of aleglitazar was halted by Roche in 2013 due to concerns about its safety and efficacy (ALECARDIO 2013).

Four studies compared different type, dosages, or modes of administration of insulin. One study compared 0.25 U/kg to 0.5 U/kg of insulin glulisine and glargine in those with an eGFR ≤ 45 mL/min/1.73 m^2 (Baldwin 2012), and one cross-over study compared insulin lispro to regular insulin in those with a GFR 50 to 60 mL/min (Ruggenenti 2003a). One parallel study (Diez 1987) and one cross-over study (Scarpioni 1994) compared intraperitoneal (IP) to subcutaneous (SC) insulin in those receiving PD. None of the studies could be included in the meta-analysis due to heterogeneity in the intervention or presentation of the results.

See Characteristics of included studies.

Excluded studies

We excluded 124 studies due to the following reasons:

- Wrong study population: 90 studies
- Inadequate information (data for people with an eGFR < 60 was not available from authors): 4 studies
- Wrong intervention: 27 studies
- No relevant outcomes: 3 studies

See Characteristics of excluded studies.

Risk of bias in included studies

Summaries of risk of bias are reported in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

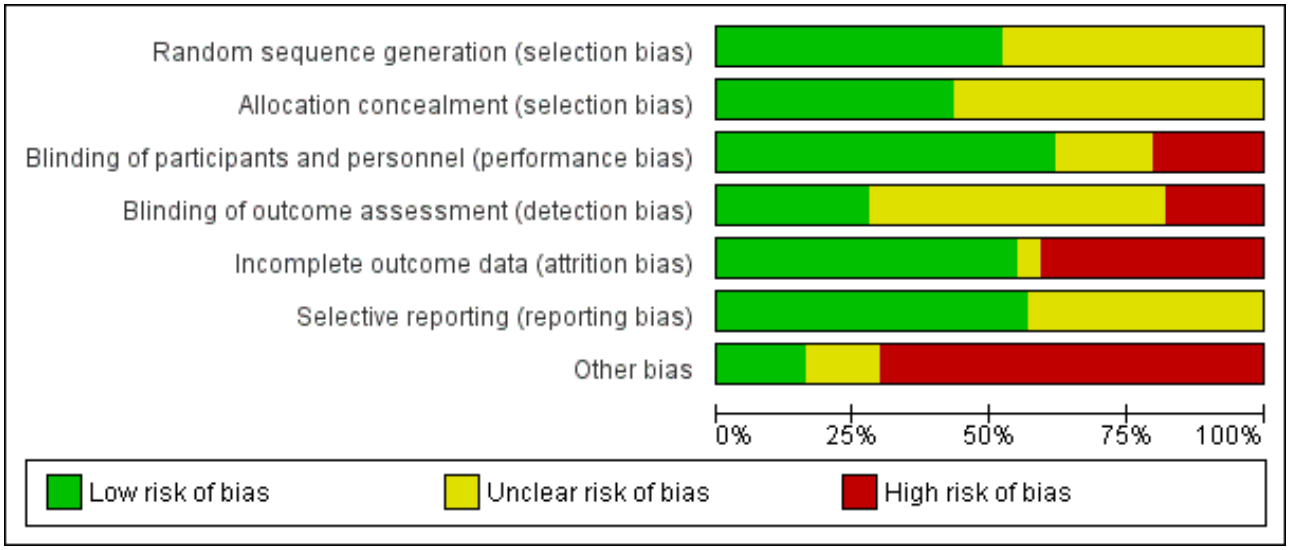


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

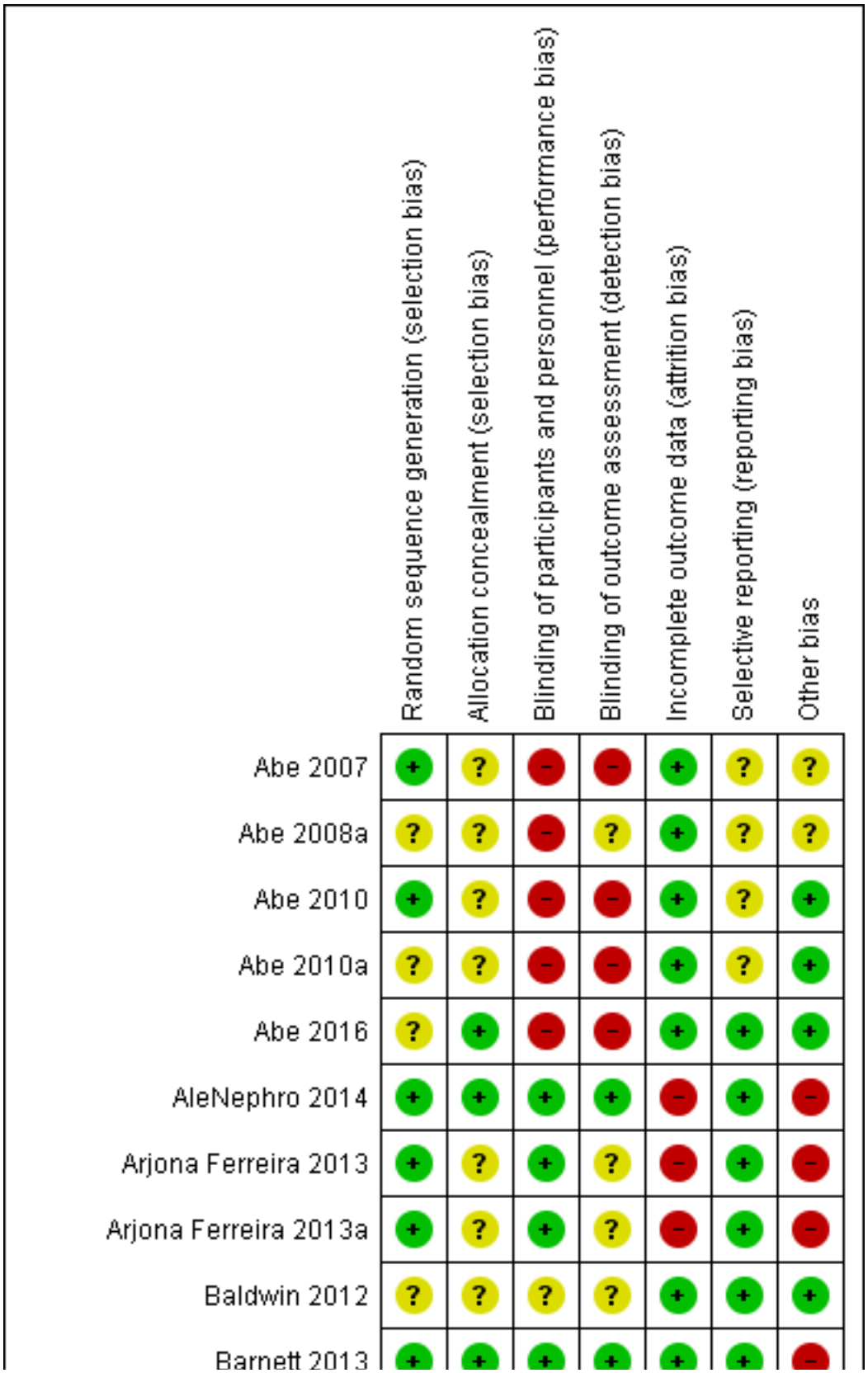


Figure 3. (Continued)

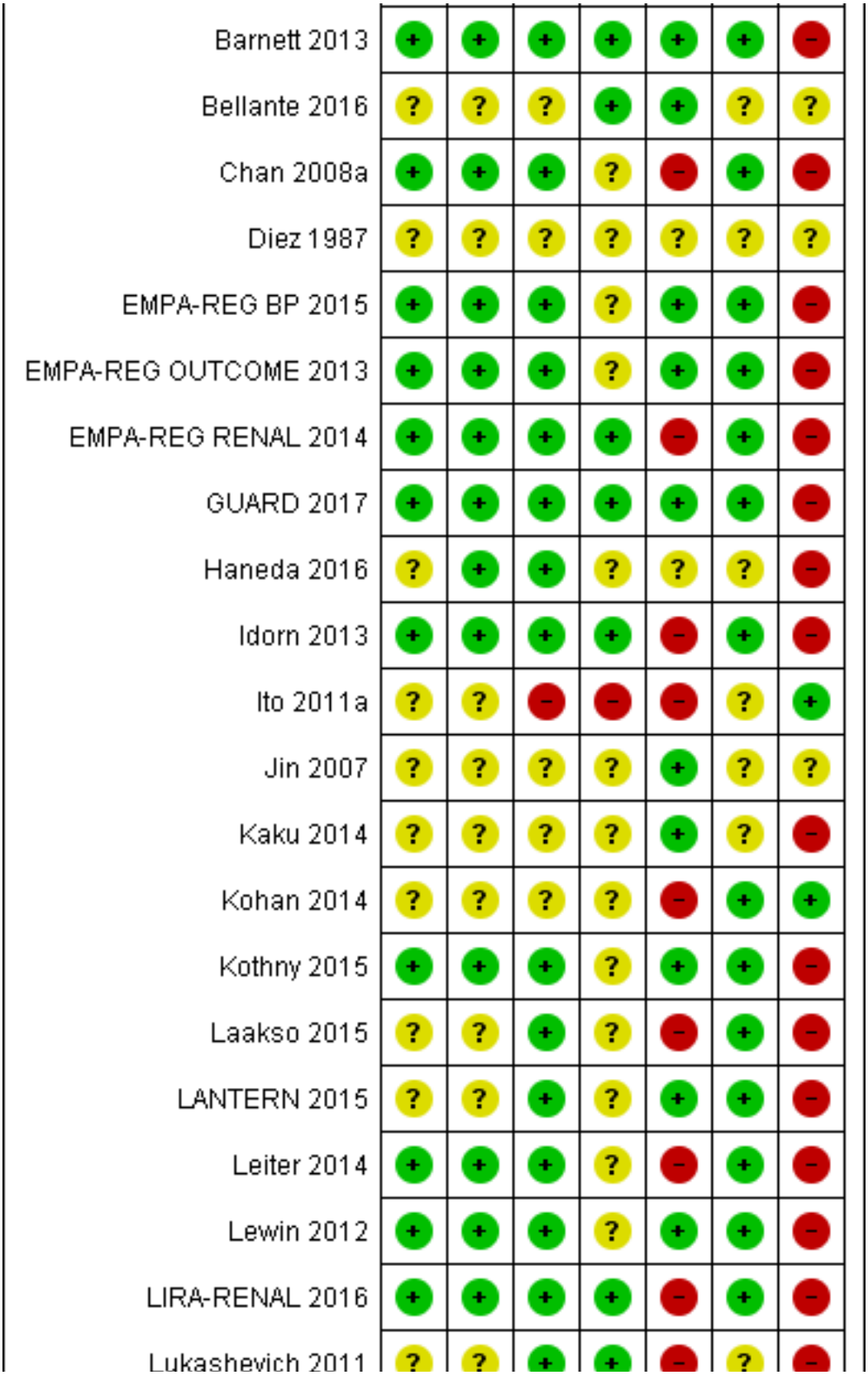
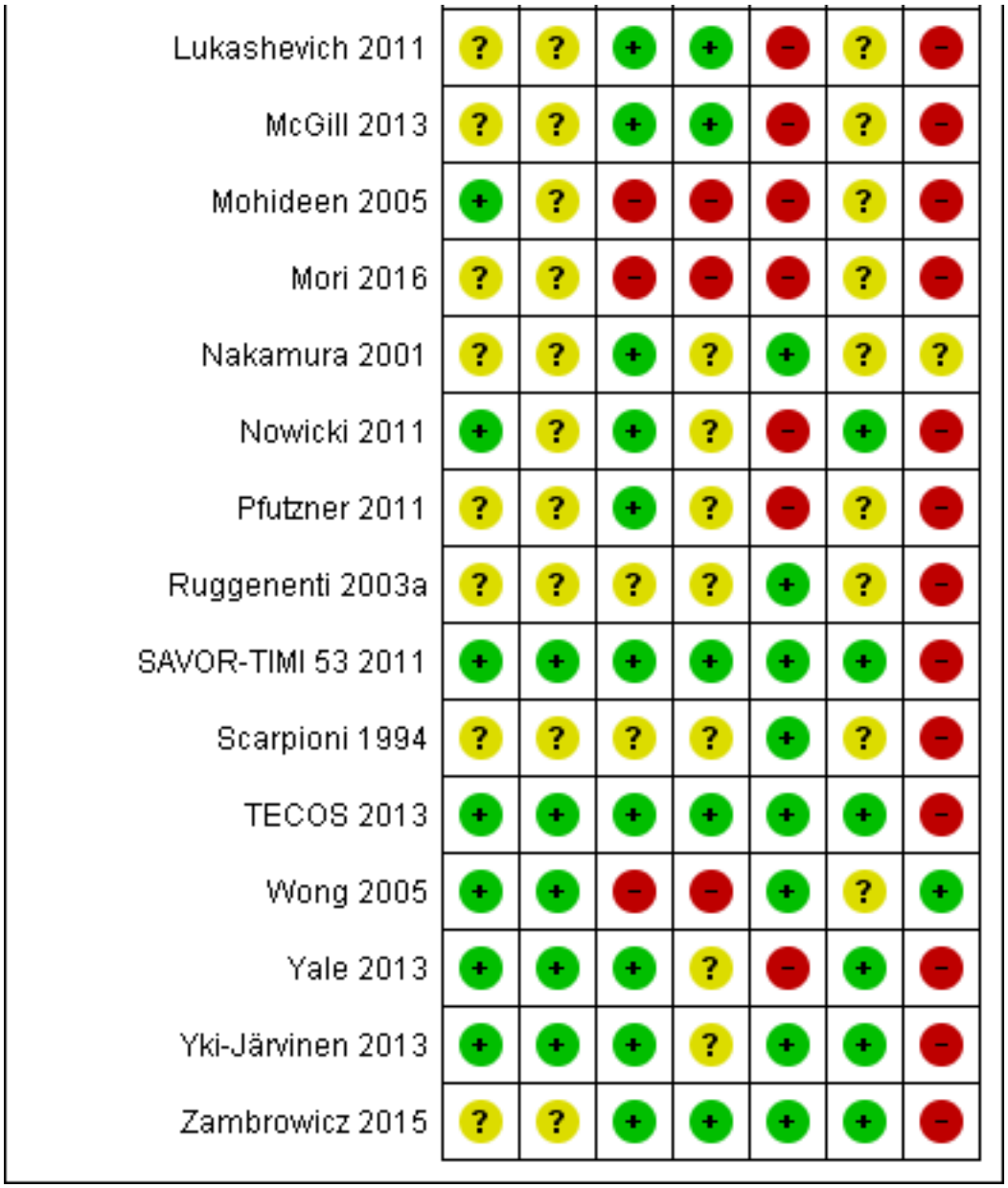


Figure 3. (Continued)



Allocation

Random sequence generation

Random sequence generation was judged to be at low risk of bias in 23 studies (Abe 2007; Abe 2010; AleNephro 2014; Arjona Ferreira 2013; Arjona Ferreira 2013a; Barnett 2013; Chan 2008a; EMPA-REG BP 2015; EMPA-REG OUTCOME 2013; EMPA-REG RENAL 2014; GUARD 2017; Idorn 2013; Kothny 2015; Leiter 2014; Lewin 2012; LIRA-RENAL 2016; Mohideen 2005; Nowicki 2011; SAVOR-TIMI 53 2011; TECOS 2013; Wong 2005; Yale 2013; Yki-Järvinen 2013) and unclear in 21 studies (Abe 2008a; Abe 2010a; Abe 2016; Baldwin 2012; Bellante 2016; Diez 1987; Haneda 2016; Ito 2011a; Jin 2007; Kaku 2014; Kohan 2014; Laakso 2015; LANTERN 2015; Lukashevich 2011; McGill 2013; Mori 2016; Nakamura 2001; Pfutzner 2011; Ruggenenti 2003a; Scarpioni 1994; Zambrowicz 2015).

Allocation concealment

Allocation concealment was judged to be at low risk of bias in 19 studies (Abe 2016; AleNephro 2014; Barnett 2013; Chan 2008a; EMPA-REG BP 2015; EMPA-REG OUTCOME 2013; EMPA-REG RENAL 2014; GUARD 2017; Haneda 2016; Idorn 2013; Kothny 2015; Leiter 2014; Lewin 2012; LIRA-RENAL 2016; SAVOR-TIMI 53 2011; TECOS 2013; Wong 2005; Yale 2013; Yki-Järvinen 2013) and unclear in 25 studies (Abe 2007; Abe 2008a; Abe 2010; AleNephro 2014; Arjona Ferreira 2013; Arjona Ferreira 2013a; Baldwin 2012; Bellante 2016; Diez 1987; Ito 2011a; Jin 2007; Kaku 2014; Kohan 2014; Laakso 2015; LANTERN 2015; Lukashevich 2011; McGill 2013; Mohideen 2005; Mori 2016; Nakamura 2001; Nowicki 2011; Pfutzner 2011; Ruggenenti 2003a; Scarpioni 1994; Zambrowicz 2015).

Blinding

Performance bias

Performance bias (blinding of participants and investigators) was judged to be at low risk of bias in 27 studies (AleNephro 2014; Arjona Ferreira 2013; Arjona Ferreira 2013a; Barnett 2013; Chan 2008a; EMPA-REG BP 2015; EMPA-REG OUTCOME 2013; EMPA-REG RENAL 2014; GUARD 2017; Haneda 2016; Idorn 2013; Kothny 2015; Laakso 2015; LANTERN 2015; Leiter 2014; Lewin 2012; LIRA-RENAL 2016; Lukashevich 2011; McGill 2013; Nakamura 2001; Nowicki 2011; Pfutzner 2011; SAVOR-TIMI 53 2011; TECOS 2013; Yale 2013; Yki-Järvinen 2013; Zambrowicz 2015) and at high risk of bias in 9 studies (Abe 2007; Abe 2008a; Abe 2010; Abe 2010a; Abe 2016; Ito 2011a; Mohideen 2005; Mori 2016; Wong 2005). The risk of bias was unclear in eight studies (Baldwin 2012; Bellante 2016; Diez 1987; Jin 2007; Kaku 2014; Kohan 2014; Ruggenenti 2003a; Scarpioni 1994).

Detection bias

Detection bias (blinding of outcome assessors) was judged to be at low risk of bias in 12 studies (AleNephro 2014; Barnett 2013; Bellante 2016; EMPA-REG RENAL 2014; GUARD 2017; Idorn 2013; Lukashevich 2011; LIRA-RENAL 2016; McGill 2013; SAVOR-TIMI 53 2011; TECOS 2013; Zambrowicz 2015) and at high risk of bias in eight studies (Abe 2007; Abe 2010; Abe 2010a; Abe 2016; Ito 2011a; Mohideen 2005; Mori 2016; Wong 2005). The risk of bias was unclear in 24 studies (Abe 2008a; Arjona Ferreira 2013; Arjona Ferreira 2013a; Baldwin 2012; Chan 2008a; Diez 1987; EMPA-REG BP 2015; EMPA-REG OUTCOME 2013; Haneda 2016; Jin 2007; Kaku 2014; Kohan 2014; Kothny 2015; Laakso 2015; LANTERN 2015; Leiter 2014; Lewin 2012; Nakamura 2001; Nowicki 2011; Pfutzner 2011; Ruggenenti 2003a; Scarpioni 1994; Yale 2013; Yki-Järvinen 2013).

Incomplete outcome data

Attrition bias was judged to be at low risk of bias in 24 studies (Abe 2007; Abe 2008a; Abe 2010; Abe 2010a; Abe 2016; Baldwin 2012; Barnett 2013; Bellante 2016; EMPA-REG BP 2015; EMPA-REG OUTCOME 2013; GUARD 2017; Jin 2007; Kaku 2014; Kothny 2015; LANTERN 2015; Lewin 2012; Nakamura 2001; Ruggenenti 2003a; SAVOR-TIMI 53 2011; Scarpioni 1994; TECOS 2013; Wong 2005; Yki-Järvinen 2013; Zambrowicz 2015) and at high risk of bias in 18 studies (AleNephro 2014; Arjona Ferreira 2013; Arjona Ferreira 2013a; Chan 2008a; EMPA-REG RENAL 2014; Idorn 2013; Ito 2011a; Kohan 2014; Laakso 2015; Leiter 2014; LIRA-RENAL 2016; Lukashevich 2011; McGill 2013; Mohideen 2005; Mori 2016; Nowicki 2011; Pfutzner 2011; Yale 2013). The risk of bias was unclear in two studies (Diez 1987; Haneda 2016).

Selective reporting

Reporting bias was judged to be at low risk of bias in 25 studies (Abe 2016; AleNephro 2014; Arjona Ferreira 2013; Baldwin 2012; Barnett 2013; Chan 2008a; EMPA-REG BP 2015; EMPA-REG OUTCOME 2013; EMPA-REG RENAL 2014; GUARD 2017; Idorn 2013; Kaku 2014; Kohan 2014; Kothny 2015; Laakso 2015; LANTERN 2015; Leiter 2014; Lewin 2012; LIRA-RENAL 2016; Nowicki 2011; SAVOR-TIMI 53 2011; TECOS 2013; Yale 2013; Yki-Järvinen 2013; Zambrowicz 2015) and was unclear in 19 studies (Abe 2007; Abe 2008a; Abe 2010; Abe 2010a; Arjona Ferreira 2013a; Bellante 2016; Diez 1987; Haneda 2016; Ito 2011a; Jin 2007; Lukashevich 2011; McGill 2013; Mohideen 2005; Mori 2016; Nakamura 2001; Pfutzner 2011; Ruggenenti 2003a; Scarpioni 1994; Wong 2005).

Other potential sources of bias

Thirty-one studies had a high risk of funding bias (AleNephro 2014; Arjona Ferreira 2013; Arjona Ferreira 2013a; Barnett 2013; Chan 2008a; EMPA-REG BP 2015; EMPA-REG OUTCOME 2013; EMPA-REG RENAL 2014; GUARD 2017; Haneda 2016; Idorn 2013; Kaku 2014; Kothny 2015; Laakso 2015; LANTERN 2015; Leiter 2014; Lewin 2012; LIRA-RENAL 2016; Lukashevich 2011; McGill 2013; Mohideen 2005; Mori 2016; Nowicki 2011; Pfutzner 2011; Ruggenenti 2003a; SAVOR-TIMI 53 2011; Scarpioni 1994; TECOS 2013; Yale 2013; Yki-Järvinen 2013; Zambrowicz 2015) due to the studies being supported by pharmaceutical companies and the majority of the authors receiving funding or being employees of these companies. Six studies did not report their funding source and conflicts of interest (Abe 2007; Abe 2008a; Bellante 2016; Diez 1987; Jin 2007; Nakamura 2001) and seven studies had a low risk of funding bias (Abe 2010; Abe 2010a; Abe 2016; Baldwin 2012; Ito 2011a; Kohan 2014; Wong 2005).

Effects of interventions

See: **Summary of findings for the main comparison** SGLT2 inhibitors versus placebo for treating people with diabetes and chronic kidney disease (CKD); **Summary of findings 2** DPP-4 inhibitors versus placebo for treating people with diabetes and chronic kidney disease (CKD); **Summary of findings 3** GLP-1 agonists versus placebo for treating people with diabetes and chronic kidney disease (CKD); **Summary of findings 4** Glitazone versus placebo for treating people with diabetes and chronic kidney disease (CKD); **Summary of findings 5** Sitagliptin versus glipizide for treating people with diabetes and chronic kidney disease (CKD)

Primary outcomes

Glycated haemoglobin A1c (HbA1c)

SGLT2 Inhibitors versus placebo

In people with an eGFR 30 to < 60 mL/min/1.73 m^2, SGLT2 inhibitors probably reduce HbA1c (MD -0.29%, 95% CI -0.38 to -0.19 (-3.2 mmol/mol, -4.2 to -2.2); I^2 = 0%; Analysis 1.1) compared to placebo (7 studies, 1092 participants; moderate certainty evidence) (EMPA-REG RENAL 2014; Haneda 2016; Kaku 2014; Kohan 2014; LANTERN 2015; Yale 2013).

DPP-4 inhibitors versus placebo

In people with an eGFR < 60 mL/min/1.73 m^2 including those people with ESKD receiving dialysis, DPP-4 inhibitors may reduce HbA1c (MD -0.62%, 95% CI -0.85 to -0.39 (-6.8 mmol/mol, -9.3 to -4.3); I^2 = 59%; Analysis 2.1) compared to placebo (7 studies, 867 participants; low certainty evidence) (Barnett 2013; Chan 2008a; GUARD 2017; Laakso 2015; McGill 2013; Nowicki 2011; Yki-Järvinen 2013).

GLP-1 agonists versus placebo

In people with an eGFR < 60 mL/min/1.73 m^2 including those people receiving HD, GLP-1 agonists probably reduce HbA1c (MD -0.53%, 95% CI -1.01 to -0.06 (-5.8 mmol/mol, -11.0 to -0.7); I^2 = 41%; Analysis 3.1), compared to placebo (2 studies, 283 participants; moderate certainty evidence) (Idorn 2013; LIRA-RENAL 2016).

Glitazones versus placebo/control

In people receiving HD and PD it is uncertain whether glitazones have any effect on HbA1c (MD -0.41%, 95% CI -1.15 to 0.32 (-4.5 mmol/mol, -12.6 to 3.5); I^2 = 66%; Analysis 4.1) compared to placebo (2 studies, 88 participants; very low certainty evidence) (Pfutzner 2011; Wong 2005).

Glinides versus placebo/control

Abe 2010 compared glinide to no glinide treatment (36 participants) in people receiving dialysis. Mitiglinide was reported to reduce HbA1c compared to placebo over 24 weeks.

Sitagliptin versus glipizide

In people with an eGFR < 50 mL/min/1.73 m^2, including those on dialysis, sitagliptin may make little or no difference to HbA1c (MD -0.05%, 95% CI -0.39 to 0.29 (-0.6 mmol/mol, -4.3 to 3.2); I^2 = 67%; Analysis 6.1) compared to glipizide (2 studies, 398 participants; low certainty evidence) (Arjona Ferreira 2013; Arjona Ferreira 2013a).

Vildagliptin versus sitagliptin

Kothny 2015 compared vildagliptin to sitagliptin (148 participants) in people with an eGFR < 30 mL/min/1.73 m^2 including those receiving HD. In this study vildagliptin had little or no effect on HbA1c compared to sitagliptin (MD 0.02%, 95% CI -0.33 to 0.37 (0.2 mmol/mol, -3.6 to 4.0); P = 0.91; Analysis 7.1).

Albiglutide versus sitagliptin

Leiter 2014 compared albiglutide to sitagliptin (507 participants) in people with an eGFR 15 to < 60 mL/min/1.73 m^2. Albiglutide was reported to reduce HbA1c (MD -0.52%, 95% CI -0.77 to -0.27 (-5.7 mmol/mol, -8.4 to -3.0); P < 0.0001) compared to sitagliptin (Analysis 8.1).

Sitagliptin versus insulin

Bellante 2016 compared sitagliptin to insulin (49 participants) in people with an eGFR < 45 mL/min/1.73 m^2, including those people receiving HD. HbA1c was reported to be reduced from 8.2 ± 1.9% (66.1 ± 20.8 mmol/mol) at baseline to 7.3 ± 1.4% (56.3 ± 15.3 mmol/mol) at 52 weeks (P = 0.058) in the insulin group and was unchanged in the sitagliptin group (7.1 ± 1.0% (54.1 ± 10.9 mmol/mol) to 6.9 ± 0.8% (51.9 ± 8.7 mmol/mol)).

Linagliptin versus voglibose

Mori 2016 compared linagliptin to voglibose (78 participants) in people receiving HD. Linagliptin was reported to reduce HbA1c to a greater extent than voglibose (-0.60% (-6.6 mmol/mol) compared to -0.20% (-2.2 mmol/mol); treatment difference (-0.40%, 95% CI -0.74 to -0.06 (MD -4.4 mmol/mol, 95% CI -8.1 to -0.7); P = 0.022).

Aleglitazar versus pioglitazone

AleNephro 2014 compared aleglitazar to pioglitazone (302 participants) in people with an eGFR of 30 to < 60 mL/min/1.73 m^2. In this study aleglitazar made little or no difference to HbA1c compared to pioglitazone (MD 0.09%, 95% CI -0.19 to 0.37 (1.0 mmol/mol, -2.1 to 4.0); P = 0.53; Analysis 9.1).

Insulin

Two studies compared insulin administered IP to SC in people receiving PD (Diez 1987; Scarpioni 1994). In Diez 1987 (22 participants) there was no difference in HbA1c between the groups while Scarpioni 1994 (6 participants in a cross-over study) did not report HbA1c as an outcome.

Studies comparing regular insulin to lispro insulin (Ruggenenti 2003a; 11 participants) and 0.25 U/kg of insulin glulisine and glargine compared to 0.5 U/kg (Baldwin 2012; 107 participants) did not report HbA1c as an outcome.

Fasting blood glucose

SGLT2 inhibitors versus placebo

In people with an eGFR of 15 to < 60 mL/min/1.73 m^2, SGLT2 inhibitors probably reduce FBG by 0.48 mmol/L (95% CI -0.78 to -0.19; I^2 = 0%; Analysis 1.2) compared to placebo (5 studies; 855 participants; moderate certainty evidence) (EMPA-REG RENAL 2014; Haneda 2016; Kohan 2014; Yale 2013; Zambrowicz 2015).

DPP-4 inhibitors versus placebo

In people with an eGFR < 60 mL/min/1.73 m^2, inclusive of people with ESKD receiving dialysis, DPP-4 inhibitors may make little or no difference to FBG (MD -0.47 mmol/L, 95% CI -1.08 to 0.15; I^2 = 16%; Analysis 2.2,) compared to placebo (4 studies; 589 participants; low certainty evidence) (Chan 2008a; Laakso 2015; McGill 2013; Nowicki 2011).

GLP-1 agonists versus placebo

LIRA-RENAL 2016 (279 participants) quantified the difference in effect of liraglutide compared to placebo in people with an eGFR of 30 to < 60 mL/min/1.73 m^2. Liraglutide was reported to reduce FBG by 1.08 mmol/L (95% CI -1.71 to -0.45; P = 0.0008) compared to placebo (Analysis 3.2). Idorn 2013 (24 participants) did not report FBG.

Glitazones versus placebo/control

Meta-analysis of data was not possible due to heterogeneity in the outcomes and reporting of outcomes. Qualitative synthesis of the studies showed that glitazones, particularly pioglitazone may reduce FBG compared to placebo in people with an eGFR < 60 mL/min/1.73 m^2, including people on HD.

Two studies (71 participants) in HD people reported that pioglitazone reduced FBG more so than in the group not receiving pioglitazone (both P < 0.05; Abe 2007 (31 participants); Abe 2008a (40 participants)). Similarly, another study in HD people (Pfutzner 2011 (39 participants)) reported that pioglitazone reduced the FBG by 2.91 mmol/L (95% CI -5.44 to -0.38; P = 0.02) compared to placebo (Analysis 4.2).

In people with stage 3 CKD (60 participants), after 12 months, Jin 2007 reported pioglitazone-losartan treatment resulted in a higher rate of decline for FBG values compared to losartan-only treatment (change after 12 months –22.7 ± 6.9% for pioglitazone-losartan therapy as compared with –15.1 ± 6.3% for losartan alone; P < 0.01). In stage 4 CKD, this drug combination was reported to have had little or no effect on FBG after 12 months compared with single-drug treatment (–22.9 ± 8.9% versus –17.6 ± 5.9%; P = 0.07).

Conversely Abe 2010a (63 participants) reported that in HD people, pioglitazone reduced FBG at the end of the study compared to the start (7.72 ± 2.50 versus 6.89 ± 2.67 mmol/L; P < 0.05). However pioglitazone makes little or no difference to FBG compared to

people not receiving pioglitazone (6.89 ± 2.67 mmol/L versus 7.33 ± 2.56 mmol/L; P > 0.05).

Data were unavailable from three studies (Mohideen 2005; Nakamura 2001; Wong 2005).

Glinides versus placebo/control

Abe 2010 compared glinides to a control group (36 participants) in people receiving HD. Mitiglinide was reported to reduce FBG compared to placebo over 24 weeks.

Sitagliptin versus glipizide

In people with an eGFR < 60 mL/min/1.73 m^2 including those people receiving HD, sitagliptin may make little or no difference to FBG (MD 0.36 mmol/L, 95% CI -0.10 to 0.82; I^2 = 0%; Analysis 6.2) compared to glipizide (2 studies; 397 participants; low certainty evidence) (Arjona Ferreira 2013; Arjona Ferreira 2013a).

Vildagliptin versus sitagliptin

Kothny 2015 compared vildagliptin to sitagliptin (148 participants) in people with an eGFR < 30 mL/min/1.73 m^2 including those receiving HD. This study reported vildagliptin made little or no difference to FBG compared to sitagliptin (MD -0.63 mmol/L, 95% CI -1.74 to 0.48; P = 0.27; Analysis 7.2).

Albiglutide versus sitagliptin

Leiter 2014 compared albiglutide to sitagliptin (507 participants) in people with an eGFR of 15 to < 60 mL/min/1.73 m^2. Albiglutide was reported to reduce the FBG by 1.61 mmol/L (95% IC -2.35 to -0.87, P < 0.0001), compared to sitagliptin (Analysis 8.2).

Sitagliptin versus insulin

Bellante 2016 did not report FBG.

Linagliptin versus voglibose

Mori 2016 did not report FBG.

Aleglitazar versus pioglitazone

AleNephro 2014 compared aleglitazar to pioglitazone (302 participants) in people with an eGFR of 30 to < 60 mL/min/1.73 m^2. This study reported aleglitazar had little or no effect on FBG compared to pioglitazone (MD -0.32 mmol/L, 95% CI -0.91 to 0.27; P = 0.29; Analysis 9.2).

Insulin

Two studies compared IP versus SC insulin in people receiving PD (Diez 1987; Scarpioni 1994). Diez 1987 (22 participants) reported no difference in the FBG between groups, while Scarpioni 1994 (6 participants in a cross-over study) did not report FBG.

Baldwin 2012 (107 participants), compared 0.25 U/kg of insulin glulisine and glargine to 0.5 U/kg in people with an eGFR ≤ 45 mL/min/1.73 m^2. A SC insulin regimen of 0.25 U/kg/d (half of the dose insulin glulisine three times a day and half the dose glargine once a day) was reported to have had little or no effect on FBG compared to a regimen of 0.5 U/kg/d (half of the dose insulin glulisine three times a day and half of the dose glargine once a day; i.e. 8.62 ± 2.97 mmol/L versus 8.44 ± 3.48 mmol/L; P = 0.78) in people with an eGFR < 45 mL/min/1.73 m^2.

Ruggenenti 2003a did not report FBG.

Secondary outcomes

Kidney function (creatinine, eGFR, albuminuria)

SGLT2 inhibitors versus placebo

In people with an eGFR of 30 to < 60 mL/min/1.73 m^2, SGLT2 inhibitors probably increase SCr by 3.82 µmol/L (95% CI 1.45 to 6.19 (0.04 mg/dL, 0.02 to 0.07); I^2 = 16%; Analysis 1.12) and probably reduces eGFR by 1.85 mL/min/1.73 m^2 (95% CI -2.76 to -0.94; I^2 = 0%; Analysis 1.9) compared to placebo (4 studies, 848 participants; moderate certainty evidence) (EMPA-REG RENAL 2014; Haneda 2016; Kohan 2014; LANTERN 2015). However, SGLT2 inhibitors may reduce albuminuria (MD -8.14 mg/mmol creatinine, 95% CI -14.51 to -1.77 (-71.89 mg/g creatinine, -128.17 to -15.60); I^2 = 11%; Analysis 1.13) compared to placebo (5 studies; 1153 participants; low certainty evidence) (EMPA-REG RENAL 2014; Haneda 2016; Kohan 2014; LANTERN 2015; Yale 2013) (Analysis 1.13).

Relevant data suitable for incorporation in meta-analyses were not available from EMPA-REG OUTCOME 2013.

DPP-4 inhibitors versus placebo

Meta-analysis of data was not possible due to heterogeneity in, and reporting of, outcomes; as well as the different CKD stages of the participants studied. Two studies were in people undergoing dialysis making reporting of kidney function (creatinine, eGFR and albuminuria) meaningless (Abe 2016; Ito 2011a).

Several studies reported no significant or a small difference in the effects of DPP-4 inhibitors compared to placebo on kidney function. In McGill 2013 (133 participants), linagliptin made little or no difference to the risk of kidney failure compared to placebo. Similarly, in Yki-Järvinen 2013 (127 participants) there were no between-group imbalance in shifts in stage of CKD. Two studies compared the effect of saxagliptin to placebo on kidney function. In SAVOR-TIMI 53 2011, for people with an eGFR of 15 to < 50 mL/min/1.73 m^2 (2576 participants) saxagliptin was reported to reduce eGFR to a similar extent as placebo. In Nowicki 2011 (571 participants) which compared the effects of saxagliptin with placebo in people with a creatinine clearance (CrCl) < 50 mL/min, saxagliptin doubled the SCr concentration from baseline in three people during the 52-week treatment period. For those people not on dialysis, both saxagliptin and placebo were reported to slightly reduce the mean GFR (estimated by the Cockcroft-Gault and MDRD equations). Two studies compared the effect of sitagliptin to placebo on the eGFR. In Chan 2008a (91 participants), which compared sitagliptin to placebo in people with a CrCl ≥ 30 to < 50 mL/min, sitagliptin made little or no difference to SCr compared to placebo (MD 4.42 µmol/L, 95% CI -9.59 to 18.43 (0.05 mg/dL, -0.11 to 0.21); P = 0.54; Analysis 2.10). In TECOS 2013 (3324 participants) there was a reported small reduction with sitagliptin in eGFR compared to placebo (mean between group treatment difference -1.33 mL/min/1.73 m^2 (95% CI -2.45 to -0.21) for people with an eGFR 45 to 59 mL/min/1.73 m^2; and -2.25 mL/min/1.73 m^2 (95% CI -4.27 to -0.23) for people with an eGFR of 30 to 44 mL/min/1.73 m^2. Additionally in a study comparing vildagliptin to placebo (Lukashevich 2011; 525 participants), there was a reported small and similar decline in eGFR over the year in both groups.

Three studies reported an improvement in albuminuria. Chan 2008a (91 participants) compared sitagliptin to placebo in people with an eGFR < 50 mL/min/1.73 m^2 to people on dialysis. In both groups, there was an increase from baseline (mean ± SE) in the UACR of 25,425 ± 21,470 mg/mmol (225 ± 190 mg/mg) and 56,161 ± 49,494 mg/mmol (497 ± 438 mg/mg) for the sitagliptin and placebo groups respectively (Analysis 2.11). GUARD 2017 (130 participants) compared gemigliptin to placebo in people with an eGFR of 15 to 59 mL/min/1.73 m^2. Gemigliptin reduced the UACR at week 12 by 28.0% (95% CI -40.2 to -13.3) compared with 4.3% (95% CI -19.7 to 14.2) with placebo with a between-group difference of 24.8% (95% CI -41.8 to -2.9; P = 0.0294). However, Gemigliptin also reduced eGFR compared to placebo (MD -1.99 mL/min/1.73 m^2, 95% CI -3.49 to -0.49; P = 0.009; Analysis 2.9). In SAVOR-TIMI 53 2011, for people with an eGFR of 15 to < 50 mL/min/1.73 m^2 (2576 participants) saxagliptin reduced UACR compared to placebo. From baseline to two years, saxagliptin was reported to reduce UACR to a greater extent compared to placebo for those with an eGFR ≤ 50 and ≥ 30 mL/min/1.73 m^2 (-11.87 mg/mmol (-105 mg/g); P = 0.011) and an eGFR < 30 mL/min/1.73 m^2 (-27.71 mg/mmol (-245.2 mg/g); P = 0.086). In TECOS 2013 (3324 participants), for people with an eGFR of 30 to < 60 mL/min/1.73 m^2, sitagliptin did not reduce the UACR compared to placebo (mean between group treatment difference -0.03 mg/mmol, 95% CI -0.08 to 0.01 (-0.30 mg/g, -0.70 to 0.09) for people with an eGFR of 45 to 59 mL/min/1.73 m^2; and 0.03 mg/mmol, 95% CI -0.06 to 0.11 (0.23 mg/g, -0.54 to 1.00) for people with an eGFR of 30 to 44 mL/min/1.73 m^2)).

Data for kidney function were not available for three studies (Barnett 2013; Lewin 2012; SAVOR-TIMI 53 2011).

GLP-1 agonists versus placebo/control

Meta-analysis of data was not possible due to heterogeneity in, and reporting of, outcomes.

Qualitative synthesis of studies (303 participants) show that liraglutide made little or no difference to kidney function compared to placebo, although one of the studies occurred in people on dialysis (Idorn 2013). In Idorn 2013 (24 participants), for people with ESKD on dialysis, it was reported that liraglutide had little or no effect on SCr compared to placebo (MD -0.88 µmol/L, 95% CI -5.30 to 3.5 (-0.01 mg/dL, -0.06 to 0.04); P = 0.69; Analysis 3.9). However, this is meaningless given that the included people were on dialysis. Similarly in LIRA-RENAL 2016 (279 participants), liraglutide made little or no difference to kidney function parameters compared to placebo. Liraglutide makes little or no difference to the ratio of week 26 to baseline for SCr compared to placebo (P = 0.26). Liraglutide changed the mean eGFR from baseline to week 26 by -0.35 mL/min/1.73 m^2 compared to placebo (0.37 mL/min/1.73 m^2). The estimated ratio of the week 26 to baseline UACR was 0.87 with liraglutide and 1.05 with placebo.

Glitazones versus placebo/control

Meta-analysis of data was not possible.

The majority of studies included people who had ESKD and were on dialysis making reporting of eGFR, creatinine and albuminuria pointless (Abe 2007 (pioglitazone); Abe 2008a (pioglitazone); Abe 2010 (pioglitazone); Nakamura 2001 (pioglitazone); Pfutzner 2011 (pioglitazone); Wong 2005 (rosiglitazone)).

Jin 2007 (60 participants) compared pioglitazone added to losartan to losartan alone in people with an eGFR of 15 to < 60 mL/min/1.73 m^2. Pioglitazone plus losartan was reported to reduce SCr more than losartan alone in stage 3 and 4 CKD. GFR was reported to decline more sharply and significantly in those with losartan alone compared to pioglitazone plus losartan. In people with stage 3 CKD, the median change in proteinuria was reported to be significantly greater after treatment with pioglitazone plus losartan compared with losartan alone at 12 months (–50.0 versus –26.2 g/L, P < 0.001, respectively). In people with stage 4 CKD, the change in proteinuria at 12 months was reported to be significantly greater after treatment with the pioglitazone plus losartan than with losartan alone (–44.7 versus –28.0 g/L, P < 0.001).

Data were not available from Mohideen 2005.

Glinides versus placebo/control

Abe 2010 did not report data for SCr, eGFR and albuminuria.

Sitagliptin versus glipizide

Meta-analysis of the two included studies was not possible.

Arjona Ferreira 2013 (423 participants) enrolled people with an eGFR < 50 mL/min/1.73 m^2 and not on dialysis. Both sitagliptin and glipizide were reported to reduce eGFR similarly from baseline (sitagliptin, 23.9 mL/min/1.73 m^2; glipizide, 23.3 mL/min/1.73 m^2). Arjona Ferreira 2013a (129 participants) enrolled in people receiving dialysis, so measures of eGFR, SCr, and UACR between sitagliptin and glipizide are meaningless.

Vildagliptin versus sitagliptin

Kothny 2015 (148 participants) compared vildagliptin to sitagliptin in people with an eGFR < 30 mL/min/1.73 m^2 including those receiving HD. No deterioration of kidney function was reported with either vildagliptin or sitagliptin.

Albiglutide to sitagliptin

Leiter 2014 (507 participants) compared albiglutide to sitagliptin in people with an eGFR of 15 to < 60 mL/min/1.73 m^2. Shifts from baseline in kidney impairment category, as assessed by eGFR, were reported to be similar between groups, with no treatment-associated trends evident in either SCr or UACR.

Sitagliptin versus insulin

Bellante 2016 (49 participants) compared sitagliptin to insulin in people with an eGFR < 45 mL/min/1.73 m^2, including those people receiving HD. It was reported that neither insulin nor sitagliptin resulted in a change in eGFR.

Linagliptin versus voglibose

Mori 2016 (78 participants) compared linagliptin to voglibose in people receiving HD. Reporting change in kidney function in this study is meaningless.

Aleglitazar versus pioglitazone

AleNephro 2014 (302 participants) compared aleglitazar to pioglitazone in people with an eGFR of 30 to < 60 mL/min/1.73 m^2. A reduction in the mean eGFR from baseline was reported in the aleglitazar group by week 2 and plateaued after 8 weeks, returning towards baseline following cessation of treatment. Mean eGFR

change at end of treatment with aleglitazar was –15.0% (95% CI –19.1 to –10.8) versus –5.4% (95% CI –9.6 to –1.2) with pioglitazone (P = 0.001) (Analysis 9.9: MD -9.60%, 95% CI -15.50 to -3.70). The treatment difference in eGFR at the end of follow-up was 0.77% (95% CI: –4.5 to 6.0; P = 0.77).

Aleglitazar was reported to reduce UACR by the end of treatment to 35.0% (95% CI –46.8 to –20.5) compared to 29.4% with pioglitazone (95% CI –42.4 to –13.4). Additionally, Aleglitazar reduced UACR by the end of follow-up to 19.8% (95% CI –36.3 to 0.9) compared to 18.2% with pioglitazone (95% CI –35.3 to 3.3).

Insulin

Two studies (28 participants) compared insulin administered IP compared to SC (Diez 1987; Scarpioni 1994) in people with ESKD receiving PD. Reporting change in kidney function in these studies is meaningless.

Ruggenenti 2003a (11 participants) compared regular insulin to lispro insulin in people with a GFR 50 to 60 mL/min. Both insulin lispro and regular insulin administration were reported to result in acute changes in GFR estimated by paraminohippuric acid clearance, two hours post-prandially. Insulin lispro reduced mean (± SE) GFR compared to regular insulin respectively (-6.3 ± 4.7% versus 5.8 ± 5.0%; P < 0.05).

Baldwin 2012 (107 participants), compared 0.25 U/kg of glulisine insulin and glargine insulin to 0.5 U/kg in people with an eGFR ≤ 45 mL/min/1.73 m^2. Kidney function markers including creatinine, eGFR, and albuminuria were not reported.

Systolic and diastolic blood pressure

SGLT2 Inhibitors versus placebo

In people with an eGFR 15 to < 60 mL/min/1.73 m^2, SGLT2 inhibitors probably reduce systolic BP by 4.68 mmHg (-6.69 to -2.68; I^2 = 40%; Analysis 1.10; 7 studies; 1198 participants; moderate certainty evidence) (EMPA-REG BP 2015; EMPA-REG RENAL 2014; Haneda 2016; Kohan 2014; LANTERN 2015; Yale 2013; Zambrowicz 2015) and diastolic BP by 1.72 mmHg (-2.77 to -0.66; I^2 = 0%; Analysis 1.11; 6 studies; 1142 participants; moderate certainty evidence) (EMPA-REG BP 2015; Haneda 2016; Kohan 2014; LANTERN 2015; Yale 2013; Zambrowicz 2015).

DPP-4 inhibitors versus placebo

Meta-analysis was not possible.

DPP-4 inhibitors may have no to minimal effect on BP compared to placebo. Two studies (144 participants) report no change in BP with the use of DPP-4 inhibitors compared to placebo in people receiving HD (saxagliptin (Abe 2016: 84 participants); vildagliptin (Ito 2011a: 60 participants)). Two studies (261 participants) reported small reductions in BP compared to placebo. Chan 2008a (91 participants), comparing sitagliptin to placebo in people with an eGFR < 50 mL/min/1.73 m^2, reported a small (approximately 2 mmHg), mean reduction in systolic, diastolic and mean arterial BP compared to those on placebo. Nowicki 2011 (170 participants) reported a "*trend toward reduction in mean systolic and diastolic blood pressure from baseline to week 52 with saxagliptin (-6.6 and -2.7 mmHg respectively) vs. placebo (2.1 and 0.7 mmHg respectively)*" in people with a CrCl < 50 mL/min.

Nine studies did not report BP data (Barnett 2013; GUARD 2017; Laakso 2015; Lewin 2012; Lukashevich 2011; McGill 2013; SAVOR-TIMI 53 2011; TECOS 2013; Yki-Järvinen 2013).

GLP-1 agonists versus placebo

Meta-analysis was not possible.

From qualitative synthesis of two studies, liraglutide had little or no effect on systolic or diastolic BP compared to placebo. Idorn 2013 (24 participants) reported liraglutide did not change systolic or diastolic BP significantly in people receiving dialysis. Liraglutide had little or no effect on systolic BP (MD 0.00 mmHg, -23.63 to 23.63; Analysis 3.7) and diastolic BP (MD 4.00 mmHg, -5.34 to 13.34; Analysis 3.8) compared to placebo. LIRA-RENAL 2016 (279 participants), reported a reduction of systolic BP occurs in people with an eGFR of 30 to < 60 mL/min/1.73 m^2 when given liraglutide (-2.45 mmHg) or placebo (-0.33 mmHg) but there was no difference between groups (P = 0.25). There is no difference in the diastolic BP reported between the groups (P = 0.89).

Glitazones versus placebo/control

Meta-analysis of data was not possible.

The majority of studies reported glitazones reduced systolic and diastolic BP compared to those not receiving glitazones. Abe 2007 (31 participants) compared pioglitazone to control in people on HD. Pioglitazone reduced (mean ± SE) systolic BP (162.3 ± 7.1 mmHg compared to 148.5 ± 6.2 mmHg P < 0.05) whilst the absence of pioglitazone did not (161.0 ± 7.0 mmHg compared to 159.6 ± 6.2 mmHg P > 0.05). Similarly, pioglitazone reduced diastolic BP (85.5 ± 4.2 mmHg versus 75.0 ± 3.3 mmHg P < 0.05) whilst the absence of pioglitazone does not (84.4 ± 4.5 mmHg versus 83.8 ± 3.6 mmHg P > 0.05). In Abe 2008a (40 participants), amongst people receiving HD, pioglitazone reduced systolic and diastolic BP compared to baseline (P < 0.01) and compared to placebo (P < 0.01). In another study (63 participants) amongst people receiving HD (Abe 2010a) pioglitazone reduced (mean ± SD) systolic (159.2 ± 22.1 mmHg versus 147.0 ± 21.1 mmHg, P < 0.05) and diastolic BP (83.8 ± 12.6 mmHg versus 78.1 ± 12.1 mmHg, P < 0.05) compared to baseline and systolic (147.0 ± 21.1 mmHg versus 159.8 ± 19.7 mmHg, P < 0.05) and diastolic BP (78.1 ± 12.1 mmHg versus 85.6 ± 11.2 mmHg, P < 0.05) compared to placebo.

Wong 2005 (52 participants) reported rosiglitazone reduced systolic BP by 11 mmHg (-21.99 to -0.01; P = 0.05; Analysis 4.5) and diastolic BP by 13.79 mmHg (-24.13 to -3.45; P = 0.009; Analysis 4.6) compared to placebo.

In contrast, Jin 2007 (60 participants; eGFR 15 to 59 mL/min/1.73 m^2) reported little or no difference in BP between pioglitazone and the control group. Similarly, Pfutzner 2011 (39 participants) reported pioglitazone had little or no effect on BP in people on HD.

BP data were not available from Mohideen 2005; and Nakamura 2001.

Sitagliptin versus glipizide

Meta-analysis of data was not possible.

There may be little or no difference in BP between sitagliptin and glipizide (2 studies, 555 participants) in people with an eGFR < 50 mL/min/1.73 m^2 (Arjona Ferreira 2013: 423 participants) but not on

dialysis, and in people with ESKD on dialysis (Arjona Ferreira 2013a: 129 participants).

Linagliptin versus voglibose

Mori 2016 did not report BP data.

Sitagliptin versus insulin

Bellante 2016 compared sitagliptin to insulin in people with an eGFR < 45 mL/min/1.73 m^2, including those on HD (49 participants); there was no reported change in BP after treatment with either sitagliptin or insulin.

Aleglitazar versus pioglitazone

AleNephro 2014 compared aleglitazar to pioglitazone in people with an eGFR of 30 to 59 mL/min/1.73 m^2 (302 participants). In this study, aleglitazar had little or no effect on systolic BP (MD - 0.60 mmHg, 95% CI - 4.49 to 3.29 mmHg; P = 0.76; Analysis 9.10) or diastolic BP (MD-1.70 mmHg, 95% CI- 4.14 to 0.74 mmHg; P = 0.17; Analysis 9.11) compared to pioglitazone.

Other comparisons

Data for the following comparisons were not available: vildagliptin versus sitagliptin; albiglutide versus sitagliptin; IP to SC insulin; 0.5 U/kg compared to 0.25 U/kg of insulin glulisine and glargine; and regular insulin versus insulin lispro.

Lipids (total cholesterol, HDL, LDL, triglyceride)

SGLT2 inhibitors versus placebo

In people with an eGFR of 30 to < 60 mL/min/1.73 m^2, SGLT2 inhibitors probably has little or no effect on total cholesterol (MD 0.09 mmol/L, 95% CI -0.05 to 0.24; I^2 = 0%; Analysis 1.15) compared to placebo (2 studies; 529 participants; moderate certainty evidence) (EMPA-REG RENAL 2014; LANTERN 2015). However, SGLT2 inhibitors probably raise HDL levels (MD 0.04 mmol/L, 95% CI 0.01 to 0.07; I^2 = 0%; Analysis 1.16) compared to placebo (4 studies; 918 participants; moderate certainty evidence) (EMPA-REG RENAL 2014; Haneda 2016; LANTERN 2015; Yale 2013). SGLT2 inhibitors probably has little or no effect on LDL cholesterol (MD 0.04 mmol/L, 95% CI -0.06 to 0.14; I^2 = 22%; Analysis 1.17) and triglycerides (MD 0.01 mmol/L, 95% CI -0.11 to 0.14; I^2 = 0%; Analysis 1.18) compared to placebo (4 studies; 918 participants; moderate certainty evidence) (EMPA-REG RENAL 2014; Haneda 2016; LANTERN 2015; Yale 2013).

DPP-4 inhibitors versus placebo

Meta-analysis of data was not possible.

Abe 2016 (84 participants) compared saxagliptin to placebo in people receiving HD. Saxagliptin was reported to not reduce total cholesterol or increase HDL cholesterol from baseline to the end of the study, and had a similar effect to placebo. However, saxagliptin reduced triglyceride concentrations from baseline to the end of the study (median 1.11 mmol/L, IQR 0.64 to 1.58 versus 0.97 mmol/L, 0.63 to 1.40; P = 0.0015) and also compared to placebo (0.97; 0.63 to 1.40 versus 1.26; 0.95 to 1.89 mmol/L; P = 0.041).

Ito 2011a (60 participants) compared vildagliptin to placebo amongst HD people. In this study, vildagliptin had little or no effect on total cholesterol, HDL cholesterol or triglyceride levels.

In people with less severe CKD with an eGFR of 15 to 59 mL/min/1.73 m^2, GUARD 2017 compared gemigliptin to placebo (130 participants). Gemigliptin was reported to reduce total cholesterol (MD 0.33 mmol/L, 95% CI-0.54 to -0.12; P = 0.003) and LDL (MD 0.23 mmol/L, 95% CI-0.42 to -0.04 mmol/L; P = 0.02) (Analysis 2.12; Analysis 2.13).

No data were available from 10 studies (Barnett 2013; Chan 2008a; Laakso 2015; Lewin 2012; Lukashevich 2011; McGill 2013; Nowicki 2011; SAVOR-TIMI 53 2011; TECOS 2013; Yki-Järvinen 2013).

GLP-1 agonists versus placebo

Meta-analysis of data was not possible.

Idorn 2013 (24 participants) reported liraglutide may have a similar effect to placebo in people with ESKD receiving HD on total cholesterol (Analysis 3.10: MD 0.20 mmol/L, 95% CI -0.85 to 1.23; P = 0.71); LDL (Analysis 3.11: MD 0.10 mmol/L, 95% CI -0.77 to 0.97; P = 0.82); HDL (Analysis 3.12: MD -0.10 mmol/L, 95% CI -0.38 to 0.18 ; P = 0.48) and triglyceride levels (Analysis 3.13: MD 0.43 mmol/L, 95% CI -0.29 to 1.15; P = 0.24) and in people with an eGFR of 30 to < 60 mL/min/1.73 m^2 (LIRA-RENAL 2016: 279 participants).

Glitazones versus placebo/control

In people receiving HD and PD, glitazones may have little or no effect on total cholesterol (MD 0.60 mmol/L, 95% CI -0.02 to 1.23; I^2 = 0%; Analysis 4.7) compared to placebo (2 studies; 72 participants; low certainty evidence) (Pfutzner 2011; Wong 2005). It is uncertain if glitazones have any effect on HDL cholesterol (MD 0.07 mmol/L, 95% CI -0.25 to 0.40; I^2 = 85%; Analysis 4.8), LDL cholesterol (MD 0.39 mmol/L,95% CI - 0.60 to 1.39; I^2 = 68%; Analysis 4.9) and triglyceride levels (MD - 0.34 mmol/L, 95% CI -2.99 to 2.30; I^2 = 94%; Analysis 4.10) compared to placebo (2 studies; 72 participants; very low certainty evidence) (Pfutzner 2011; Wong 2005).

Glinides versus placebo/control

In people receiving HD, Abe 2010 reported mitiglinide did not result in a change in total cholesterol or HDL levels compared to placebo (36 participants). However, mitiglinide resulted in lower triglyceride levels (mean ± SD) compared to the start of the study (1.91 ± 1.10 mmol/L versus 1.37 ± 0.90 mmol/L; P = 0.002) and reduced triglyceride levels compared to placebo (1.37 ± 0.90 mmol/L versus 1.80 ± 0.73 mmol/L; P < 0.05)

Sitagliptin versus glipizide

Meta-analysis of data was not possible.

Arjona Ferreira 2013 reported that in people with an eGFR < 50 mL/min/1.73 m^2 but not on HD (423 participants), sitagliptin reduced total cholesterol by 0.18 mmol/L (95% CI -0.33 to -0.03; P = 0.015; Analysis 6.6) and LDL cholesterol by 0.30 mmol/L (95% CI -0.54 to -0.06; P = 0.016; Analysis 6.8) more than glipizide. Additionally, sitagliptin had little or no effect on HDL cholesterol (MD 0.07 mmol/L, 95% CI -0.06 to 0.20; P = 0.28; Analysis 6.7).

However, Arjona Ferreira 2013a reported that in people on dialysis (129 participants) receiving either sitagliptin or glipizide, there were no within-group changes or differences between groups in cholesterol-related parameters. For triglyceride levels, glipizide reduced levels from baseline (median percent change, -10.3%, 95% CI, -19.0 to -1.6) while sitagliptin did not (0.0%, 95% CI -16.6 to 16.6).

Aleglitazar versus pioglitazone

In people with an eGFR of 30 to < 60 mL/min/1.73 m^2 AleNephro 2014 (302 participants) reported aleglitazar reduced LDL cholesterol -7.3% (95% CI -13.2 to -1.0) while pioglitazone did not (-0.3%, 95% CI -6.8 to 6.6). Aleglitazar resulted in a greater rise in HDL (22.0%, 95% CI 17.4 to 26.6) compared to pioglitazone (11.6%, 95% CI 6.9 to 16.3%) and a greater reduction in triglycerides (-33.6%, 95% CI -41.1 to -26.1%) compared to pioglitazone (-14.1%, 95% CI -21.7 to -6.5).

Other comparisons

Data for the following comparisons were not available: vildagliptin versus sitagliptin; albiglutide versus sitagliptin; linagliptin versus voglibose; sitagliptin versus insulin; IP versus SC insulin; 0.5 U/kg versus 0.25 U/kg of insulin glulisine and glargine; and regular insulin versus insulin lispro.

Body weight

SGLT2 inhibitors versus placebo

In people with an eGFR of 30 to < 60 mL/min/1.73 m^2 (1029 participants), SGLT2 inhibitors may reduce weight (MD -1.41 kg, 95% CI -1.80 to -1.02; I^2 = 28%; Analysis 1.8) compared to placebo (5 studies; 1029 participants; low certainty evidence) (EMPA-REG RENAL 2014; Haneda 2016; Kohan 2014; LANTERN 2015; Yale 2013).

DPP-4 inhibitors versus placebo

In people with an eGFR < 60 mL/min/1.73 m^2 to ESKD (210 participants), DPP-4 inhibitors may have little or no effect on weight (MD 0.16 kg, 95% CI -0.58 to 0.90; I^2 = 29%; Analysis 2.8) versus placebo (2 studies; 210 participants; low certainty evidence) (Chan 2008a; GUARD 2017).

GLP-1 agonists versus placebo

Meta-analysis of data was not possible.

In two studies (303 participants), liraglutide may reduce body weight to a greater extent than control in people with an eGFR < 60 mL/min/1.73 m^2, including people receiving HD (Idorn 2013; LIRA-RENAL 2016).

In people with ESKD receiving HD (24 participants), Idorn 2013 reported liraglutide resulted in a 2.20 kg reduction in weight (-3.87 to 0.53; P = 0.01) (Analysis 3.6), compared to placebo. However, weight (mean ± SE) was not reduced compared to baseline (91.1 ± 4.9 kg to 88.7 ± 5.2 kg; P = 0.22).

In people with an eGFR of 30 to < 60 mL/min/1.73 m^2 LIRA-RENAL 2016 reported both liraglutide and placebo groups exhibited gradual weight reduction (279 participants). Liraglutide causes a greater reduction in body weight compared to placebo (-2.41 kg and -1.09 kg respectively) with an estimated treatment different of -1.32 kg (95% CI -2.24 to -0.4; P = 0.0052).

Glitazones versus placebo

Meta-analysis of data was not possible.

In 3 studies (total of 110 participants), pioglitazone does not result in a significant increase of dry weight compared to placebo in people receiving HD (Abe 2007; Abe 2008a; Pfutzner 2011) or significant increase of body weight compared to placebo in people with an eGFR 15 to < 60 mL/min/1.73 m^2 (Jin 2007: 60 participants). Conversely, rosiglitazone results in more weight gain (mean ± SD) compared to placebo (2.0% ± 5.6% versus -0.8% ± 4.4%; P = 0.049) in people receiving PD (Wong 2005: 52 participants).

Data on weight was not available from three studies (Abe 2010; Mohideen 2005; Nakamura 2001).

Glinides versus placebo

Amongst people receiving HD randomised to either mitiglinide or placebo (36 participants), Abe 2010 reported there was little or no effect on body weight.

Sitagliptin versus glipizide

Meta-analysis of data was not possible.

In people with an eGFR < 50 mL/min/1.73 m^2 but not on dialysis (423 participants) Arjona Ferreira 2013 reported sitagliptin reduced body weight (-0.6 kg) compared to glipizide which increased (1.2 kg) body weight, resulting in a between-group difference of -1.8 kg (P < 0.001).

Conversely in people with ESKD on dialysis (129 participants) Arjona Ferreira 2013a reported sitagliptin had a similar effect to glipizide on weight -1.00 kg (-2.80 to 0.80 kg; P = 0.28).

Aleglitazar versus pioglitazone

In people with an eGFR of 30 to < 60 mL/min/1.73 m^2 (302 participants) AleNephro 2014 reported aleglitazar showed similar weight gain (MD 2.4 kg, 95% CI 1.6 to 3.2) to pioglitazone (MD 2.5 kg, 95% CI 1.7 to 3.3; Analysis 9.8).

Other comparisons

Data for the following comparisons were not available: vildagliptin versus sitagliptin; albiglutide versus sitagliptin; linagliptin versus voglibose; sitagliptin versus insulin; IP versus SC insulin; 0.5 U/kg versus 0.25 U/kg of insulin glulisine and glargine; and regular insulin versus insulin lispro.

Death (all causes)

SGLT2 inhibitors

In people with an eGFR 30 to < 60 mL/min/1.73 m^2 it is uncertain whether SGLT2 inhibitors have any effect on death (RR 0.78, 95% CI 0.60 to 1.02; I^2 = 0%; Analysis 1.3) compared to placebo (5 studies; 2933 participants; very low certainty evidence) EMPA-REG OUTCOME 2013; EMPA-REG RENAL 2014; Haneda 2016; Kohan 2014; Yale 2013).

DPP-4 inhibitors

In people with an eGFR < 60 mL/min/1.73 m^2 including ESKD on dialysis, DPP-4 inhibitors may make little or no difference to the risk of death (RR 0.89, 95% CI 0.75 to 1.07; I^2 = 0%; Analysis 2.3) compared to placebo (6 studies; 4211 participants; low certainty evidence) (Chan 2008a; Lukashevich 2011; McGill 2013; Nowicki 2011; TECOS 2013; Yki-Järvinen 2013).

GLP-1 agonists

In people with an eGFR < 60 mL/min/1.73 m^2 including ESKD on dialysis, GLP-1 agonists may make little or no difference to the risk of death (RR 3.91, 95% CI 0.44 to 34.58; Analysis 3.3) compared to

placebo (2 studies; 301 participants; low certainty evidence) (Idorn 2013; LIRA-RENAL 2016).

Glitazones versus placebo

In people receiving PD Wong 2005 reported rosiglitazone made little or no difference to the risk of death compared to placebo (RR 0.50, 95% CI 0.05 to 5.18; P = 0.56; 52 participants; Analysis 4.3).

Sitagliptin versus glipizide

In people with an eGFR < 50 mL/min/1.73 m^2, including those on dialysis, it is uncertain if sitagliptin has an effect on the risk of death (RR 0.55, 95% CI 0.22 to 1.36; I^2 = 0%; Analysis 6.3) compared to glipizide (2 studies; 551 participants; very low certainty evidence) (Arjona Ferreira 2013; Arjona Ferreira 2013a).

Aleglitazar versus pioglitazone

In people with an eGFR of 30 to < 60 mL/min/1.73 m^2 AleNephro 2014 (302 participants) reported aleglitazar had little or no effect on the risk of death compared to pioglitazone (RR 1.02, 95% CI 0.21 to 4.97; P = 0.98; 302 participants; Analysis 9.4).

Vildagliptin versus sitagliptin

In people with an eGFR < 30 mL/min/1.73 m^2, including ESKD on HD, Kothny 2015 reported vildagliptin had little or no effect on death compared to sitagliptin (RR 0.78, 95% CI 0.11 to 5.41; P = 0.80; 148 participants; Analysis 7.3).

Linagliptin versus voglibose

Mori 2016 compared linagliptin to voglibose in people receiving HD (78 participants). Although one death occurred in the voglibose group during the study period, it was not considered treatment-related.

Other comparisons

Data for the following comparisons were not available: glinide versus no glinide; albiglutide versus sitagliptin; sitagliptin versus insulin; IP versus SC insulin; 0.5 U/kg versus 0.25 U/kg of insulin glulisine and glargine; and regular insulin versus insulin lispro.

Macrovascular events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke)

SGLT2 inhibitors

In people with an eGFR of 30 to < 60 mL/min/1.73 m^2 SGLT2 inhibitors may have little or no effect on the risk of cardiovascular death compared to placebo (RR 0.78, 95% CI 0.56 to 1.10; I^2 = 0%; Analysis 1.4; 4 studies, 2788 participants; low certainty evidence) (EMPA-REG OUTCOME 2013; EMPA-REG RENAL 2014; Kohan 2014; Yale 2013).

Additionally, it is uncertain whether SGLT2 inhibitors have any effect on the risk of myocardial infarction (RR 0.63, 95% CI 0.30 to 1.34; I^2 = 30%; Analysis 1.5; 4 studies, 2788 participants; very low certainty evidence; EMPA-REG OUTCOME 2013; EMPA-REG RENAL 2014;Kohan 2014; Yale 2013) or stroke (RR 0.96, 95% CI 0.63 to 1.48; I^2 = 0%; Analysis 1.6) compared to placebo (5 studies, 2933 participants; very low certainty evidence) (EMPA-REG OUTCOME 2013;EMPA-REG RENAL 2014; Haneda 2016; Kohan 2014; Yale 2013).

DPP-4 inhibitors

In people with an eGFR < 60 mL/min/1.73 m^2 but not on dialysis (5897 participants), DPP-4 inhibitors probably has little or no effect on the risk of cardiovascular death (RR 0.93, 95% CI 0.77 to 1.11; I^2 = 0%; Analysis 2.4) compared to placebo (2 studies, 5897 participants; moderate certainty evidence) (SAVOR-TIMI 53 2011; TECOS 2013).

Additionally, in people with an eGFR < 60 mL/min/1.73 m^2 inclusive of those with ESKD on dialysis, DPP-4 inhibitors may have little or no effect on the risk of myocardial infraction (RR 1.08, 95% CI 0.88 to 1.33; I^2 = 0%; Analysis 2.5) compared to placebo (4 studies, 6121 participants; low certainty evidence) (Chan 2008a; McGill 2013; SAVOR-TIMI 53 2011; TECOS 2013).

Similarly, in people with an eGFR < 60 mL/min/1.73 m^2 but not on dialysis, DPP-4 inhibitors may have little or no effect on the risk of stroke (RR 0.92, 95% CI 0.69 to 1.24; I^2 = 0%; Analysis 2.6) compared to placebo (3 studies, 6030 participants; low certainty evidence) (McGill 2013; SAVOR-TIMI 53 2011; TECOS 2013).

GLP-1 agonists

LIRA-RENAL 2016 reported macrovascular outcomes. In people with an eGFR of 30 to < 60 mL/min/1.73 m^2 (279 participants), liraglutide was reported to have had little or no effect on the risk of myocardial infarction compared to placebo (0.98, 95% CI 0.06 to 15.49; P = 0.99; Analysis 3.4).

Sitagliptin versus glipizide

Arjona Ferreira 2013 reported macrovascular events (423 participants). In people with an eGFR < 60 mL/min/1.73 m^2 but not on dialysis, sitagliptin was reported to have had little or no effect on the risk of myocardial infarction (RR 0.20, 95% CI 0.01 to 4.18; P = 0.30; Analysis 6.4), or stroke (RR 0.34, 95% CI 0.01 to 8.21; P = 0.50; Analysis 6.5) compared to glipizide.

Aleglitazar versus pioglitazone

In people with an eGFR of 30 to < 60 mL/min/1.73 m^2 (AleNephro 2014: 302 participants) aleglitazar was reported to have had little or no effect on the risk of cardiovascular death (RR 1.02, 95% CI 0.15 to 7.15; P = 0.98; Analysis 9.5), myocardial infarction (RR 0.34, 95% CI 0.01 to 8.28; P = 0.51; Analysis 9.6) or stroke (RR 0.34, 95% CI 0.01 to 8.28; P = 0.51; Analysis 9.7) compared to pioglitazone.

Other comparisons

Data for the following comparisons were not available: glinides versus no glinide use; glitazones versus placebo; vildagliptin versus sitagliptin; albiglutide versus sitagliptin; linagliptin compared voglibose; sitagliptin versus insulin; IP versus SC insulin; 0.5 U/kg versus 0.25 U/kg of insulin glulisine and glargine; and regular insulin versus insulin lispro.

Microvascular events (new or worsening kidney disease, or retinopathy)

SGLT2 inhibitors

In people with an eGFR of 30 to < 60 mL/min/1.73 m^2 it is uncertain whether SGLT2 inhibitors have any effect on the risk of ESKD (RR 0.71, 95% CI 0.10 to 4.98; I^2 = 0%; Analysis 1.21) and doubling of SCr (RR 0.96, 95% CI 0.49 to 1.88; I^2 = 0%; Analysis 1.32) compared to placebo (700 participants; 2 studies;

very low certainty evidence) (EMPA-REG RENAL 2014; Kohan 2014). Additionally, SGLT2 inhibitors may reduce the risk of acute kidney injury (AKI) compared to placebo (RR 0.78, 95% CI 0.61 to 1.00; I^2 = 0%; Analysis 1.31), although the 95% CI indicates there may not be a difference (4 studies; 2788 participants; low certainty evidence) (EMPA-REG OUTCOME 2013; EMPA-REG RENAL 2014; Kohan 2014; Yale 2013).

DPP-4 inhibitors

McGill 2013 reported AKI (133 participants). In people with an eGFR < 30 mL/min/1.73 m^2, excluding dialysis, linagliptin was reported to have had little or no effect on the risk of AKI compared to placebo (RR 1.19, 95% CI 0.34 to 4.25; P = 0.78; Analysis 2.29).

TECOS 2013 reported worsening of retinopathy (3324 participants). In people with an eGFR of 30 to < 60 mL/min/1.73 m^2, sitagliptin was reported to have had little or no effect on the risk of retinopathy compared to placebo (RR 0.84, 95% CI 0.62 to 1.14; P = 0.27; Analysis 2.18).

Vildagliptin versus sitagliptin

There was no reported deterioration of kidney function with either vildagliptin or sitagliptin in people with an eGFR < 30 mL/min/1.73 m^2 including ESKD on HD (Kothny 2015: 148 participants).

Other comparisons

Data for the following comparisons were not available: GLP-1 agonists versus placebo; glinides versus no glinides; glitazones versus placebo; sitagliptin versus glipizide; albiglutide versus sitagliptin; linagliptin versus voglibose; sitagliptin versus insulin; aleglitazar versus pioglitazone; IP versus SC insulin; 0.5 U/kg versus 0.25 U/kg of insulin glulisine and glargine; and regular insulin versus insulin lispro.

Safety

Hypoglycaemia

SGLT2 inhibitors

In people with an eGFR of 30 to < 60 mL/min/1.73 m^2 SGLT2 inhibitors may have little or no effect on the risk of hypoglycaemia (RR 0.88, 95% CI 0.73 to 1.07; I^2 = 0%; Analysis 1.19) compared to placebo (7 studies; 3086 participants; low certainty evidence; EMPA-REG OUTCOME 2013; EMPA-REG RENAL 2014; Haneda 2016; Kaku 2014; Kohan 2014; LANTERN 2015; Yale 2013). Similarly, it is uncertain whether SGLT2 inhibitors have any effect on the risk of hypoglycaemia requiring third party assistance (RR 0.47, 95% CI 0.17 to 1.28; I^2 = 0%; Analysis 1.23) compared to placebo (3 studies, 845 participants; very low certainty evidence) (EMPA-REG RENAL 2014; Haneda 2016; Kohan 2014).

DPP-4 inhibitors

In people with an eGFR < 60 mL/min/1.73 m^2 inclusive of those on dialysis it is uncertain whether DPP-4 inhibitors have any effect on the risk of hypoglycaemia (RR 1.07, 95% CI 0.80 to 1.42; I^2 = 45%; Analysis 2.14; 11 studies, 1443 participants; very low certainty evidence) (Abe 2016; Barnett 2013; Chan 2008a; GUARD 2017; Ito 2011a; Laakso 2015; Lewin 2012; Lukashevich 2011; McGill 2013; Nowicki 2011; Yki-Järvinen 2013) and hypoglycaemia requiring third party assistance (RR 0.72, 95% CI 0.25 to 2.03; I^2 = 60%; Analysis 2.17; 6 studies; 3383 participants; very low certainty evidence) (Abe 2016; Chan 2008a; GUARD 2017; Lukashevich 2011; McGill 2013; SAVOR-TIMI 53 2011) compared to placebo.

GLP-1 agonists

In people with an eGFR of 30 to < 60 mL/min/1.73 m^2 (279 participants) LIRA-RENAL 2016 reported liraglutide had little or no effect on the risk of hypoglycaemia to placebo (RR 0.79, 95% CI 0.51 to 1.21; P = 0.28; Analysis 3.14). Similarly, in people with ESKD on HD, Idorn 2013 reported liraglutide made little or no difference to the number of hypoglycaemic episodes compared to placebo (24 participants).

Glinides

In people receiving HD (36 participants), Abe 2010 reported no episodes of hypoglycaemia or hypoglycaemia requiring third party assistance in those receiving mitiglinide compared to those not receiving mitiglinide.

Glitazones

In people receiving HD (70 participants) it is uncertain whether pioglitazone has an effect on the risk of hypoglycaemia (RR 0.95; 0.15 to 6.08; Analysis 4.11) compared to those not receiving pioglitazone/placebo (2 studies, 70 participants; very low certainty evidence) (Abe 2007; Pfutzner 2011).

In one study reporting 'hypoglycaemia requiring third party assistance' in people receiving pioglitazone or no pioglitazone, there were no reported episodes in either group (Abe 2007: 31 participants; Analysis 4.12).

Sitagliptin versus glipizide

In people with an eGFR < 50 mL/min/1.73 m^2 including those with ESKD on dialysis (551 participants), sitagliptin probably reduces the risk of hypoglycaemia by 60% (RR 0.40, 95% CI 0.23 to 0.69; I^2 = 0%; Analysis 6.10) compared to glipizide (2 studies, 551 participants; moderate certainty evidence) (Arjona Ferreira 2013; Arjona Ferreira 2013a). However it is uncertain if sitagliptin has an effect on the risk of hypoglycaemia requiring third party assistance (RR 0.35, 95% CI 0.09 to 1.37; I^2 = 8%) compared to glipizide (2 studies, 551 participants; very low certainty evidence) (Arjona Ferreira 2013; Arjona Ferreira 2013a; Analysis 6.12).

Vildagliptin versus sitagliptin

In people with an eGFR < 30 mL/min/1.73 m^2 including ESKD on HD (148 participants), Kothny 2015 reported vildagliptin had little or no effect on the risk of hypoglycaemia compared to sitagliptin (RR 1.02, 95% CI 0.48 to 2.17; P = 0.96; Analysis 7.4).

Linagliptin versus voglibose

In one study comparing linagliptin to voglibose (78 participants) in people receiving HD (Mori 2016), both glucose-lowering agents did not result in hypoglycaemia.

Aleglitazar versus pioglitazone

In people with an eGFR of 30 to < 60 mL/min/1.73 m^2 (302 participants), AleNephro 2014 reported aleglitazar had little or no effect on the risk of hypoglycaemia (RR 1.34, 95% CI 0.81 to 2.23; P = 0.25; Analysis 9.13), and hypoglycaemia requiring third party assistance (RR 5.10, 95% CI 0.25 to 105.34; P = 0.29; Analysis 9.14) compared to pioglitazone.

Insulins

Baldwin 2012 and Diez 1987 reported on both hypoglycaemia and/or severe hypoglycaemia. In a hospital inpatient setting, an insulin regimen based on 0.25 U/kg compared to 0.5 U/kg had little to no effect on the rate of hypoglycaemia (defined as a blood glucose level < 3.89 mmol/L) - 15% versus 30%, respectively; P = 0.08 (Analysis 10.1), or severe hypoglycaemia (defined as a blood glucose level < 2.78 mmol/L) – 1.8% versus 6%, respectively; P = 0.34 (Baldwin 2012: 107 participants; Analysis 10.2). In a study comparing IP to SC routes of administration of insulin, the rate of hypoglycaemia was two per month in all participants (Diez 1987: 22 participants).

Other comparisons

Data for the following comparisons were not available: albiglutide versus sitagliptin and sitagliptin versus insulin.

Discontinuation of medication due to adverse events

SGLT2 inhibitors

In people with an eGFR of 30 to < 60 mL/min/1.73 m^2 (917 participants) it is uncertain whether SGLT2 inhibitors have any effect on the risk of discontinuation due to adverse events (RR 0.86, 95% CI 0.56 to 1.32; I^2 = 14%; Analysis 1.20) compared to placebo (4 studies, 917 participants; very low certainty evidence) (EMPA-REG RENAL 2014; Haneda 2016; Kaku 2014; Kohan 2014).

DPP-4 inhibitors

In people with an eGFR < 60 mL/min/1.73 m^2 inclusive of those with ESKD on dialysis, it is uncertain whether DPP-4 inhibitors have any effect on the risk of discontinuation due to adverse events (RR 0.94, 95% CI 0.61 to 1.45; I^2 = 0%; Analysis 2.15) compared to placebo (7 studies, 1257 participants; very low certainty evidence) (Chan 2008a; GUARD 2017; Laakso 2015 ;Lukashevich 2011; McGill 2013; Nowicki 2011; Yki-Järvinen 2013).

GLP-1 agonists

In people with ESKD comparing liraglutide to placebo, Idorn 2013 reported no discontinuations due to adverse events in the liraglutide or placebo group (24 participants). In people with an eGFR of 30 to < 60 mL/min/1.73 m^2 LIRA-RENAL 2016 reported a 4.65 times higher risk of discontinuation due to adverse events with liraglutide compared to placebo (RR 4.65, 95% CI 1.62 to 13.31; P = 0.004; 279 participants; Analysis 3.15).

Glinides

Abe 2010 compared mitiglinide to no mitiglinide in people on HD (36 participants). There were no reported increases in adverse effects such as hypoglycaemia, liver impairment, skin rash, fluid overload or oedema in either study group.

Glitazones

Abe 2010a (63 participants) compared pioglitazone to no treatment in people on HD and reported nobody withdrew prematurely from pioglitazone therapy because of an adverse event.

Sitagliptin versus glipizide

In people with an eGFR < 50 mL/min/1.73 m^2 inclusive of those with ESKD on dialysis it is uncertain whether sitagliptin has an effect on the risk of discontinuation due to adverse events (RR 0.93, 95% CI 0.54 to 1.60; I^2 = 0%; Analysis 6.11) compared to glipizide (2 studies, 551 participants; very low certainty evidence) (Arjona Ferreira 2013; Arjona Ferreira 2013a).

Vildagliptin versus sitagliptin

In people with an eGFR < 30 mL/min/1.73 m^2 including those with ESKD on HD (48 participants), Kothny 2015 reported vildagliptin had little or no effect on the risk of discontinuation due to adverse events compared to sitagliptin (RR 0.78, 95% CI 0.26 to 2.32; P = 0.66).

Linagliptin versus voglibose

In one study comparing linagliptin to voglibose (78 participants) in people receiving HD (Mori 2016), one patient receiving voglibose discontinued on the advice of the attending physician due to severe hyperglycaemia (blood glucose level: 30.2 mmol/L).

Other comparisons

Data for the following comparisons were not available: albiglutide versus sitagliptin; aleglitazar versus pioglitazone; sitagliptin versus insulin; IP versus SC insulin; 0.5 U/kg versus 0.25 U/kg of insulin glulisine and glargine; and regular insulin versus insulin lispro.

Other adverse events described by the study authors

SGLT2 inhibitors

Heart failure

In people with an eGFR of 30 to < 60 mL/min/1.73 m^2 SGLT2 inhibitors probably reduce the risk of heart failure by 41% (RR 0.59, 95% CI 0.41 to 0.87; I^2 = 0%; Analysis 1.7) compared to placebo (3 studies, 2519 participants; moderate certainty evidence) (EMPA-REG OUTCOME 2013; EMPA-REG RENAL 2014; Kohan 2014).

Hyperkalaemia

In people with an eGFR of 30 to < 60 mL/min/1.73 m^2, SGLT2 inhibitors probably reduce the risk of hyperkalaemia by 42% (RR 0.58, 95% CI 0.42 to 0.81; I^2 = 0%; Analysis 1.22) compared to placebo (4 studies, 2788 participants; moderate certainty evidence) (EMPA-REG OUTCOME 2013; EMPA-REG RENAL 2014; Kohan 2014; Yale 2013).

Hypovolaemia

In people with an eGFR of 30 to < 60 mL/min/1.73 m^2 it is uncertain whether SGLT2 inhibitors have any effect on the risk of hypovolaemia (RR 1.07, 95% CI 0.62 to 1.84; I^2 = 31%; Analysis 1.24) compared to placebo (6 studies, 3005 participants; very low certainty evidence) (EMPA-REG OUTCOME 2013; EMPA-REG RENAL 2014; Haneda 2016; Kaku 2014; Kohan 2014; Yale 2013).

Fractures

In people with an eGFR 30 to < 60 mL/min/1.73 m^2, it is uncertain whether SGLT2 inhibitors have any effect on the risk of fracture (RR 0.81, 95% CI 0.31 to 2.10; I^2 = 51%; Analysis 1.25) compared to placebo (5 studies, 2860 participants; very low certainty evidence) (EMPA-REG OUTCOME 2013; EMPA-REG RENAL 2014; Kaku 2014; Kohan 2014; Yale 2013).

Diabetic ketoacidosis

In people with an eGFR 30 to < 60 mL/min/1.73 m^2 it is uncertain whether SGLT2 inhibitors have any effect on the risk of diabetic ketoacidosis (RR 1.00, 95% CI 0.09 to 11.02; Analysis 1.27) compared to placebo (2 studies,1962 participants; very low certainty evidence) (EMPA-REG OUTCOME 2013; Haneda 2016).

Upper respiratory tract infection

In people with an eGFR 30 to < 60 mL/min/1.73 m^2, it is uncertain whether SGLT2 inhibitors have any effect on the risk of upper respiratory tract infections (RR 0.79, 95% CI 0.43 to 1.44; I^2 = 6%; Analysis 1.28) compared to placebo (2 studies, 593 participants; very low certainty evidence) (EMPA-REG RENAL 2014; Haneda 2016).

Urinary tract infection

In people with an eGFR 30 to < 60 mL/min/1.73 m^2, SGLT2 inhibitors may have little or no effect on the risk of urinary tract infection (UTI) (RR 1.09, 95% CI 0.82 to 1.43; I^2 = 0%; Analysis 1.29) compared to placebo (7 studies, 3086 participants; low certainty evidence) (EMPA-REG OUTCOME 2013; EMPA-REG RENAL 2014; Haneda 2016; Kaku 2014; Kohan 2014; LANTERN 2015; Yale 2013).

Genital infections.

In a meta-analysis of in people with eGFR 30 to < 60 mL/min/1.73 m^2, SGLT2 inhibitors probably increase the risk of genital infections 2.5 times more (RR 2.50, 95% CI 1.52 to 4.11; I^2 = 0%; Analysis 1.30) than placebo (7 studies, 3086 participants; moderate certainty evidence; EMPA-REG OUTCOME 2013; EMPA-REG RENAL 2014; Haneda 2016; Kaku 2014; Kohan 2014; LANTERN 2015; Yale 2013).

DPP-4 inhibitors

Heart failure

In people with an eGFR < 60 mL/min/1.73 m^2 inclusive of those with ESKD on dialysis, DPP-4 inhibitors may have little or no effect on the risk of heart failure (RR 1.18, 95% CI 0.98 to 1.44; I^2 = 0%; Analysis 2.7) compared to placebo (4 studies, 6115 participants; low certainty evidence; Chan 2008a; SAVOR-TIMI 53 2011; TECOS 2013; Yki-Järvinen 2013).

Hyperkalaemia

In people with an eGFR < 50 mL/min/1.73 m^2 inclusive of ESKD, DPP-4 inhibitors may have little or no effect on hyperkalaemia (RR 1.30, 95% CI 0.81 to 2.08; I^2 = 0%; Analysis 2.16) compared to placebo (2 studies, 502 participants; low certainty evidence) (Lukashevich 2011; McGill 2013).

Peripheral oedema

In people with an eGFR < 50 mL/min/1.73 m^2 inclusive of ESKD, DPP-4 inhibitors may have little or no effect on the risk of peripheral oedema (0.84, 95% CI 0.58 to 1.22; I^2 = 0%; Analysis 2.19) compared to placebo (4 studies, 763 participants; low certainty evidence) (Chan 2008a; Lukashevich 2011; McGill 2013; Nowicki 2011).

Liver impairment

In people with an eGFR < 50 mL/min/1.73 m^2 inclusive of ESKD and people on HD, DPP-4 inhibitors may have little or no effect on the risk of liver impairment (RR 1.42, 95% CI 0.26 to 7.64; Analysis 2.25) compared to placebo (2 studies, 451 participants; low certainty evidence) (Abe 2016; Lukashevich 2011).

Malignancy

TECOS 2013 reported in people with an eGFR 30 to < 60 mL/min/1.73 m^2 (3324 participants), sitagliptin had little or no effect on the risk of malignancy compared to placebo (RR 1.01, 95% CI 0.69 to 1.48; P = 0.94; Analysis 2.22).

Pancreatic cancer

Chan 2008a reported in people with an eGFR < 50 mL/min/1.73 m^2 inclusive of ESKD on dialysis (91 participants), sitagliptin had little or no effect on the risk of pancreatic cancer compared to placebo (RR 1.23, 95% CI 0.05 to 29.19; Analysis 2.23).

Pancreatitis

In people with an eGFR < 50 mL/min/1.73 m^2 inclusive of ESKD, it is uncertain whether DPP-4 inhibitors have any effect on the risk of pancreatitis (RR 0.99, 95% CI 0.14 to 7.05; Analysis 2.24) compared to placebo (2 studies, 3693 participants; very low certainty evidence; Lukashevich 2011; TECOS 2013)

Constipation

In people with an eGFR < 50 mL/min/1.73 m^2 including people with ESKD on dialysis, it is uncertain whether DPP-4 inhibitors have any effect on the risk of constipation (RR 0.79, 95% CI 0.09 to 6.84; I^2 = 65%; Analysis 2.21) compared to placebo (2 studies, 224 participants; very low certainty evidence) (Chan 2008a; McGill 2013)

Diarrhoea

In people with an eGFR < 50 mL/min/1.73 m^2 including people with ESKD, DPP-4 inhibitors may have little or no effect on the risk of diarrhoea (RR 1.39, 95% CI 0.80 to 2.41; I^2 = 0%; Analysis 2.20) compared to placebo (2 studies, 502 participants; low certainty evidence) (Lukashevich 2011; McGill 2013)

Upper respiratory tract infection

In people with an eGFR < 50 mL/min/1.73 m^2 inclusive of people with ESKD on dialysis, DPP-4 inhibitors may have little or no effect on the risk of upper respiratory tract infections (RR 0.63, 95% CI 0.38 to 1.04; I^2 = 0%; Analysis 2.26) compared to placebo (3 studies, 593 participants; low certainty evidence) (Chan 2008a; Lukashevich 2011; McGill 2013).

Cellulitis

Ito 2011a reported no episodes of cellulitis in people on HD (60 participants) with either vildagliptin or placebo.

Urinary tract infection

In people with an eGFR < 50 mL/min/1.73 m^2 inclusive of people with ESKD on dialysis, it is uncertain whether DPP-4 inhibitors have any effect on UTI (RR 0.82, 95% CI 0.50 to 1.35; I^2 = 0%; Analysis 2.28) compared to placebo (4 studies, 763 participants; very low certainty evidence) (Chan 2008a; Lukashevich 2011; McGill 2013; Nowicki 2011).

GLP-1 agonists

LIRA-RENAL 2016 (279 participants) reported in people with an eGFR of 30 to < 60 mL/min/1.73 m^2, liraglutide had little or no

effect on the risk of heart failure compared to placebo (RR 2.94, 95% CI 0.12 to 71.46; P = 0.51; Analysis 3.5). Additionally, compared to placebo, liraglutide was reported to have had a 2 times increased risk of GI disorders (RR 2.04, 95% CI 1.33 to 3.12; P = 0.001; Analysis 3.16), 4.9 times increased risk of nausea (RR 4.89, 95% CI 2.10 to 11.38; P = 0.0002; Analysis 3.19) and had an increased, reduced or no effect on the risk of vomiting (RR 2.45, 95% CI 0.79 to 7.71; P = 0.12; Analysis 3.17) pancreatitis compared to placebo (RR 2.94, 95% CI 0.12 to 71.46; P = 0.51; Analysis 3.18).

Conversely Idorn 2013 reported in people with ESKD on dialysis (24 participants), nausea and vomiting occurred more frequently in liraglutide-treated people with ESKD than in the other treatment arms (P < 0.04). Both nausea and vomiting were however temporary in most people and primarily related to initiation of treatment and dose escalation. There was more dyspepsia in the liraglutide group compared to the placebo group.

Glitazones

Heart failure

In people with an eGFR < 60 mL/min/1.73 m^2 inclusive of those on HD, it is uncertain whether glitazones have any effect on the risk of heart failure (RR 0.34, 95% CI 0.01 to 8.13; Analysis 4.4) compared to the control group not receiving glitazones (2 studies, 123 participants; very low certainty evidence) (Abe 2010a; Jin 2007).

Peripheral oedema

In people on HD it is uncertain whether pioglitazone has an effect on the risk of peripheral oedema (RR 3.05, 95% CI 0.33 to 28.32; I^2 = 0%; Analysis 4.13) compared to the control group not on pioglitazone (3 studies, 134 participants; very low certainty evidence) (Abe 2007; Abe 2008a; Abe 2010a).

Fluid overload

In people on HD (Abe 2007; Abe 2008a) (71 participants) receiving pioglitazone and in people on PD receiving rosiglitazone (Wong 2005) (52 participants) there were no episodes of fluid overload (Analysis 4.14).

Fracture

In people on HD receiving pioglitazone (Abe 2008a: 40 participants), there were no reported fractures (Analysis 4.15).

Gastrointestinal disorders

Pfutzner 2011 reported in people on HD, pioglitazone had little or no effect on the risk of having a GI disorder (RR 0.51; 0.26 to 1.00; P = 0.05) compared to placebo (39 participants; Analysis 4.16).

Liver impairment

In people on HD receiving pioglitazone (Abe 2007; Abe 2008a; Abe 2010a) and in people on PD receiving rosiglitazone (Wong 2005), there were no episodes of liver impairment (186 participants). Additionally, in one study comparing pioglitazone to no pioglitazone in people with an eGFR of 15 to < 60 mL/min/1.73 m^2 (Jin 2007: 60 participants), the aspartate aminotransferase concentrations increased slightly after six months in five people (1 with stage 3, and 4 with stage 4 CKD) treated with the pioglitazone. These concentrations subsequently return to normal values without specific treatment.

Glinides

Abe 2010 reported no episodes of peripheral oedema, fluid overload, skin rash or liver impairment amongst patient receiving HD (36 participants) in either the mitiglinide or control group.

Sitagliptin versus glipizide

In people with an eGFR < 50 mL/min/1.73 m^2 including those receiving dialysis, it is uncertain whether sitagliptin has an effect on the risk of peripheral oedema (RR 0.71, 95% CI 0.11 to 4.80; I^2 = 67%; Analysis 6.13), diarrhoea (RR 0.79, 95% CI 0.39 to 1.60; I^2 = 0%; Analysis 6.16), or UTI (RR 1.29, 95% CI 0.24 to 6.94; I^2 = 76%; Analysis 6.20) compared to glipizide (2 studies, 551 participants; very low certainty evidence) (Arjona Ferreira 2013; Arjona Ferreira 2013a). Additionally, sitagliptin may have little or no effect on the risk of upper respiratory tract infections (RR 0.60, 95% CI 0.31 to 1.17; I^2 = 0%; Analysis 6.19) compared to glipizide (2 studies, 551 participants; low certainty evidence) (Arjona Ferreira 2013; Arjona Ferreira 2013a).

Arjona Ferreira 2013a reported in people with ESKD on dialysis (129 participants), sitagliptin had little or no effect on the risk of fracture (RR 0.34, 95% CI 0.01 to 8.16; P = 0.50; Analysis 6.14), vomiting (RR 2.03, 95% CI 0.39 to 10.70; P = 0.40; Analysis 6.15), and cellulitis (RR 9.14, 95% CI 0.50 to 166.35; P = 0.14; Analysis 6.21) compared to glipizide.

Arjona Ferreira 2013 reported in people with an eGFR < 50 mL/min/1.73 m^2 but not on dialysis (422 participants) sitagliptin had little or no effect on the risk of malignancy (RR 7.07, 95% CI 0.37 to 135.97; P = 0.19; Analysis 6.17) and pancreatic cancer compared to glipizide (3.03, 95% CI 0.12 to 73.92; P = 0.50; Analysis 6.18).

Aleglitazar versus pioglitazone

AleNephro 2014 reported in people with an eGFR of 30 to < 60 mL/min/1.73 m^2 (302 participants), aleglitazar had little or no effect on the risk of heart failure (RR 9.12, 95% CI 0.50 to 167.92; P = 0.14; Analysis 9.3), peripheral oedema (RR 0.61, 95% CI 0.36 to 1.05; P = 0.07; Analysis 9.15), fracture (RR 1.53, 95% CI 0.26 to 9.03; P = 0.64; Analysis 9.16), and malignancy (RR 3.06, 95% CI 0.32 to 29.09; P = 0.33; Analysis 9.17) compared to placebo.

Vildagliptin versus sitagliptin

Kothny 2015 reported in people with an eGFR < 30 mL/min/1.73 m^2 including those receiving HD (148 participants), vildagliptin had little or no effect on the risk of peripheral oedema (RR 0.93, 95% CI 0.52 to 1.66; P = 0.81; Analysis 7.6) and liver impairment (0.16, 95% CI 0.01 to 3.22; P = 0.23) compared to sitagliptin (Analysis 7.8). The most common adverse events were peripheral oedema (which occurred at a similar frequency in the vildagliptin (23%) and sitagliptin (25%) groups). There were no episodes of pancreatitis in either group. Two people on sitagliptin had ALT elevations (one patient with ALT > 3 times the upper limit of normal in the context of a gastritis, one asymptomatic with ALT > 5 time the upper limit of normal); both events resolving on treatment. No liver enzyme elevations occurred in people on vildagliptin.

Insulin

Diez 1987 reported in people receiving PD (22 participants), the peritonitis incidence was 3.2 times higher in the intraperitoneal group compared to the subcutaneous insulin group.

Other comparisons

No further data concerning other adverse events were available for the following comparisons: sitagliptin versus insulin; linagliptin versus voglibose; and albiglutide versus sitagliptin.

DISCUSSION

Summary of main results

There are currently 11 different classes of glucose-lowering agents available for managing diabetes and CKD, each with varying mechanisms of action and adverse effect profiles. In this systematic review we aim to provide a contemporary comprehensive review of the efficacy and safety of glucose-lowering agents in people with diabetes and CKD to inform clinical practice and policy. Consequently, we included all 11 different classes in our inclusion criteria, resulting in 14 different comparisons.

Evidence for the current use of glucose-lowering agents in diabetes and CKD is of limited certainty. The majority of studies explored the efficacy and safety of SGLT2 inhibitors, mainly in people with an eGFR of 30 to < 60 mL/min/1.73 m^2; DPP-4 inhibitors and GLP-1 agonists in people with an eGFR < 60 mL/min/1.73 m^2; glitazones, mainly in people with ESKD on dialysis; and compared sitagliptin to glipizide in people with an eGFR < 60 mL/min/1.73 m^2.

Compared to placebo, SGLT2 inhibitors probably reduce HbA1c (7 studies, 1092 participants: MD -0.29%, 95% CI -0.38 to -0.19% (-3.2 mmol/mol, -4.2 to -2.2); I^2 = 0%; moderate certainty evidence), FBG (5 studies, 855 participants: MD -0.48 mmol/L, 95% CI -0.78 to -0.19; I^2 = 0%; moderate certainty evidence), systolic BP (7 studies, 1198 participants: MD -4.68 mmHg, 95% CI -6.69 to -2.68; I^2 = 40%; moderate certainty evidence), diastolic BP (6 studies, 1142 participants: MD -1.72 mmHg, 95% CI -2.77 to -0.66; I^2 = 0%; moderate certainty evidence), heart failure (3 studies, 2519 participants: RR 0.59, 95% CI 0.41 to 0.87; I^2 = 0%; moderate certainty evidence) and hyperkalaemia (4 studies, 2788 participants: RR 0.58, 0.42 to 0.81; I^2 = 0%; moderate certainty evidence); but increase genital infections (7 studies, 3086 participants: RR 2.50, 95% CI 1.52 to 4.11; I^2 = 0%; moderate certainty evidence) and serum creatinine (4 studies, 848 participants: MD 3.82 µmol/L, 95% CI 1.45 to 6.19, (0.04 mg/dL, 0.02 to 0.07); I^2 = 16%; moderate certainty evidence). SGLT2 inhibitors may reduce weight (5 studies, 1029 participants: MD -1.41 kg, 95% CI -1.8 to -1.02; I^2 = 28%; low certainty evidence) and albuminuria (MD -8.14 mg/mmol creatinine, 95% CI -14.51 to -1.77 (-71.89 mg/g creatinine, -128.17 to -15.60); I^2 = 11%; low certainty evidence). SGLT2 inhibitors may have little or no effect on the risk of cardiovascular death, hypoglycaemia, AKI, and UTI (low certainty evidence). It is uncertain whether SGLT2 inhibitors have any effect on death (all causes), ESKD, hypovolaemia, fractures, diabetic ketoacidosis, and discontinuation due to adverse effects (very low certainty evidence).

Compared to placebo, DPP-4 inhibitors may reduce HbA1c (7 studies, 867 participants: MD -0.62 %, 95% CI -0.85 to -0.39% (-6.8 mmol/mol, -9.3 to -4.3); I^2 = 59%) but may have little or no effect on FBG (low certainty evidence). DPP-4 inhibitors probably have little or no effect on cardiovascular death (2 studies, 5897 participants: RR 0.93, 95% CI 0.77 to 1.11; I^2 = 0%) and weight (2 studies, 210 participants: MD 0.16 kg, 95% CI -0.58 to 0.90; I^2 = 29%; moderate certainty evidence). Compared to placebo, DPP-4 inhibitors may have little or no effect on heart failure, upper respiratory tract infection and liver impairment (low certainty evidence). Compared to placebo, it is uncertain whether DPP-4 inhibitors have any effect on eGFR, hypoglycaemia, pancreatitis, pancreatic cancer, and discontinuation due to adverse effects (very low certainty evidence).

Compared to placebo, GLP-1 agonists probably reduce HbA1c (2 studies, 283 participants: MD -0.53%, 95% CI -1.01 to -0.06 (-5.8 mmol/mol, -11.0 to -0.7); I^2 = 41%; moderate certainty evidence) and may reduce weight (low certainty evidence). GLP-1 agonists may have little or no effect on hypoglycaemia and discontinuation due to adverse effects (low certainty evidence). It is uncertain whether GLP-1 agonists reduce FBG, increase GI symptoms, or alter the risk of pancreatitis (very low certainty evidence).

Compared to placebo, it is uncertain whether glitazones have any effect on HbA1c, FBG, death (all causes), weight, and risk of hypoglycaemia (very low certainty evidence).

Compared to glipizide, sitagliptin probably reduces hypoglycaemia (2 studies, 551 participants: RR 0.40, 95% CI 0.23 to 0.69; I^2 = 0%; moderate certainty evidence). Compared to glipizide, sitagliptin may have little or no effect on HbA1c, FBG, and weight (low certainty evidence). Compared to glipizide, it is uncertain if sitagliptin has any effect on death (all causes) and discontinuation due to adverse effects (very low certainty).

For types, dosages or modes of administration of insulin and other head-to-head comparisons only individual studies were available so no conclusions could be made.

This review highlights the lack of high certainty evidence to guide clinical decision making for glucose-lowering in people with diabetes and CKD.

Overall completeness and applicability of evidence

In some studies, outcomes were not reported or were not in a suitable format to be used in meta-analyses. Despite attempting to contact authors for outcome data not reported in studies, the majority of unpublished data were not obtained. In addition, many of the studies from China did not have the authors' contact details on the report, negating the ability to contact authors with data queries. Fourteen studies are still awaiting classification (Characteristics of studies awaiting classification) and three studies are currently ongoing (Characteristics of ongoing studies). Once further data becomes available, the review will be updated.

For completeness, studies including troglitazone (Mohideen 2005) and aleglitazar (AleNephro 2014) were included in our systematic review. Troglitazone was withdrawn from the market by the FDA in 2000 due to the risk of liver failure and hepatotoxicity (FDA 2000), and the development of aleglitazar was halted by Roche in 2013 due to concerns about its safety and efficacy (ALECARDIO 2013). The data from these studies were not incorporated into any meta-analyses, and did not affect any treatment estimates in our results.

Out of all the contemporary glucose-lowering agent classes, evidence is most certain for the glucose-lowering efficacy of SGLT2 inhibitors and GLP-1 agonists in diabetes and CKD. Additionally, SGLT2 inhibitors probably reduce BP, heart failure and hyperkalaemia but probably increase serum creatinine and slightly

reduce eGFR, and increase the rate of genital infections. Evidence for the safety profile of GLP-1 agonists is of low to very low certainty.

Consequently, evidence to guide clinical decision making and choice of glucose-lowering agents in diabetes and CKD is lacking, and more studies are required to address this evidence gap.

Quality of the evidence

The certainty of the evidence for most outcomes examined is low to very low according to GRADE (GRADE 2008). The main contributors to the low certainty of evidence are: the majority of studies had a high risk of funding bias; many studies had attrition bias; the majority of studies had an unclear risk of detection bias; the imprecision of results with wide CIs; and the absence of quantitative data for some outcomes for several glucose-lowering agent classes.

Potential biases in the review process

Key strengths of the review process are the pre-published peer-reviewed protocol, a systematic search of electronic databases and the methodological soundness of the data extraction, analysis and assessment of the risk of bias. Two independent review authors assessed the majority of the studies in English. Two other independent reviewers assessed the majority of the studies in Chinese. Any differences in interpretation were discussed with disagreements resolved by a fifth author. None of the authors assessing the studies or performing data extraction had any conflicts of interest to declare. A potential weakness is that despite a comprehensive search through appropriate databases, we cannot exclude the possibility that studies with negative findings remain unpublished.

Agreements and disagreements with other studies or reviews

To our knowledge, this is the first contemporary systematic review comprehensively examining the safety and efficacy of all glucose-lowering agents including insulin in diabetes and CKD.

Our systematic review provides the first meta-analysis of SGLT2 inhibitors amongst people with diabetes and CKD. We found that SGLT2 inhibitors probably reduce HbA1c, FBG, systolic and diastolic BP, heart failure, and hyperkalaemia compared to placebo. This is broadly consistent with systematic reviews of the efficacy and safety of SGLT2 inhibitors amongst people with diabetes (Shyangdan 2016; Storgaard 2016; Zaccardi 2016). Recent literature suggests that SGLT2 inhibitors may be renoprotective mechanistically (Andrianesis 2016; Scheen 2015, Zanoli 2015) with the most compelling clinical trial evidence coming from EMPA-REG OUTCOME 2013 (included in our systematic review and meta-analysis). In EMPA-REG OUTCOME 2013, empagliflozin slowed the progression of kidney disease and reduced the rates of kidney events such as doubling of SCr, incident or worsening kidney disease, and the need for renal replacement therapy compared to placebo. In contrast, systematic reviews of canagliflozin in diabetes and CKD (Patel 2016) and SGTL2 inhibitors in diabetes (Storgaard 2016) report a small decline in eGFR and small rise in serum creatinine. The systematic review by Patel 2016 also reported an increase in kidney impairment and SCr but a reduction in eGFR and albuminuria with canagliflozin. We found that SGLT2 inhibitors probably increase serum creatinine and reduce eGFR, and may reduce albuminuria. However there may be little or no effect of SGLT2 inhibitors on the risk of AKI, and it is uncertain whether SGLT2 inhibitors have any effect on ESKD. Furthermore, the natriuretic effect of SGLT2 inhibitors (Vallon 2007) and resultant increase in serum creatinine concentration, has to be considered when interpreting the effect of SGLT2 inhibitors on albuminuria (measured by the urine albumin:creatinine ratio) and eGFR (derived from serum creatinine). Thus, the effect of SGLT2 inhibitors on kidney function in people with diabetes and CKD remains unclear.

In our meta-analysis, SGLT2 inhibitors probably increase the risk of genital infections compared to placebo. This is consistent with previous meta-analyses of the safety of SGLT2 inhibitors amongst people with type 2 diabetes (Storgaard 2016; Wu 2016; Zaccardi 2016). Additionally, we found that SGLT2 inhibitors may reduce weight and may have little or no effect on the risk of UTI and hypoglycaemia. Other meta-analyses of studies amongst people with diabetes report a beneficial effect of SGLT2 inhibitors on weight, an increase in UTI, and a variable effect on hypoglycaemia (Storgaard 2016; Wu 2016; Zaccardi 2016). Due to recent concerns about euglycaemic diabetic ketoacidosis and fractures with SGLT2 inhibitors, we examined these outcomes with the rationale that the presence of CKD may increase the risk of both. The effect of SGLT2 inhibitors on either outcome was uncertain. Other meta-analyses amongst people with diabetes have been similarly inconclusive (Zaccardi 2016) or have not noted an increased risk of diabetic ketoacidosis (Storgaard 2016) and fractures with SGLT2 inhibitors (Ruanpeng 2016; Wu 2016). Thus these risks in people with diabetes and CKD remain unclear.

In our review, DPP-4 inhibitors probably have little or no effect on the risk of cardiovascular death and weight compared to placebo. While other systematic reviews examining the efficacy and safety of DPP-4 inhibitors amongst people with diabetes and CKD have not evaluated cardiovascular death as an outcome, Cheng 2014 confirmed our findings of no effect of DPP-4 inhibitors on weight. We are only able to report the effect of DPP-4 inhibitors on glycaemic control, kidney function, BP, lipid profile, death (all causes), hypoglycaemia, and discontinuation due to adverse effects, with a low degree of certainty (GRADE 2008). The systematic review by Cheng 2014 also reports low certainty evidence for most outcomes according to GRADE (GRADE 2008). Other systematic reviews report that DPP-4 inhibitors reduced HbA1c (Singh-Franco 2016; Walker 2017) and either increased or reduced the risk of hypoglycaemia compared to placebo (Singh-Franco 2016; Walker 2017) without grading the certainty of evidence. As DPP-4 inhibitors have been linked to pancreatic cancer (Elashoff 2011), pancreatitis (Rehman 2017), and heart failure (Xu 2017) amongst people with diabetes, we explored these outcomes in our systematic review. These outcomes have not been explored in other meta-analyses of DPP-4 use in people with diabetes and CKD (Cheng 2014; Singh-Franco 2016; Walker 2017). Unfortunately, evidence for the effect of DPP-4 inhibitors on these outcomes is of low to very low certainty (GRADE 2008).

Compared to glipizide, we found that sitagliptin probably reduces the risk of hypoglycaemia. This is also reported in several other systematic reviews (Cheng 2014; Singh-Franco 2016).

We report that GLP-1 agonists probably reduce HbA1c by 0.53% (5.8 mmol/mol) compared to placebo (-0.53%, 95% CI -1.01 to -0.06 (-5.8 mmol/mol, -11.0 to -0.7); I^2 = 41%). This effect size seems slightly blunted amongst people with diabetes and CKD in comparison

to the effects reported by meta-analyses of people with diabetes only (Orme 2017). However, direct comparisons are not completely valid as head-to-head comparisons have not been undertaken. The HbA1c lowering effect seen in our review is comparable to that of a meta-analysis examining the effect of incretins in CKD (Howse 2016). However, this meta-analysis (Howse 2016) did not do a sub-analysis of the effects of GLP-1 agonists on the other outcomes, but rather pooled GLP-1 agonist data with DPP-4 inhibitor data.

We are unable to report the efficacy and safety of glitazones in diabetes and CKD for any outcome with a moderate to high degree of certainty (GRADE 2008). To our knowledge, there are no other systematic reviews examining glitazones in diabetes and CKD. Guidelines and consensus statement recommendations for the management of co-morbid diabetes and CKD acknowledge this lack of evidence (ERBP 2015; Tuttle 2014). The American Diabetes Association concludes that glitazones should generally be avoided in diabetes and CKD due to adverse effects such as refractory fluid retention, hypertension, and increased fracture risk (Tuttle 2014). The European Renal Best Practice Group guidelines do not make a recommendation, citing that glitazones are under regular scrutiny, are not available on most markets, and that public access to the entire body of information for this drug class may not be available (ERBP 2015).

There is also little evidence to evaluate the safety and efficacy of insulin and to guide choice of, type, dosing and optimal route of administration of insulin. The most widely quoted recommendations for insulin dosing in CKD are from the American College of Physicians. They suggest a reduction in insulin dosage of 25% for an eGFR between 10 to 50 mL/min/1.73 m^2 and of 50% if the eGFR is < 10 mL/min/1.73 m^2 (Bennett 1983). However, insulin dose reduction with the development of CKD is likely to be more complex and has not been studied. Several case series of people with diabetes and CKD requiring insulin, have demonstrated a variable reduction in insulin requirements with one series demonstrating a linear correlation between CrCl and insulin dosage (Charpentier 2000). Secondly, the dose reduction requirements may differ for different types of insulin. In a two-way, double-blind cross-over euglycaemic (5 mmol/L) glucose clamp study of people with type 1 diabetes with and without CKD, regular and lispro insulin levels were higher in CKD (Rave 2001). Despite this the metabolic response to regular insulin but not to insulin lispro (assessed by the maximal glucose infusion rate) was reduced (Rave 2001) highlighting the fact that dose reduction for different insulins may not be uniform.

AUTHORS' CONCLUSIONS

Implications for practice

Currently, there is a lack of high certainty evidence to guide the use of glucose-lowering agents in people with diabetes and CKD.

SGLT2 inhibitors and GLP-1 agonists are probably efficacious in reducing HbA1c in diabetes and CKD with SGLT2 inhibitors probably having the added benefits of reducing BP, heart failure, and hyperkalaemia. This must be balanced with the probable increase in genital infections and serum creatinine, and mild reduction in eGFR. Additionally, the effect of SGLT2 inhibitors on the risk of ESKD and the safety profile of GLP-1 agonists is uncertain.

DPP-4 inhibitors may be efficacious in reducing HbA1c in diabetes and CKD. Sitagliptin probably has a lower risk of hypoglycaemia compared to glipizide.

The efficacy and safety of other classes of glucose-lowering agents is unclear.

More evidence is required to help guide choice of agents for glucose-lowering in diabetes and CKD.

Implications for research

The lack of high certainty evidence reviewed, highlights the urgent need for more large-scale RCTs of glucose-lowering agents in people with both diabetes and CKD.

Given that the majority of moderate certainty evidence concerns the glucose-lowering efficacy of SGLT2 inhibitors and GLP-1 agonists in diabetes and CKD, the safety profile of both classes need further study. Specifically, the effects of SGLT2 inhibitors on kidney function and the overall safety profile of GLP-1 agonists need to be characterised.

Additionally, as there is low certainty evidence for the efficacy of DPP-4 inhibitors in glucose-lowering, larger double-blind RCTs are warranted to confirm their glucose-lowering efficacy and characterise their safety profile people with diabetes and CKD.

Finally, appropriately blinded RCTs comparing different glucose-lowering agents to sulphonylureas, metformin, and insulin are now required to clarify the place of the newer and older classes of glucose-lowering agents in treating people with diabetes and CKD. In particular, given that insulin is widely used as a glucose-lowering agent in CKD, especially in moderate to severe disease, further studies are required to help guide insulin dosing, ascertain the safety and efficacy of various insulin types (including insulin analogues), and ascertain the safety and efficacy of various modalities of insulin delivery – especially subcutaneous multiple dose injections, subcutaneous continuous infusion of insulin, and intraperitoneal insulin in PD.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Abe 2007

Methods	• Study design: open-label parallel RCT • Study time frame: not reported • Duration of follow-up: 12 weeks
Participants	• Country: Japan • Setting: single centre • Inclusion criteria: HD patients with type 2 DM untreated with insulin; unstable glycaemic control ≥ 7.0% after 12 consecutive weeks of daily administration of 0.9 mg voglibose • Number: treatment group (16); control group (15) • Mean age ± SEM (years): treatment group (70.1 ± 5.1); control group (65.6 ± 2.8) • Sex (M/F): treatment group (9/7); control group (9/6) • Exclusion criteria: deranged liver function; decompensated congestive heart failure; infectious disease; thyroid disease; malignant tumour; treatment with steroids
Interventions	Treatment group

Abe 2007 *(Continued)*

	• Pioglitazone: 30 mg for 12 weeks • Voglibose: 0.9 mg for 12 weeks Control group • Voglibose: 0.9 mg for 12 weeks
Outcomes	• HbA1c and plasma glucose levels • Insulin resistance via HOMA-IR • Hb • AST, ALT, creatinine phosphokinase, total cholesterol, HDL, triglyceride • Mean corpuscular volume, mean HbA1c, body weight before and after dialysis, BMI, CTR by chest X-ray and predialysis SBP and DBP • Safety variables and adverse events
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer generated list was used
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	Low risk	No people dropped out
Selective reporting (reporting bias)	Unclear risk	The prespecified outcomes were not available on a clinical trials database
Other bias	Unclear risk	Conflicts of interest and funding source were not reported

Abe 2008a

Methods	• Study design: open-label, parallel RCT • Study time frame: not reported • Duration of follow-up: 24 weeks
Participants	• Country: Japan • Setting: single centre • Inclusion criteria: HD patients with type 2 DM; poor glycaemic control (HbA1c > 6.5% (48 mmol/mol) over previous 3 months); hypertension; not receiving insulin therapy

Abe 2008a *(Continued)*

	• Number: treatment group (20); control group (20) • Mean age ± SEM (years): treatment group (71.1 ± 7.1); control group (68.8 ± 5.8) • Sex (M/F): treatment group (12/8); control group (12/8) • Exclusion criteria: abnormal liver function at baseline; congestive heart failure; ischaemic heart disease; thyroid disease or malignant tumours; under steroid treatment
Interventions	Treatment group • Pioglitazone: 30 mg over 24 weeks • Conventional oral antidiabetic agents for 24 weeks Control group • Conventional oral antidiabetic agents for 24 weeks
Outcomes	• HbA1c and plasma glucose levels • Insulin resistance via HOMA-IR • Hb • AST, ALT, creatinine phosphokinase, total cholesterol, HDL, triglyceride • Body weight before and after dialysis • BMI • CTR by chest X-ray • Predialysis SBP and DBP • Safety assessments and serious adverse events
Notes	• Further data required for meta-analysis was not available from the authors • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients dropped out in either group
Selective reporting (reporting bias)	Unclear risk	The prespecified outcomes were not available on a clinical trials database
Other bias	Unclear risk	Conflicts of interest and funding source were not reported

Abe 2010

Methods	• Study design: open-label parallel RCT • Study time frame: not reported • Duration of follow-up: 24 weeks
Participants	• Country: Japan • Setting: single centre • Inclusion criteria: HD patients with type 2 DM; poor glycaemic control (HbA1c ≥ 6.5% (48 mmol/mol) after 8 weeks on oral voglibose therapy of 0.9 mg daily • Number: treatment group (18); control group (18) • Mean age ± SD (years)**:** treatment group (67.0 ± 9.2). control group (66.0 ± 9.0) • Sex (M/F): treatment group (11/7); control group (11/7) • Exclusion criteria: deranged liver function at baseline; decompensated congestive heart failure; infectious disease; thyroid disease; malignant tumour; treatment with steroids
Interventions	Treatment group • Oral mitiglinide: started with 5 mg 3 times/d before each meal. This dose was increased up to 10 mg 3 times/d if target HbA1c values < 6.5% (48 mmol were not reached after 12 weeks). Elderly HD patients (> 75 years) initially received 2.5 mg 3 times/d. The dose was escalated to 5 mg 3 times/d at week 12, if necessary. Voglibose: dose was reduced from 0.9 to 0.6 mg/d if necessary to avoid hypoglycaemia. On the other hand, if the physician judged that mitiglinide 5 mg 3 times/d presented a safety problem, its dose could be reduced to 2.5 mg 3 times/d or 2.5 mg 2 times/d in elderly patients. Treated for 24 weeks Control group • Voglibose: 0.9 mg/d for 24 weeks
Outcomes	• HbA1c, GA and plasma glucose levels were measured as the criteria for glycaemic control • Insulin resistance was assessed using HOMA-IR • Plasma insulin • Levels of Hb, total bilirubin, AST, ALT, lactate dehydrogenase, alkaline phosphatase, g-GTP, total cholesterol, HDL and triglycerides • Body weight before and after dialysis • BMI • CTR determined by radiographic examination of the chest • Predialysis SBP and DBP
Notes	• Funding source: "The author states that Kissei Pharmaceutical had no involvement the preparation/approval of the paper. However, Kissei Pharmaceutical have paid for the FastTrack prioritization of the manuscript and they are the developers of mitiglinide."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated list was used for randomisation.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	High risk	Open-label study

Abe 2010 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients dropped out in either arm
Selective reporting (reporting bias)	Unclear risk	The prespecified outcomes were not available on a clinical trials database
Other bias	Low risk	No conflicts of interest

Abe 2010a

Methods	• Study design: open-label, parallel RCT • Study time frame: June 2007 to October 2009 • Duration of follow-up: 96 weeks
Participants	• Country: Japan • Setting: single centre • Inclusion criteria: HD with type 2 DM; clinically stable on maintenance HD for ≥ 12 months; ability to tolerate a 4 hr HD session with a blood flow rate of 200 mL/min; poor glycaemic control defined as a HbA1c > 7.0% (53 mmol/mol) after 12 consecutive weeks of daily administration of conventional antidiabetic agents; • Number (randomised/analysed): treatment group (31/30); control group (32/30) • Mean age ± SD (years)**:** treatment group: (65.2 ± 12.1); control group (67.2 ± 9.4) • Sex (M/F): treatment group (21/10); control group (22/10) • Exclusion criteria: cirrhosis or liver dysfunction at baseline; History of heart failure (both SBP and DBP), MI, or symptomatic coronary artery disease; significant aortic or mitral valve disease; NYHA class III or IV cardiac status); thyroid disease or malignancy; history of GI or other major bleeding within the last 6 months; treatment with steroids; receiving thiazolidinedione or insulin therapy at enrolment
Interventions	Treatment group • Pioglitazone: 15 to 30 mg/d plus their other therapy at the time, including oral antidiabetic agents. All patients received advice on diet and exercise. The dose of antidiabetic agents, including pioglitazone, was adjusted as judged by the investigators to achieve a glycaemic target of HbA1c < 7.0% (53 mmol/mol) Control group • Conventional oral antidiabetic agents (not insulin). All patients received advice on diet and exercise. The dose of antidiabetic agents was adjusted as judged by the investigators to achieve a glycaemic target of HbA1c < 7.0% (53 mmol/mol)
Outcomes	• Glycaemic control: HbA1c, GA, and plasma fasting glucose levels • Insulin resistance was assessed using the HOMA-IR • Plasma immunoreactive insulin • Levels of serum iron, transferrin saturation and ferritin • Hb • Total cholesterol, HDL, triglyceride, plasma albumin, albumin-corrected serum calcium, and serum phosphorus

Abe 2010a *(Continued)*

- High-sensitivity CRP
- iPTH
- Measurement of arterial blood pH and bicarbonate concentration
- Body weight before and after dialysis, interdialytic weight gain
- BMI
- CTR by chest X-ray
- Predialysis SBP and DBP
- High-molecular-weight adiponectin and TNF-a and IL-6

Notes	• Funding source: "The authors state no conflict of interest and have received no payment in preparation of this manuscript."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout rate with 3.2% of intervention group and 6.3% of control group dropping out
Selective reporting (reporting bias)	Unclear risk	The prespecified outcomes were not available on a clinical trials database
Other bias	Low risk	No conflict of interest reported

Abe 2016

Methods	• Study design: open-label, parallel RCT • Study time frame: June 2014 to October 2015 • Duration of follow-up: 24 weeks
Participants	• Country: Japan • Setting: multicentre (4) • Inclusion criteria: HD patients with type 2 DM; aged ≥ 20 years and ≤ 80 years; HD duration > 6 months at enrolment; poor glycaemic control defined as a GA level exceeding 20.0% after 8 consecutive weeks of daily administration of conventional therapy (dietary therapy alone, oral antidiabetic agents and/or insulin) • Number: treatment group (42); control group (42) • Mean age ± SD (years): treatment group (66.9 ± 9.4); control group (66.3 ± 9.4)

Abe 2016 *(Continued)*

	• Sex (M/F): treatment group (27/14); control group (28/13) • Exclusion criteria: history of severe heart failure, angina, MI or stroke within the past 6 months; presence of infectious disease, liver dysfunction, thyroid disease, malignant tumours, or treatment with steroids or immunosuppressants; current hospitalisation; treatment with any DPP-4 inhibitor within the past 6 months
Interventions	Both groups • Before randomisation, patients received fixed doses of conventional antidiabetic drugs (oral hypoglycaemic agents and/or insulin) for 8 weeks, and these drugs were continued during the 24-week treatment period. If the GA remained ≥20.0% after 12 weeks of treatment in either group, the dose(s) of other antidiabetic drugs could be increased Treatment group • Oral saxagliptin: 2.5 mg/d • Continued their regular medications, such as antihypertensive drugs, ESA, phosphate binders and lipid lowering agents, during the study period Control group • Continued their regular medications, such as antihypertensive drugs, ESA, phosphate binders and lipid lowering agents, during the study period.
Outcomes	• Change in GA • Changes in vital signs and laboratory/biochemical tests during the study, and safety. GA and HbA1c levels were measured as indices of glycaemic control • Postprandial plasma glucose levels • Vital signs: body weight, interdialytic weight gain, BMI, CTR on chest X-ray, and predialysis SBP and DBP • Hb • AST, ALT, lactate dehydrogenase, alkaline phosphatase, c-glutamyl transpeptidase, total cholesterol, HDL, triglyceride, total protein, and albumin concentrations
Notes	• Funding source: "Publication of this report was financially supported by a grant from Kyowa Hakko Kirin Co. Ltd. No financial support was received for implementation of this study.) Medical writing support was provided by Dr. Nicholas D. Smith (Edanz Group Ltd.) and Elsevier/ELMCOMTM. Kyowa Hakko Kirin Co. Ltd. was not involved in the study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Low risk	The randomisation of subjects was monitored by an independent investigator with no previous knowledge of the subjects
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study

Abe 2016 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout rate with 2.3% of each group dropping out
Selective reporting (reporting bias)	Low risk	All outcomes reported. The prespecified outcomes were available on a clinical trials database
Other bias	Low risk	"MA has received honoraria from Kyowa Hakko Kirin Co. Ltd. The other authors have no conflict of interest to declare"

AleNephro 2014

Methods	• Study design: phase IIb, double-blind, parallel RCT • Recruitment period: 27 May 2010 to 13 May 2011 • Duration of follow-up: 60 weeks
Participants	• Countries: 13 countries (Europe, South America, Asia, Australia) • Setting: international (62 sites) • Inclusion criteria: aged ≥ 18 years; diagnosis of type 2 DM and moderately impaired kidney function (CKD stage 3, as defined by eGFR MDRD ≥ 30 and < 60 mL/min/1.73 m^2); naive to the use of oral antihyperglycaemic agents or on monotherapy or combination therapy with no more than 2 antihyperglycaemic medications; HbA1c 6.5% to 10% (48-86 mmol/mol); FBG ≤ 13.3 mmol/L; UACR ≤ 3000 µg/mg; BMI from 25.0 kg/m^2 (Asian patients: from 23.0 kg/m^2) to 35.0 kg/m^2 • Number (randomised/analysed): treatment group (150/149); control group (152/148) • Mean age ± SD (years): treatment group (66.9 ± 8.0); control group (68.2 ± 7.6) • Sex (M/F): treatment group (75/74); control group (70/78) • Exclusion criteria: known diagnosis of kidney disease (except DKD); Congestive heart failure NYHA class II to IV; known macular oedema or impaired liver function (ALT or AST > 3 times the ULN); currently on, or had previously received, the following treatments: thiazolidinedione or insulin (with the exception of emergency cases, in which insulin was given for < 7 consecutive days), or medications interfering with measurement of creatinine (e.g. cimetidine, trimethoprim, probenecid, sulphonamides, procaine or thiazolsulfone); treatment with fibrates in the 3 months; chronic therapy with NSAID (with the exception of prophylactic stable low-dose aspirin) 1 month prior to screening; or changes in antihypertensive therapy in the last 3 months or in statins in the last month before screening or likely to require changes during the study
Interventions	Treatment group • Patients received a once-daily dose of 150 µg aleglitazar tablets and placebo capsules matching pioglitazone capsules, for 52 weeks, added to pre-existing antihyperglycaemic therapy and/or diet and exercise Control group • Patients received a once-daily dose of 45 mg pioglitazone capsules and placebo tablets matching aleglitazar tablets, for 52 weeks, added to pre-existing antihyperglycaemic therapy and/or diet and exercise Both groups • 2-week screening period prior to treatment • After termination of treatment, patients were followed for 8 weeks, with visits in Weeks 4 and 8 to evaluate reversibility of kidney effects
Outcomes	• Changes in eGFR following 52 weeks of daily treatment with 150 µg aleglitazar and 8 weeks of follow-up observation after the last study medication, in comparison with 45 mg pioglitazone

AleNephro 2014 *(Continued)*

	• Percentage and absolute change from baseline in eGFR and lipid profiles at end of treatment • Change from baseline to end of treatment and after 8 weeks of follow-up in additional kidney parameters, and time to first occurrence of any component of the triple-composite kidney endpoint (ESKD, confirmed doubling of SCr from baseline, (confirmed at least 4 weeks later) or confirmed increase in SCr of 50% (confirmed within 1 week and leading to discontinuation of treatment)), or the double-composite kidney endpoint (ESRD or any doubling of SCr from baseline) • Safety endpoints: adverse events, clinical laboratory tests, ECG, vital signs, physical examination, peripheral oedema, and cardiovascular symptoms including events
Notes	• Funding source: "The AleNephro study was funded by F. Hoffmann-La Roche AG"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“At the baseline visit, patients were randomly assigned (via an interactive voice-response system) in a 1:1 ratio to receive orally either 150 µg aleglitazar tablets and placebo capsules matching pioglitazone capsules, or 45 mg pioglitazone capsules and placebo tablets matching aleglitazar tablets. The patient randomisation numbers were generated by Roche and maintained by an unblinded statistician. The investigator or designee entered the case report form number (CRF; patient number) on the electronic CRF (given to a patient at visit 2 at the time of randomisation) and entered the corresponding randomisation number for allocation to the treatment groups in the appropriate place on each patient’s eCRF."
Allocation concealment (selection bias)	Low risk	"The patient randomisation numbers were allocated sequentially in the order in which the patients were enrolled according to the specification document agreed with the randomisation company (S-Clinica). The password-protected and/or encrypted electronic master randomisation list was kept in a central repository by the Roche Biometrics and Drug Safety Departments. No open key to the code was available at the study centre, to the Roche monitors, project statisticians, or to the project team at Roche.”
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients, study site personnel and sponsor were all blinded to treatment assignment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Patients, study site personnel and sponsor were all blinded to treatment assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	21.3% dropped out from the aleglitazar group and 22.4% dropped out from the pioglitazone group
Selective reporting (reporting bias)	Low risk	The prespecified outcomes were available on a clinical trials database was available and reported
Other bias	High risk	Conflicts of interest were present. The sponsor F. Hoffmann-La Roche contributed to dosing, data collection, statistical analysis and interpretation of data in collaboration with the investigators. Authors were either employees of F. Hoffmann-La Roche or serve as advisors to the company, or have received speaker honoraria, consulting fees, research grants from the company

Arjona Ferreira 2013

Methods	• Study design: double-blind, parallel RCT • Study time frame: not reported • Duration of follow-up: 54 weeks
Participants	• Countries: multinational (number of countries not reported) • Setting: multicentre (number of centres not reported) • Inclusion criteria: patients with type 2 DM; moderate to severe chronic kidney insufficiency (eGFR < 50 mL/min/1.73 m^2 using the MDRD equation); not on dialysis and unlikely to require dialysis for the duration of the study; HbA1c 7.0 to ≥ 9.0%, and were ≥ 30 years of age at the screening visit • Number: treatment group (211); control group (212) • Mean age ± SD (years)**:** treatment group (64.8 ± 10.6); control group (64.3 ± 9.2) • Sex (M/F): treatment group (80/55); control group (78/64) • Exclusion criteria: taking insulin within 12 weeks of the screening visit; type 1 DM; history of ketoacidosis, AKI, kidney transplant or liver disease; recent (within 3 months) cardiovascular event; hepatic transaminase levels ≥ 2 times the ULN; thyroid stimulating hormone outside the reference range; triglycerides > 6.78 mmol/L; met one of the following prespecified glycaemic criteria: visit 2, FBG > 14.44 mmol/L, unlikely to improve with diet/exercise; visit 3, FBG > 13.89 mmol/L consistently (i.e. measurement repeated and confirmed within 7 days); visit 4, FBG > 13.33 mmol/L consistently; and visit 5, finger-stick glucose > 13.33 or < 6.67 mmol/L
Interventions	Treatment group • Patients with moderate kidney insufficiency received 50 mg/d of sitagliptin (2 x 25 mg tablets). The dose of sitagliptin was reduced from 50 mg/d to 25 mg/d for patients whose kidney status changed from moderate to severe • Patients with severe kidney insufficiency received 25 mg/d of sitagliptin (1 x 25 mg tablet) • After maximally titrating the matching placebo to glipizide, patients had insulin rescue therapy initiated, with the regimen and dose determined by investigator, if they met the following criteria: confirmed FBG > 13.33 mmol/L any time from randomisation to week 6; confirmed FBG > 12.22 mmol/L from week 6 to 12; confirmed FBG > 11.11 mmol/L from week 12 to 24; and confirmed HbA1c > 8% after week 24. Once insulin rescue therapy was initiated, patients continued to take blinded sitagliptin or matching placebo, but discontinued the matching placebo to glipizide. Control group • Glipizide was administered at a starting dose of 2.5 mg/d, prior to the morning meal, and electively titrated to a maximum of 20 mg/d as considered appropriate by the investigator based on the patient's glycaemic control. The dose of glipizide could also be reduced or interrupted to prevent hypoglycaemia. Patients received a placebo for sitagliptin. After maximally titrating glipizide, patients had insulin rescue therapy initiated, with the regimen and dose determined by investigator, if they met the following criteria: confirmed FBG > 13.33 mmol/L any time from randomisation to week 6; confirmed FBG > 12.22 mmol/L from week 6 to 12; confirmed FBG > 11.11 mmol/L from week 12 to 24; and confirmed HbA1c > 8% after week 24. Once insulin rescue therapy was initiated, patients continued to take blinded sitagliptin or matching placebo, but discontinued blinded glipizide
Outcomes	• Change from baseline in HbA1c at week 54 • FBG, fasting serum insulin and proinsulin, and plasma lipid profiles (total cholesterol, LDL, HDL, non–HDL-cholesterol, triglycerides) • Homeostasis model assessment–B-cell function, HOMA-IR, proinsulin/insulin ratio were calculated from fasting measurements of FBG, insulin, and proinsulin • Proportion of individuals whose HbA1c values met glycaemic goals (< 7.0% as primary; < 6.5% as secondary) at week 54 • Post hoc analysis evaluated the effect of sitagliptin versus glipizide on a composite end point consisting of glycaemic control (reduction in HbA1c > 0.5%), no body weight gain, and no hypoglycaemia • Adverse events, physical examination and vital signs, and ECG • Laboratory safety studies included serum chemistry, haematology, and urinalysis • Hypoglycaemia were considered of special interest

Arjona Ferreira 2013 *(Continued)*

- Events of hypoglycaemia requiring (non-medical) assistance of others, requiring medical intervention, or exhibiting markedly depressed level of consciousness, loss of consciousness, or seizure were considered severe
- Change in body weight and GI adverse events (nausea, vomiting, diarrhoea, and abdominal pain)

Notes

- The study included a 1-week screening period, a diet/exercise and oral glucose-lowering agent wash-off period of up to 14 weeks, a 2-week, single-blind placebo run-in period, and a 54-week, double-blind treatment period.
- At screening, patients not taking glucose-lowering agents for ≥ 12 weeks with an HbA1c of 7–9% directly entered the single-blind placebo run-in period and those with an HbA1c > 9% entered a 6-week diet and exercise period. Patients taking oral glucose-lowering agents with an HbA1c of 7–9% entered an 8-week drug wash-off and diet and exercise period (those taking thiazolidinediones underwent a 10-week wash-off period), and those with an HbA1c of 6.5 to < 7% entered an 8–12-week drug wash-off and diet and exercise period (those on thiazolidinediones underwent a 10–14-week wash-off period). Patients received diet and exercise counselling throughout the study, consistent with American Diabetes Association recommendations and appropriate for their kidney insufficiency status. Following the placebo run-in, eligible patients were randomised (1:1) using a computer-generated randomisation schedule to receive sitagliptin or glipizide and their matching placebo.
- Data from one study site (3 patients) were considered potentially unreliable due to lack of compliance with Good Clinical Practice and excluded from all analyses.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomised (1:1) using a computer-generated randomisation schedule to receive sitagliptin or glipizide. Randomization was stratified based on: 1) kidney insufficiency status (moderate or severe), 2) history of cardiovascular disease (yes or no), and 3) history of heart failure (yes or no)".
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Sitagliptin and glipizide matching placebos were used to maintain blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study was described as double-blind, but the methods to ensure blinding of outcome assessment were not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	22.3% of the sitagliptin group and 19.8% of the glipizide group dropped out
Selective reporting (reporting bias)	Low risk	The prespecified outcomes were available on a clinical trials database. All outcomes were reported
Other bias	High risk	Conflicts of interest: The study was sponsored by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, the manufacturer of sitagliptin. J.C.A.F., H.G., G.T.G., C.M.S., K.D.K., and B.J.G. are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., and may have stock or stock options in the company. N.B. has served on the National Diabetes Advisory Board. M.M. is a consultant for Association Diabete Risque Vasculaire, serves on the Merck global advisory board and the French subsidiary advisory board, and is a speaker for Merck, Sanofi, Novo Nordisk, Servier, and Abbott Diagnostics. No other potential conflicts of interest relevant to this.

Arjona Ferreira 2013a

Methods	• Study design: double-blind, parallel RCT • Study time frame: not reported • Duration of follow-up: 54 weeks
Participants	• Countries: 13 (countries not reported) • Setting: multicentre (3 sites) • Inclusion criteria: patients with type 2 DM on HD or PD for at least 6 months; ≥ 30 years; patients on monotherapy or low-dose combination therapy with oral antihyperglycaemic agents could participate if their treatment regimen could be discontinued during the run-in period • Number: treatment group (64); control group (65) • Mean age ± SD (years)**:** treatment group (60.5 ± 9.1); control group (58.5 ± 9.9) • Sex (M/F): treatment group (40/24); control group (37/28) • Exclusion criteria: on insulin therapy within 12 weeks of the screening visit; type 1 DM or a history of ketoacidosis; AKI; kidney transplant; liver disease; recent (within 6 months) cardiovascular event; hepatic transaminase levels ≥ 2 times the ULN; repeated FBG > 13.3 mmol/L, or triglyceride > 6.7 mmol/L
Interventions	Treatment group • Sitagliptin 25 mg daily and a glipizide placebo pill. Glipizide placebo was initiated at 2.5 mg daily and progressively titrated in 2-week intervals to a potential maximum dose of 10 mg twice daily. In general, uptitration of glipizide placebo was to occur if the prior week's fasting and preprandial glucose measurements were ≥ 6.7 mmol/L and there were no episodes of hypoglycaemia. However, investigators were allowed to increase the dose of glipizide placebo as considered appropriate, deviating from the parameters outlined above. Downtitration, including interruption of treatment, could occur if a patient had unexplained hypoglycaemia documented by fingerstick glucose level < 3.9 mmol/L or at the clinical judgment of the investigator, to reduce the risk of hypoglycaemia. Treatment adherence was assessed by patient query at prespecified visits throughout the study. Glycaemic rescue therapy (i.e. insulin) was available after randomisation for patients whose glipizide placebo tablets had been uptitrated to the maximum tolerated dose and who met predefined glycaemic parameters as follows: confirmed FBG > 13.33 mmol/L at any time after randomisation (day 1) until week 6, confirmed FBG > 12.2 mmol/L after week 6 through week 12, confirmed FBG > 11.1 mmol/L after week 12 through week 24, and confirmed HbA1c > 8% (64 mmol/mol) after week 24. Prior to initiating rescue therapy, patients were to undergo efficacy and safety measurements and procedures. Investigators were responsible for the management of insulin therapy. Control group • Glipizide initiated at 2.5 mg daily and progressively titrated in 2-week intervals to a potential maximum dose of 10 mg twice daily and a sitagliptin placebo pill. In general, uptitration of glipizide was to occur if the prior week's fasting and preprandial glucose measurements were ≥ 6.67mmol/L and there were no episodes of hypoglycaemia. However, investigators were allowed to increase the dose of glipizide as considered appropriate, deviating from the parameters outlined above. Downtitration, including interruption of treatment, could occur if a patient had unexplained hypoglycaemia documented by fingerstick glucose level < 3.89 mmol/L or at the clinical judgment of the investigator, to reduce the risk of hypoglycaemia. Treatment adherence was assessed by patient query at prespecified visits throughout the study. Glycaemic rescue therapy (i.e. insulin) was available after randomisation for patients whose glipizide tablets had been uptitrated to the maximum tolerated dose and who met predefined glycaemic parameters as follows: confirmed FBG > 13.3 mmol/L at any time after randomisation (day 1) until week 6, confirmed FBG > 12.2 mmol/L after week 6 through week 12, confirmed FBG > 11.1 mmol/L after week 12 through week 24, and confirmed HbA1c > 8% (64 mmol/mol) after week 24. Prior to initiating rescue therapy, patients were to undergo efficacy and safety measurements and procedures. Investigators were responsible for the management of insulin therapy
Outcomes	• Change in HbA1c, tolerability - vital signs, electrocardiograms, blood chemistry, haematology, and urinalysis • Incidence of symptomatic hypoglycaemia

Arjona Ferreira 2013a *(Continued)*

- FBG, fasting serum insulin and proinsulin, and plasma lipid profiles (total cholesterol, LDL cholesterol, HDL and triglycerides)
- Homeostasis model assessment of B-cell function, HOMA-IR, and proinsulin to insulin ratio were calculated from fasting measurements of glucose, insulin, and/or proinsulin

Notes

- At the screening visit, patients not on antihyperglycaemic therapy for 12 weeks or longer with an HbA1c level of 7% to 9% (53 to 75 mmol/mol) directly entered a 2-week, single-blind, placebo run-in period. Patients not on therapy with an HbA1c level > 9% (75 mmol/mol) entered a 6-week diet and exercise period. Patients on an oral antihyperglycaemic regimen with an HbA1c level of 7%-9% entered an 8-week drug washout and diet and exercise period; those using thiazolidinediones underwent a 10-week washout period. Patients on an oral antihyperglycaemic regimen with an HbA1c level of 6.5% to < 7% (48 to <53 mmol/mol) entered an 8- to 12-week drug washout and diet and exercise period; those using thiazolidinediones underwent a 10- to 14-week washout period. Patients received counselling throughout the study on diet and exercise consistent with American Diabetes Association recommendations and appropriate for patients with ESKD on dialysis therapy. Following the diet and exercise and washout period, patients with an HbA1c level of 7% to 9% (53 to 75 mmol/mol) entered the 2-week placebo run-in period.
- Funding source: "The study was sponsored by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co. Inc., the manufacturer of sitagliptin."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were “randomly assigned 1:1, using a computer-generated randomisation schedule, to receive sitagliptin, 25 mg daily or glipizide”.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	“Sitagliptin or glipizide placebo pills were used to maintain blinding”.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	Large dropout rates for both groups - 26.6% for the sitagliptin group and 30.8% for the glipizide group
Selective reporting (reporting bias)	Low risk	The prespecified outcomes were available on a clinical trials database and all outcomes were reported
Other bias	High risk	1) The study was underpowered. From the report: “Due to enrolment challenges, the sample size was revised from 150 (original design) to 125. The following calculations were based on the revised sample size. Assuming 10% of patients discontinued without a post randomisation measurement, the study had 76% power to detect a true difference of 0.40% in the within-group mean reduction in HbA1c level from baseline, using a standard deviation of 1.1%”. However, 28.7% of cohort discontinued. 2) Conflict of interest: The study was sponsored by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co. Inc., the manufacturer of sitagliptin. Doctors Arjona Ferreira, Xu, Golm, Davies, Kaufman, and Goldstein and Mr Gonzalez are employees of Merck Sharp & Dohme Corp., a subsidiary

Arjona Ferreira 2013a *(Continued)*

	of Merck & Co. Inc., and may have stock or stock options in the company. Dr Sloan has served on an advisory board for sitagliptin and has been a speaker and consultant for Merck Sharp & Dohme Corp. The other authors declare that they have no other relevant financial interests.

Baldwin 2012

Methods	• Study design: parallel RCT • Study time frame: June 2009 to June 2011 • Duration of follow-up: 6 days
Participants	• Country: USA • Setting: multicentre (3 sites) • Inclusion criteria: patients with type 2 DM > 1 year of duration; > 18 years; eGFR ≤ 45 mL/min/1.73 m^2; at least one hospital blood glucose level > 10 mmol/L; if on insulin, outpatient dose ≥ 0.5 U/kg • Number: treatment group (57); control group (50) • Mean age ± SD (years)**:** treatment group (63.7 ± 13.0); control group (65.3 ± 10.6) • Sex (M/F): treatment group (28/29); control group (20/30) • Exclusion criteria: type 1 DM; pregnancy; chronic dialysis; solid-organ transplant within the past 12 months; steroid therapy > 7.5 mg/d of prednisolone or equivalent medication; known hypopituitarism or adrenal insufficiency; known hypoglycaemia unawareness; length of stay < 48 h; severe liver disease
Interventions	Both groups • All oral antidiabetic agents were stopped on hospital admission Treatment group • SC insulin: 0.25 U/kg, half the dose given as glargine and half the dose as glulisine 3 times/d equally Control group • SC insulin: 0.5 U/Kg, half the dose glargine and half the dose as glulisine 3 times/d equally
Outcomes	• Percentage of BGL within the range of 5.6 to 10 mmol/L, and the percentage of subjects experiencing a hypoglycaemic event defined as a blood glucose < 3.9 mmol/L • Hypoglycaemic events were further separated into moderate hypoglycaemia (2.8 to 3.8 mmol/L) and severe hypoglycaemia (< 2.8 mmol/L)
Notes	• Funding source: "This study was sponsored by an investigator-initiated grant from sanofi-aventis."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of random sequence generation was not reported. All the paper reports was: “Eligible patients gave informed consent and were randomised 1:1 into two protocol groups by a research pharmacist”.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement

Baldwin 2012 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no drop-outs in each group, and all subjects were analysed in the groups to which they were randomised
Selective reporting (reporting bias)	Low risk	The prespecified outcomes were available on a clinical trials database and all outcomes were reported
Other bias	Low risk	No conflicts of interest were reported

Barnett 2013

Methods	• Study design: phase 3, parallel RCT • Study time frame: 10 March 2010 to 22 June 2011 • Duration of follow-up: 24 weeks
Participants	• Countries: Australia, Canada, Denmark, the Netherlands; Sweden • Setting: multinational (33 clinics) • Inclusion criteria: Men and women ≥ 70 years with type 2 DM; had insufficient glycaemic control (HbA1c ≥ 7.0%; 53 mmol/mol); receiving stable doses of metformin, sulphonylureas, or basal insulin, or combinations of these drugs, for at least 8 weeks • Number (randomised/analysed): treatment group (162/146); control group (79/74) • Mean age ± SD (years): treatment group (74.9 ± 4.4); control group (74.9 ± 4.2) • Sex (M/F): treatment group (116/46); control group (49/30) • 36 patients had an eGFR < 60 included in the analysis • Exclusion criteria: FBG > 13·3 mmol/L; impaired hepatic function (ALT, AST, or ALP > 3 times the ULN); MI, stroke, or TIA within 3 months before the study; previous bariatric surgery; present treatment with rapid-acting or premixed insulin or systemic steroids; treatment within the previous 3 months with a thiazolidinedione, α-glucosidase inhibitor, meglitinide, GLP1 analogue, DPP-4 inhibitor, or anti-obesity drug
Interventions	Both groups • After screening, eligible patients underwent a 2 week, open-label, placebo run-in period. Patients were then randomised • Maintained existing glucose-lowering treatment throughout the study Treatment group • Oral linagliptin: 5 mg once/d for 24 weeks Control group • Oral placebo: once/d for 24 weeks Other information • Doses of background treatments were maintained for the first 12 weeks of randomised treatment, after which dose adjustments were permitted. Rescue medication for hyperglycaemia (confirmed glucose level: fasting >13·3 mmol/L in weeks 1–12, > 11·1 mmol/L in weeks 13–24; or random test > 22·2 mmol/L; two or more measurements on different days, one done after an overnight fast) was permitted during randomised treatment
Outcomes	• Change in HbA1c from baseline to week 24

Barnett 2013 *(Continued)*

	• Proportion of patients achieving HbA1c < 7.0% (53 mmol/mol) after 24 weeks • Proportion of patients with a 0·5% or greater reduction in HbA1c after 24 weeks • Change in HbA1c from baseline over time • Change in FBG from baseline at week 24 • Change in FBG from baseline over time, and use of rescue therapy • Incidence and intensity of adverse events (including adverse changes noted during physical examinations or 12-lead ECGs) • Withdrawals because of adverse events; hypoglycaemia; cardiovascular events; and changes in vital signs, laboratory variables, and background treatment
Notes	• The proportion of patients achieving other levels of HbA1c (< 7.5% (58 mmol/mol) , < 8.0% (64 mmol/mol), < 8.5%) was analysed post hoc • Funding source: Boehringer Ingelheim

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated randomisation lists were produced by the sponsor..."
Allocation concealment (selection bias)	Low risk	"...allocation concealed using a central interactive voice–web response system".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Linagliptin and placebo tablets were identical in appearance, and investigators and patients were masked to treatment assignment throughout the study"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Linagliptin and placebo tablets were identical in appearance, and investigators and patients were masked to treatment assignment throughout the study".
Incomplete outcome data (attrition bias) All outcomes	Low risk	16/162 (9.9%) linagliptin; 5/79 (6.3%) placebo dropped out
Selective reporting (reporting bias)	Low risk	The prespecified outcomes were available on a clinical trials database and all outcomes were reported.
Other bias	High risk	Conflict of interest: This study was sponsored by Boehringer Ingelheim. The sponsor was involved in study design, and data collection, review, and analysis. All authors were employees of Boehringer Ingelheim except the first author who has received honoraria for lecture and advisory work for the company.

Bellante 2016

Methods	• Study design: prospective RCT • Study time frame: not reported • Duration of follow-up: 52 weeks
Participants	• Country: Italy • Setting single centre • Inclusion criteria: patients with type 2 DM and CKD stage 3B, 4-5 and 5D • Number: treatment group (32); control group (17)

Bellante 2016 *(Continued)*

- Mean age ± SD: 73 ± 8 years
- Sex (M/F): not reported
- Exclusion criteria: not reported

Interventions	Treatment group • Sitagliptin: dose not reported Control group • Insulin: dose not reported
Outcomes	• Effects on circulating endothelial progenitor cells • Effects on endothelial progenitor cells functional properties • BMI, BP, lipids, eGFR and HbA1c
Notes	• Abstract-only publication • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The same trained operators, blind to the clinical status of each subject, performed the tests throughout the entire study."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts were reported.
Selective reporting (reporting bias)	Unclear risk	The prespecified outcomes were not available on a clinical trials database.
Other bias	Unclear risk	Insufficient information to permit judgement

Chan 2008a

Methods	• Study design: parallel RCT • Study time frame: not reported • Duration of follow-up: 54 weeks • 54-week, multinational, randomised, double-blind, parallel-group study that included a 12-week, double-blind, placebo-controlled phase and a 42-week, double-blind, continuation phase during

Chan 2008a *(Continued)*

	which all patients were eligible for active therapy (either continued treatment with sitagliptin or treatment with glipizide for those initially randomised to placebo).
Participants	• Countries: Australia; Chile; Colombia; Hong Kong; Hungary; Malaysia; Mexico; New Zealand; Philippines; Spain; USA • Setting: multinational (30 sites) • Inclusion criteria: Patients ≥ 18 years with type 2 DM and kidney insufficiency; not on oral antihyperglycaemic agents or washed off these agents during the run-in period; patients on insulin monotherapy were also allowed to participate in this study • Number: treatment group (65); control group (26) • Mean age ± SD (years): treatment group (68.9 ± 9.8); control group (65.3 ± 9.7) • Sex (M/F): treatment group (31/34); control group (16/10) • Exclusion criteria: type 1 diabetes (or a history of ketoacidosis); AKI; history of kidney transplant; liver disease; recent (within 6 months) cardiovascular event; hepatic transaminase or creatine phosphokinase levels ≥ two times the ULN; repeated FBG >15 mmol/L or triglycerides > 6.8 mmol/L

Interventions	Treatment group
	• Sitagliptin for 12 weeks. Patients with CrCl ≥ 30 to < 50 mL/min received once-daily sitagliptin 50 mg; patients with CrCl < 30 mL/min inclusive of those on dialysis received once-daily sitagliptin 25 mg. If estimated CrCl decreased to < 30 mL/min during the study, patients were instructed to down titrate their dose for the remainder of the study.
	• From week 12, patients received glipizide placebo for 42 weeks
	Control group
	• Placebo: for 12 weeks
	• From week 12 patients were eligible for active treatment with glipizide initiated at a dose of 5 mg/d and progressively titrated in 2-week intervals to a maximum dose of 10 mg twice daily. Initiation and uptitration of glipizide placebo were to occur if the FBG was > 7.2 mmol/L and if considered clinically appropriate by the investigator
	Other information
	• Both groups
	  * Patients received counselling on exercise and diet consistent with American Diabetes Association recommendations and appropriate for patients with kidney insufficiency throughout the study
	• Treatment group
	  * If the investigator considered a patient to be at significantly increased risk for hypoglycaemia, the investigator could either withhold glipizide placebo altogether, initiate dosing at the lower dose of 2.5 mg/day, or, for those patients already receiving glipizide placebo tablets, either withhold uptitration of glipizide placebo or down titrate the glipizide placebo dose. To avoid the potentially increased risk of hypoglycaemia episodes with co-administered insulin and glipizide, patients who entered the study on insulin therapy were ineligible to initiate glipizide/glipizide placebo upon entry into the continuation phase. Open-label glycaemic rescue therapy was available throughout the study. For glycaemic rescue, patients on insulin had their insulin dose uptitrated, while patients not on insulin initiated either an open-label sulphonylurea or insulin therapy (at the discretion of the investigator). To avoid accidental treatment with two sulphonylurea agents or treatment with the combination of insulin and a sulphonylurea, patients who had undergone glycaemic rescue during the first 12 weeks of the study were ineligible to initiate double-blind glipizide/glipizide placebo upon entry into the 42-week continuation phase. Similarly, patients requiring glycaemic rescue therapy during the 42-week continuation phase were to discontinue their blinded, glipizide/glipizide placebo tablets before rescue treatment was added
	• Control group
	  * If the investigator considered a patient to be at significantly increased risk for hypoglycaemia, the investigator could either withhold glipizide altogether, initiate dosing at the lower dose of 2.5 mg/day, or, for those patients already receiving glipizide tablets, either withhold uptitration of glipizide or down titrate the glipizide dose. To avoid the potentially increased risk of hypoglycaemia episodes with co-administered insulin and glipizide, patients who entered the study on insulin therapy were ineligible to initiate glipizide/glipizide placebo upon entry into the continuation

Chan 2008a *(Continued)*

	phase. Open-label glycaemic rescue therapy was available throughout the study. For glycaemic rescue, patients on insulin had their insulin dose uptitrated, while patients not on insulin initiated either an open-label sulphonylurea or insulin therapy (at the discretion of the investigator). To avoid accidental treatment with two sulphonylurea agents or treatment with the combination of insulin and a sulphonylurea, patients who had undergone glycaemic rescue during the first 12 weeks of the study were ineligible to initiate double-blind glipizide/glipizide placebo upon entry into the 42-week continuation phase. Similarly, patients requiring glycaemic rescue therapy during the 42-week continuation phase were to discontinue their blinded, glipizide/glipizide placebo tablets before rescue treatment was added.
Outcomes	• Glycaemic and lipid assessments included the change from baseline in HbA1c, FBG and the per cent change from baseline in plasma lipids (total cholesterol, low density lipoprotein cholesterol (LDL-C), HDL cholesterol (HDL-C) and triglycerides) • Physical examinations, vital signs and ECGs collected at specified study visits • Blood chemistry, haematology, urinalysis and urine microalbumin/creatinine ratio • Events of hypoglycaemia were considered of special interest
Notes	• Funding source: Merck & Co., Inc

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Following the placebo run-in period, patients underwent baseline measurements and were randomised to receive once-daily administration of sitagliptin or placebo in a 2 : 1 ratio using a computer-generated randomisation schedule".
Allocation concealment (selection bias)	Low risk	"Following the placebo run-in period, patients underwent baseline measurements and were randomised to receive once-daily administration of sitagliptin or placebo in a 2 : 1 ratio using a computer-generated randomisation schedule"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients received placebo tablets. Also described as a 54-week, multinational, randomised, double-blind, parallel-group study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	study described as a 54-week, multinational, randomised, double-blind, parallel-group study, but the method of outcome assessment blinding was not described in the report
Incomplete outcome data (attrition bias) All outcomes	High risk	29.2% 19/65 dropped out in the sitagliptin group. 23.1% 6/26 dropped out in the placebo/gliclazide group.
Selective reporting (reporting bias)	Low risk	The prespecified outcomes were available on a clinical trials database and all outcomes were reported
Other bias	High risk	Conflict of interest: This study was sponsored by Merck & Co., Inc, Whitehouse Station, NJ, USA, who make sitagliptin

Diez 1987

Methods	• Study design: parallel RCT • Study time frame: not reported

Diez 1987 *(Continued)*

	• Duration of follow-up: 9 months
Participants	• Country: Spain • Setting multicentre (2) • Inclusion criteria: DM patients on CAPD • Number: treatment group 1 (13); treatment group 2 (6) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group 1 • SC insulin Treatment group 2 • IP insulin
Outcomes	• Metabolic control • Peritonitis
Notes	• Abstract-only publications

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No drop-outs reported
Selective reporting (reporting bias)	Unclear risk	The prespecified outcomes were not available on a clinical trials database available - inadequate information
Other bias	Unclear risk	Insufficient information to permit judgement

EMPA-REG BP 2015

Methods	• Study design: phase 3, parallel RCT • Study time frame: June 2011 to July 2012

EMPA-REG BP 2015 *(Continued)*

	• Duration of follow-up: 14 weeks

Participants	• Countries: Europe, Middle East and North America
	• Setting: multinational (number of centres not reported)
	• Inclusion criteria: patients aged ≥ 18 years, BMI ≤ 45 kg/m^2, type 2 DM and hypertension (SBP 130 to 159 mmHg; DBP 80 to 99 mmHg); HbA1c ≥ 7.0 to ≤ 10.0% (≥ 53 to ≤ 86 mmol/mol); required to receive up to two antihypertensive medications at a stable dose for ≥ 4 weeks at screening and throughout a 2-week, open-label, placebo run-in period; for treatment of type 2 DM, patients were required to be on a diet and exercise regimen and be drug naive (no oral antidiabetes therapy, GLP-1 analogue, or insulin for ≥ 12 weeks (or ≥ 16 weeks for pioglitazone) prior to randomisation) or pretreated with any oral antidiabetes therapy, GLP-1 analogue, or insulin for ≥ 12 weeks prior to randomisation; antidiabetes therapy doses were to have remained unchanged for ≥ 12 weeks (or ≥ 16 weeks for pioglitazone) prior to randomisation or, for insulin, the dose was not to have been changed within 12 weeks prior to randomisation by > 10% from the dose at randomisation
	• Number: treatment group 1 (276); treatment group 2 (276); control group (271)
	  * 45 patients had eGFR < 60 mL/min at baseline
	  * Treatment group 1 (13); treatment group 2 (21); control group (11)
	• Mean age ± SD (years): treatment group 1 (60.6 ± 8.5); treatment group 2 (59.9 ± 9.7); control group (60.3 ± 8.8)
	• Sex (M/F)**:** treatment group 1 (171/105); treatment group 2 (156/120); control group (168/103)
	• Exclusion criteria: uncontrolled hyperglycaemia (plasma glucose > 13.3 mmol/L after an overnight fast during the run-in period);SBP ≥ 160 mmHg and/or DBP ≥ 100 mmHg during the run-in period; known/suspected secondary hypertension; history/evidence of hypertensive retinopathy or hypertensive encephalopathy; kidney impairment (eGFR < 60 mL/min/1.73 m^2; indication of liver disease (serum ALT, AST, or ALP > three times the ULN) during screening/run-in period; acute coronary syndrome, stroke, or TIA within 3 months of consent.; use of anti-obesity drugs within 3 months of consent or bariatric surgery within 2 years; any uncontrolled endocrine disorder except type 2 DM

Interventions	All groups • 2-week, open-label, placebo run-in, patients were then randomised (1:1:1) • Patients continued their antihypertensive and antidiabetes background therapy throughout the study at an unchanged dose and regimen, if possible Treatment group 1 • Empagliflozin: 10 mg daily for 12 weeks Treatment group 2 • Empagliflozin: 25 mg daily for 12 weeks Control group • Placebo for 12 weeks Other information • Changes in antihypertensive medication could be initiated if a patient had a mean SBP ≥ 160 mmHg and/or a mean DBP ≥ 100 mmHg at a clinic visit • Rescue medication for hyperglycaemia could be initiated at the discretion of the investigator if, after an overnight fast, a patient had plasma glucose > 13.3 mmol/L during the first 12 weeks of treatment or > 11.1 mmol/L during the follow-up period
Outcomes	• Change from baseline in HbA1c at week 12 • Change from baseline in mean 24 h SBP at week 12 • Change from baseline in mean 24 h DBP at week 12, both measured via ABPM • Changes from baseline in FBG body weight, daytime and night-time mean SBP and DBP, and mean seated office SBP and DBP • Use of rescue medication

EMPA-REG BP 2015 *(Continued)*

	• Adverse events of special interest included confirmed hypoglycaemic adverse events (plasma glucose ≤ 3.9 mmol/L and/or assistance required), • Adverse events consistent with UTI (based on a prospectively defined search of 70 preferred terms), • Adverse events consistent with genital infection (based on a prospectively defined search of 89 preferred terms) • Adverse events consistent with volume depletion (based on 8 preferred terms) • The change from baseline in the proportion of patients with a positive orthostatic BP test at week 12 was analysed
Notes	• Interested in patients with eGFR < 60 for this systematic review • Funding source: Boehringer Ingelheim and Eli Lilly

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was undertaken using a computer-generated, pseudo-random sequence and an interactive voice and web response system.
Allocation concealment (selection bias)	Low risk	Randomisation was undertaken using a computer-generated, pseudo-random sequence and an interactive voice and web response system.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Patients were randomised (1:1:1) to receive 10 mg empagliflozin o.d., 25mg empagliflozin o.d., or placebo double blind for 12 weeks."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study labelled as double blind, but the methodology for blinding was not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	11/276 (4.0%) Empagliflozin 10 mg d; 11/277 (4.0%) Empagliflozin 25 mg d; 16/272 (5.9%) placebo discontinued.
Selective reporting (reporting bias)	Low risk	The prespecified outcomes were available on a clinical trials database and all major outcomes were reported.
Other bias	High risk	Conflicts of interest: This study was funded by Boehringer Ingelheim and Eli Lilly who developed Empagliflozin. All but one of the authors works for Boehringer Ingelheim or on behalf of Boehringer Ingelheim. The remaining author has received consulting fees/payments for lectures and support for travel to meetings from Boehringer Ingelheim.

EMPA-REG OUTCOME 2013

Methods	• Study design: phase 3, parallel RCT • Study time frame: July 2010 to April 2015 • Duration of follow-up: 192 weeks
Participants	• Countries: 42, including North America, Australia, New Zealand, Latin America, Europe, Africa, Asia • Setting: multinational (590 sites) • Inclusion criteria: adults ≥18 years with type 2 DM; BMI ≤ 45 kg/m^2; eGFR ≥ 30 mL/min/1.73 m^2 (MDRD); established CVD; no glucose-lowering agents for at least 12 weeks before randomisation and had a

EMPA-REG OUTCOME 2013 *(Continued)*

HbA1c ≥ 7.0% and ≤ 9.0%, or had received stable glucose-lowering therapy for at least 12 weeks before randomisation and had a HbA1c ≥ 7.0% and ≤ 10.0%

- Number (randomised/analysed): treatment group 1 (2345/2264); treatment group 2 (2342/2279); control group (2333/2266)
  - eGFR < 60: treatment groups (1212); control group (607)
- Mean age ± SD (years): treatment groups (67.1 ± 7.6); control group (67.1 ± 8.2).
- Sex (M/F)**:** treatment groups (816/396); control group (418/189)
- Exclusion criteria: uncontrolled hyperglycaemia with glucose > 13.3 mmol/L after an overnight fast during placebo run-in; indication of liver disease, ALT, AST, or ALP > 3 x ULN during screening or run-in phase); planned cardiac surgery or angioplasty within 3 months; eGFR < 30 mL/min/1.73 m^2 (according to the MDRD equation) at screening or during run-in phase; bariatric surgery within the past 2 years and other GI surgeries that induce chronic malabsorption; blood dyscrasias or any disorders causing haemolysis or unstable RBC; medical history of cancer (except for BCC) and/or treatment for cancer within the last 5 years; contraindications to background therapy according to the local label; treatment with anti-obesity drugs 3 months prior to informed consent or any other treatment at time of screening leading to unstable body weight; treatment with systemic steroids at time of informed consent or change in dosage of thyroid hormones within 6 weeks prior to informed consent; any uncontrolled endocrine disorder except type 2 DM; pre-menopausal women (last menstruation ≤ 1 year prior to informed consent) who were nursing, pregnant, or of child-bearing potential and were not practicing an acceptable method of birth control, or did not plan to continue using this method throughout the study, or did not agree to submit to periodic pregnancy testing during the study; alcohol or drug abuse within 3 months of informed consent that would interfere with study participation or any ongoing condition leading to reduced compliance with study procedures or study drug intake. Intake of an investigational drug in another study within 30 days prior to intake of study medication in this study or participating in another study involving an investigational drug and/or follow-up; any clinical condition that would jeopardize patient safety while participating in this clinical study (in Canada, this included current genito-urinal infection or genito-urinal infection within 2 weeks prior to informed consent); acute coronary syndrome, stroke, or TIA within 2 months prior to informed consent. In South Africa: BP > 160/100 mmHg at screening

Interventions	Treatment group • Empagliflozin: dose of 10 mg or 25 mg • Standard care Control group • Placebo • Standard care

Outcomes	• Composite of three major adverse cardiovascular events (3-point MACE), which was defined as the first occurrence of death from cardiovascular causes, nonfatal MI, or nonfatal stroke.
	• A composite of the primary outcome plus hospitalisation for unstable angina (4-point MACE)
	• A composite microvascular outcome that included the first occurrence of any of the following: the initiation of retinal photocoagulation, vitreous haemorrhage, diabetes-related blindness, or incident or worsening nephropathy
	• Kidney microvascular outcomes include
	  * Incident or worsening nephropathy, defined as progression to macroalbuminuria (UACR > 300 mg/g
	  * A doubling of the SCR accompanied by an eGFR of ≤ 45 mL/min/1.73 m^2, as calculated by the MDRD formula
	  * The initiation of RRT
	  * Death from kidney disease.
	  * A composite of incident or worsening kidney disease or death from cardiovascular causes, the individual components of incident or worsening kidney disease, and incident albuminuria (UACR ≥ 30) in patients with a normal albumin level (UACR < 30) at baseline
	• Assessed on the basis of adverse events that occurred during treatment or within 7 days after the last dose of a study drug. Adverse events of special interest included confirmed hypoglycaemic adverse

EMPA-REG OUTCOME 2013 *(Continued)*

	events (plasma glucose level, ≤ 3.9 mmol/L or an event requiring assistance), and adverse events reflecting UTI, genital infection, volume depletion, AKI, bone fracture, diabetic ketoacidosis, and thromboembolic events
Notes	• Interested in patients with eGFR < 60 for this systematic review • Funding source: Boehringer Ingelheim and Eli Lilly

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was performed with the use of a computer-generated random-sequence and interactive voice- and Web-response system and was stratified according to the glycated haemoglobin level at screening (<8.5% or ≥8.5%), body mass index at randomisation (<30 or ≥30), renal function at screening (eGFR, 30 to 59 mL, 60 to 89 mL, or ≥90 mL per minute per 1.73 m^2), and geographic region (North America [plus Australia and New Zealand], Latin America, Europe, Africa, or Asia)".
Allocation concealment (selection bias)	Low risk	"Randomization was performed with the use of a computer-generated random-sequence and interactive voice- and Web-response system and was stratified according to the glycated haemoglobin level at screening (<8.5% or ≥8.5%), body mass index at randomisation (<30 or ≥30), renal function at screening (eGFR, 30 to 59 mL, 60 to 89 mL, or ≥90 mL per minute per 1.73 m2), and geographic region (North America [plus Australia and New Zealand], Latin America, Europe, Africa, or Asia)".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Patients meeting the inclusion criteria were then randomly assigned in a 1:1:1 ratio to receive either 10 mg or 25 mg of empagliflozin or placebo once daily".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study reported to be double-blind, but the methodology for blinding was not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	81/2345 (3.5%) Empagliflozin 10 mg; 63/2342 (2.7%) Empagliflozin 25 mg ; 67/2333 (2.9%) Placebo discontinued.
Selective reporting (reporting bias)	Low risk	The prespecified outcomes were available on a clinical trials database and all major outcomes were reported.
Other bias	High risk	Conflicts of interest: The study was supported by the manufacturers of Empagliflozin, Boehringer Ingelheim and Eli Lilly. Six of the authors were employees of Boehringer Ingelheim, and 3 of them either received consulting fees from Eli Lilly or research grants from Boehringer Ingelheim and/or Eli Lilly were on the advisory board of both companies.

EMPA-REG RENAL 2014

Methods	• Study design: phase 3, parallel RCT • Study time frame: 3 September 2010 to 26 July 2012 • Duration of follow-up: 55 weeks

EMPA-REG RENAL 2014 *(Continued)*

Participants	• Countries: 15 (Canada, France, Hong Kong, India, Malaysia, Philippines, Poland, Portugal, Russia, Slovakia, South Africa, Spain, Netherlands, UK, USA)
	• Setting: multinational (127 centres)
	• Inclusion criteria: patients aged ≥ years with type 2 DM; BMI ≥ 45 kg/m^2; HbA1c of 7% to 10%; eGFR; MDRD) < 90 mL/min/1.73 m^2; if receiving antidiabetes drugs (excluding SGLT2 inhibitors) were required to be on an unchanged dose (or, for insulin, within 10% of the dose at randomisation) or the maximum tolerated dose (or maximum dose according to local label) for 12 weeks or longer before randomisation
	• Number: patients stratified according to CKD stage
	  * CKD stage 2: treatment group 1 (98); treatment group 2 (97); control group (95)
	  * CKD stage 3: treatment group (188); control group (187)
	  * CKD stage 4: treatment group (37); control group (37)
	• Mean age ± SD (years)
	  * CKD stage 2: treatment group 1 (63.2 ± 8.5); treatment group 2 (62.0 ± 8.4); control group (62.6 ± 8.1)
	  * CKD stage 3: treatment group (64.6 ± 8.9); control group (65.1 ± 8.2)
	  * CKD stage 4: treatment group (65.4 ± 10.2); control group (62.9 ± 11.9)
	• Sex (M/F)
	  * CKD stage 2: treatment group 1 (60/38); treatment group 2 (61/36); control group (56/39)
	  * CKD stage 3: treatment group (107/80); control group (106/81)
	  * CKD stage 4: treatment group (21/16); control group (19/18)
	• Exclusion criteria: uncontrolled hyperglycaemia (glucose level > 13·3 mmol/L after an overnight fast); kidney transplant; eGFR < 15 mL/min/1·73 m^2; requirement for chronic or acute dialysis; history of acute coronary syndrome, stroke, or TIA within 3 months of screening; liver disease; cancer within the past 5 years; GI surgery in the past 2 years; treatment with anti-obesity drugs within 3 months of screening or any intervention leading to unstable bodyweight at screening

Interventions	CKD stage 2 (1:1:1) • Oral empagliflozin 10 mg or 25 mg once/d • Oral placebo: once /d CKD stage 3 (1:1) • Oral empagliflozin: 25 mg once/d • Oral placebo: once/d CKD stage 4 (1:1) • Oral empagliflozin: 25 mg once/d • Oral placebo: once/day All groups • All treatments for 52 weeks • Rescue therapy was to be started if, between weeks 1 and 12, a patient had a confirmed glucose level greater than 13·3 mmol/L after an overnight fast, or between weeks 12 and 24, a patient had a confirmed glucose level greater than 11·1 mmol/L after an overnight fast. The rescue medication given was at the discretion of the investigator, in accordance with local prescribing information • Adjustment of background antidiabetes medication between weeks 24 and 52 was not deemed rescue medication. Patients continued their background antidiabetes medication unchanged for the first 24 weeks; thereafter, it could be altered by the investigator to control glucose values and HbA1c according to clinical judgment • Patients received diet and exercise counselling throughout the study.
Outcomes	• Change from baseline in HbA1c at week 24 • Change from baseline in HbA1c at week 52

EMPA-REG RENAL 2014 *(Continued)*

- Proportion of patients with HbA1c ≥ 7.0% (53 mmol/mol) or greater at baseline who had HbA1c < 7.0% (53 mmol/mol) at week 24
- Changes from baseline at weeks 24 and 52 in FBG, bodyweight, and SBP and DBP
- Proportion of patients with > 5% reduction in bodyweight at week 24
- Proportion of patients with uncontrolled BP at baseline (SBP ≥ 130 mmHg or DBP ≥ 80 mmHg) who had controlled BP (SBP < 130 mmHg and DBP < 80 mmHg) at week 24
- Proportion of patients using rescue medication up to week 24
- Vital signs, clinical laboratory values, and adverse events
- Confirmed hypoglycaemic adverse events (plasma glucose ≤3·9 mmol/L or needing assistance)
- UTI
- Genital infection
- Volume depletion
- Bone fractures
- eGFR and UACR

Notes	• Interested in patients with eGFR < 60 for this systematic review • Funding source: Boehringer Ingelheim and Eli Lilly

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation was done by the study sponsor via an interactive response system using a computer-generated random sequence, and was stratified by degree of renal impairment".
Allocation concealment (selection bias)	Low risk	"Treatment allocation during the treatment period was masked from patients, investigators, and those involved in analysing study data. Access to the randomisation code was limited to non-study team functions including a randomisation operator, a person trained to generate the randomisation scheme, supply staff responsible for packaging and labelling, an independent statistician to verify the randomisation scheme, a system operator for clinical data systems to do the technical aspects of uploading the randomisation scheme, a dedicated contract research organisation responsible for the interactive voice and internet-based response system, and a dedicated contract research organisation supporting the Data Monitoring Committee".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Treatment allocation during the treatment period was masked from patients, investigators, and those involved in analysing trial data. Access to the randomisation code was limited to non-trial team functions including a randomisation operator, a person trained to generate the randomisation scheme, supply staff responsible for packaging and labelling, an independent statistician to verify the randomisation scheme, a system operator for clinical data systems to do the technical aspects of uploading the randomisation scheme, a dedicated contract research organisation responsible for the interactive voice and internet-based response system, and a dedicated contract research organisation supporting the Data Monitoring Committee"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Treatment allocation during the treatment period was masked from patients, investigators, and those involved in analysing trial data. Access to the randomisation code was limited to non-trial team functions including a randomisation operator, a person trained to generate the randomisation scheme, supply staff responsible for packaging and labelling, an independent statistician to verify the randomisation scheme, a system operator for clinical data systems to do the technical aspects of uploading the randomisation scheme, a dedicated contract research organisation responsible for the interactive voice

EMPA-REG RENAL 2014 *(Continued)*

		and internet-based response system, and a dedicated contract research organisation supporting the Data Monitoring Committee"
Incomplete outcome data (attrition bias) All outcomes	High risk	Stage 3: Empagliflozin 25 mg 23/188 12.2%; Placebo 21/187 7.3% discontinued. Stage 4: Empagliflozin 25 mg 11/37 29.7%; Placebo 12/37 32.4% discontinued
Selective reporting (reporting bias)	Low risk	The prespecified outcomes were available on a clinical trials database and all major outcomes were reported
Other bias	High risk	Conflicts of interest: Boehringer Ingelheim was involved in study design, data collection, and data analysis. Eli Lilly cosponsored the study, but was not involved in study design, data collection, or data analysis. All authors, except 2 were employees of Boehringer Ingelheim the maker of empagliflozin. The other 2 authors had received honoraria from Boehringer Ingelheim for lectures and advisory work/consultancy

GUARD 2017

Methods	• Study design: parallel RCT • Study time frame: October 2013 to January 2015 • Duration of follow-up: 12 weeks
Participants	• Country: South Korea • Setting: multicentre (number centres not reported) • Inclusion criteria: patients with type 2 DM; HbA1c 7-11%; moderate (eGFR: 30-59 mL/min/1.73 m^2) to severe (eGFR: 15-29 mL/min/1.73 m^2) kidney impairment (MDRD) • Number: treatment group (64); control group (66) • Mean age ± SD (years): treatment group (61.7 ± 7.9); control group (62.3 ± 9.0) • Sex (M/F)**:** treatment group (38/26); control group (38/28) • Exclusion criteria: ESKD; kidney transplant; hepatic cirrhosis or CVDs diagnosed within 6 months; uncontrolled thyroid dysfunction requiring medication; diabetic ketoacidosis; BMI > 40 kg/m^2; total bilirubin > 1.5 × ULN and ALT/AST (ALT/AST) > 2.5 × ULN; using strong cytochrome P450-3A4 (CYP3A4) inducers, glucagon-like peptide-1 (GLP-1)mimetics, or other agents affecting blood glucose
Interventions	Treatment group • Gemigliptin: 50 mg/d Control group • Placebo Both groups • As background medications, only insulin and/or sulphonylureas were allowed, if prescribed for more than 6 weeks before screening. Other drugs affecting blood glucose level were prohibited during the study unless they were indicated as a rescue therapy, which was regarded as a protocol violation
Outcomes	• HbA1c change at week 12. • Changes in body weight, eGFR, UACR, FBG, GA, fructosamine, fasting serum C-peptide, HOMA of beta cell function, HOMA-IR, and fasting lipid parameters at Week 12 • Adverse events • Changes in vital signs • Laboratory abnormalities

GUARD 2017 *(Continued)*

Notes	• Funding source: LG Life Sciences

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	1:1 ratio by severity of kidney impairment and the type of background antidiabetic agents, using the interactive web response system for randomisation
Allocation concealment (selection bias)	Low risk	1:1 ratio by severity of kidney impairment and the type of background antidiabetic agents, using the interactive web response system for randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The double-blind approach was maintained by providing matching placebo, labelling each study drug with a kit number, disclosing the randomisation code only to authorized personnel (statistician, IWRS manager and randomisation manager) when necessary, and by not disclosing individual data to the investigator or other study-related personnel during or before the time of this interim analysis"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The double-blind approach was maintained by providing matching placebo, labelling each study drug with a kit number, disclosing the randomisation code only to authorized personnel (statistician, IWRS manager and randomisation manager) when necessary, and by not disclosing individual data to the investigator or other study-related personnel during or before the time of this interim analysis"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	The prespecified outcomes were available on a clinical trials database. All major outcomes reported
Other bias	High risk	Conflicts of interest: 2 of the authors are employed by LG Life Sciences who manufacture gemigliptin

Haneda 2016

Methods	• Study design: parallel RCT • Study time frame: not reported • Duration of follow-up: 24 and 52 weeks
Participants	• Country: Japan • Setting: multicentre (number of centres not reported) • Inclusion criteria: patients with type 2 DM with eGFR ≥ 30 to < 60 mL/min/1.73 m^2 at weeks - 4 or - 2, who were receiving diet/exercise therapy only or were being treated with 1 or 2 OHAs at a fixed dose for 48 weeks before study entry (Week -4) were eligible • Number: treatment group (95) control group (50) • Mean age ± SD (years)**:** treatment group (67.9 ± 8.9); control group (68.4 ± 8.9) • Sex (M/F)**:** treatment group (72/23); control group (39/11) • Exclusion criteria: kidney disease accompanied with severe proteinuria; a history of dialysis within 1 year of study entry; at risk of developing ESKD before study completion
Interventions	Treatment group

Haneda 2016 *(Continued)*

	• Luseogliflozin: 2.5 mg/d for 24 weeks Control group • Placebo for 24 weeks Other information • After 24 weeks, in the open-label phase, 2.5 or 5 mg/d luseogliflozin was administered to all patients for 28 weeks, regardless of their assigned treatment in the initial double-blind phase
Outcomes	• Changes in HbA1c, FBG, and body weight from baseline to week 52. • Changes in GA, fasting insulin levels, CRP levels, intact proinsulin levels, HOMA-R, and HOMA-β • Abnormal changes in laboratory values and vital signs
Notes	• This publication reported and pooled 3 studies. This table summarises data from Study 1 (TS071-03-04) which was original research reported by the authors and the only time this data has been reported in the literature. The other 2 studies are described in Seino 2015 • Funding source: Taisho Pharmaceuticals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Low risk	"The allocations were implemented at the individual central registration office".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients were either given 2.5 mg/d luseogliflozin or placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study was reported to be placebo-controlled, randomised and double-blinded, but the method of blinding was not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The discontinuation rate was not reported
Selective reporting (reporting bias)	Unclear risk	The prespecified outcomes were not available on a clinical trials database and it was unclear what the major outcomes were for the original study
Other bias	High risk	The sponsor of the study and maker of luseogliflozin, Taisho Pharmaceuticals collected the study data and monitored the study sites. All authors are either employed by Taisho Pharmaceutical or have received advisory board consulting fees, lectures fees, research support and grants from Taisho Pharmaceuticals

Idorn 2013

Methods	• Study design: parallel RCT • Study time frame: not reported

Idorn 2013 *(Continued)*

	• Duration of follow-up: 12 weeks

Participants	• Country: Denmark
	• Setting: multicentre (2 centres)
	• Inclusion criteria: 2 groups of patients - ESKD (Group 1) and normal kidney function (Group 2)
	  * Group 1: Patients aged 18 to 85 years receiving chronic HD or PD; type 2 DM diagnosed at least 3 months prior to screening; preserved beta-cell function as evaluated by a glucagon test
	  * Group 2: Patients aged 18 to 85 years with normal kidney function (SCr < 105 µmol/L for men and < 90 µmol/L for women); type 2 DM diagnosed at least 3 months prior to screening; HbA1c > 6.5% (> 48 mmol/mol); preserved beta-cell function as evaluated by a glucagon test
	• Number (randomised/analysed)
	  * Group 1: treatment group (14/10); control group (10/10)
	  * Group 2: treatment group (11/10); control group (12/10)
	• Mean age ± SE (years)
	  * Group 1: treatment group (68.3 ± 3.1); control group (65.9 ± 4.4)
	  * Group 2: treatment group (60.7 ± 3.2); control group (63.1 ± 2.1)
	• Sex (M/F)
	  * Group 1: treatment group (8/2); control group (9/1)
	  * Group 2: treatment group (7/3); control group (8/2)
	• Exclusion criteria: type 1 DM; chronic pancreatitis or previous acute pancreatitis; known or suspected hypersensitivity to trial product(s) or related products; treatment with oral glucocorticoids, calcineurin inhibitors; dipeptidyl peptidase 4 inhibitors or other drugs, which in the investigator's opinion could interfere with glucose or lipid metabolism 90 days prior to screening; cancer (except BCC or squamous cell skin cancer) or any other clinically significant disorder, which in the investigator's opinion could interfere with the results of the trial; inflammatory bowel disease; cardiac disease defined as heart failure (NYHA Class III–IV) and/or diagnosis of unstable angina pectoris and/or myocardial infarction within the last 6 months; BMI ≤18.5 or ≥ 50.0 kg/m^2; women of childbearing potential who are pregnant, breastfeeding, intend to become pregnant or not using adequate contraceptive methods; clinical signs of diabetic gastroparesis; impaired liver function (ALT > twice upper reference level); use of any investigational product 90 days prior to this trial; known or suspected abuse of alcohol or narcotics; screening plasma calcitonin ≥ 50 ng/L; personal or family history of medullary thyroid carcinoma or a personal history of multiple endocrine neoplasia type 2

Interventions	Treatment group • SC Liraglutide: 0.6 mg once/d for 12 weeks. All participants were requested to inject the medicine in the abdomen before breakfast. Control group • Placebo: once/d for 12 weeks. All participants were requested to inject the medicine in the abdomen before breakfast Other information • Depending on glycaemic control and adverse effects, dose was escalated by up to 0.6 mg/week to a maximum 1.8 mg • Doses of baseline antidiabetic medication were individually adjusted in parallel with study medication according to prespecified treatment goals. To minimize risk of hypoglycaemia, basal insulin dose reduced by 20-50% at randomisation and suIphonylureas were paused, while metformin was continued in unchanged doses
Outcomes	• Dose corrected trough concentration of liraglutide in plasma at the final study visit (week 12) • Severe adverse events, Adverse effects, glycaemic control, change in baseline insulin, body weight, hypoglycaemic episodes (divided into minor blood glucose < 3.1 mmol/L and no need assistance) and major (blood glucose < 3.1 mmol/L and requiring assistance from third person) • Cardiovascular parameters: heart rate, BP, and prohormone brain natriuretic peptide concentration in plasma

Idorn 2013 *(Continued)*

Notes	• Only Group 1 (ESKD patients) was included in this systematic review • Funding source: Novo Nordisk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients and control subjects were assigned to receive either liraglutide or placebo according to a computer-generated randomisation list provided by Novo Nordisk".
Allocation concealment (selection bias)	Low risk	"Patients and control subjects were assigned to receive either liraglutide or placebo according to a computer-generated randomisation list provided by Novo Nordisk".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Participants, Investigators, and healthcare staff were blinded for the allocated treatment and remained so until the last patient's last visit".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Participants, Investigators, and healthcare staff were blinded for the allocated treatment and remained so until the last patient's last visit".
Incomplete outcome data (attrition bias) All outcomes	High risk	5/14 35% liraglutide group; 0/10 0% control group discontinued for the ESKD group.
Selective reporting (reporting bias)	Low risk	The prespecified outcomes were available on a clinical trials database and major outcomes were reported.
Other bias	High risk	Conflicts of interest: Novo Nordisk sponsored the study although the company did not participate in writing the protocol, collection, analysis and interpretation of data or writing the manuscript. All authors have either received research support, are on the advisory board, or hold shares with Novo Nordisk. Study was mildly underpowered: Based on the primary end point and with a liraglutide trough value of 20 000 pmol/L during steady state and standard deviation estimated to be 8000 pmol/L in people with normal kidney function, 10 completers in each liraglutide treatment arm and an $\alpha = 0.05$ would enable the investigators to detect a difference of 10,600 pmol/L with a power of 80% ($1-\beta = 0.80$) using a 2 sample Student t-test. In the ESKD arm, 9 patients completed the study.

Ito 2011a

Methods	• Study design: parallel, open-label RCT • Study time frame: not reported • Duration of follow-up: 24 weeks
Participants	• Country: Japan • Setting: multicentre (number of centres not reported). • Inclusion criteria: patients with type 2 DM patients undergoing regular HD; poor glycaemic control which was defined as HbA1c level > 7.0% and/or a GA level exceeding 21.0% after 8 consecutive weeks of daily administration of conventional therapy (dietary therapy alone or mitiglinide and/or voglibose); none were receiving insulin treatment

Ito 2011a *(Continued)*

- Number: treatment group (30); control group (21)
- Mean age ± SEM (years)**:** treatment group (67 ± 2); control group (68 ± 2).
- Sex (M/F): treatment group (21/9); control group (14/7)
- Exclusion criteria: infectious disease; thyroid disease; malignant tumours; treatment with steroids

Interventions	Both groups • An eight week observation period first for all subjects before randomisation where a fixed dose of conventional anti-diabetic agents (mitiglinide and/or voglibose) was administered orally Treatment group • Continued conventional therapy at the same dose • Oral vildagliptin: 50 mg once/d. Thereafter, if 8 weeks of continuous vildagliptin administration did not result in the target HbA1c value (<7.0% or <53 mmol/mol) or GA value (<21.0%), the vildagliptin dose was increased to 100 mg daily from week 8. On the other hand, if the physician judged that vildagliptin 50 mg daily presented a safety problem, the dose was reduced to 25 mg once daily. Patients continued their regular medications, such as antihypertensives, recombinant human erythropoietin, phosphate binders and lipid-lowering agents, during the study period Control group • Conventional oral antidiabetic agents alone (no vildagliptin). However, 9 patients in the control group took additional anti-diabetic agents for treatment. Patients continued their regular medications, such as antihypertensives, recombinant human erythropoietin, phosphate binders and lipid-lowering agents, during the study period
Outcomes	• HbA1c and GA levels were measured once monthly as indices of glycaemic control • Postprandial plasma glucose levels were measured 3 times/wk • Hb • Total bilirubin, AST, ALT, LDH, ALP, γ-glutamyl transpeptidase, total cholesterol, HDL, triglyceride, total protein and albumin • Body weight before and after dialysis to assess the interdialytic weight gain, BMI • Cardiothoracic ratio • Predialysis SBP and DBP • Safety events/adverse events • Serious adverse events were defined as medical events that resulted in death, hospitalisation or significant disability or incapacity.
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported. The text just says: “subjects were then randomly split into two groups”.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias)	High risk	Open-label study

Ito 2011a *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	High risk	None of the treatment group but 9/30 30% control group discontinued.
Selective reporting (reporting bias)	Unclear risk	The prespecified outcomes were not available on a clinical trials database.
Other bias	Low risk	There were no conflicts of interest

Jin 2007

Methods	• Study design: parallel RCT • Study time frame: not reported • Duration of follow-up: 12 months

Participants	• Country: China
	• Setting: single centre
	• Inclusion criteria: patients with type 2 diabetic kidney disease; 42 and 80 years; SCr 150–420 μM, presence of CKD stage 3 (GFR 30 - 59 mL/min/1.73 m^2) or stage 4 (GFR 15 - 29 mL/min/1.73 m^2). Nephropathy was defined clinically by the presence on two occasions of a ratio of urinary albumin (mg/L) to urinary creatinine (g/L) from a first morning specimen of at least 300, or a 24-hour urinary protein excretion value ≥ 500 mg on two consecutive determinations, by the presence of diabetic retinopathy, and by the absence of any clinical or laboratory evidence of other kidney or renal tract disease
	• Number
	  * CKD stage 3: treatment group (15); control group (15)
	  * CKD stage 4: treatment group (15); control group (15)
	• Mean age ± SD (years)
	  * CKD stage 3: treatment group (52.87 ± 12.47); control group (51.6 ±(11.19)
	  * CKD stage 4: treatment group (52.67 ± 12.5); control group (50.53 ± 11.67)
	• Sex (M/F)
	  * CKD stage 3: treatment group (8/7); control group (8/7)
	  * CKD stage 4: treatment group (8/7); control group (8/7)
	• Exclusion criteria: clinical or laboratory evidence of nondiabetic kidney disease; diagnosis of type 1 DM; abnormal liver function; heart disease

Interventions	Treatment group • Pioglitazone: 30 mg/d was given as an add-on medication • Oral losartan: 100 mg daily Control group • Oral losartan: 100 mg daily Both groups • All patients received a low-protein diet (protein content 0.6 g/kg/d) and conventional insulin therapy. Throughout the 12-month study period, the patients with hypertension received conventional antihypertensive therapies, except ACEi • Mixed human insulin (70/30) was administered twice daily at a dosage of 0.2 U/kg and was adjusted to achieve a FBG level ≤ 8.5 mM without occurrence of severe or frequent hypoglycaemia
Outcomes	• BP • Fasting glucose

Jin 2007 *(Continued)*

- HbA1c
- SCr
- 24-hour urinary protein excretion
- Endogenous CrCl
- GFR

Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Block randomisation with stratification for stage of CKD, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients discontinued.
Selective reporting (reporting bias)	Unclear risk	The prespecified outcomes were not available on a clinical trials database
Other bias	Unclear risk	Conflicts of interest were not reported.

Kaku 2014

Methods	• Study design: parallel RCT • Study time frame: not reported • Duration of follow-up: 24 weeks
Participants	• Country: Japan • Setting: multicentre (number of centres not reported) • Inclusion criteria: patients aged ≥ 20 years; confirmed diagnosis of T2 DM; drug-naive (never received medical treatment for DM or received treatment for < 30 days after diagnosis, and during the 30-day period before screening did not receive oral antidiabetic agents for > 3 consecutive or > 7 non-consecutive days, or were previously treated for DM but not within 6 weeks of enrolment), OR receiving ongoing treatment for DM within 6 weeks of enrolment (not drug-naive) • Number: treatment group 1 (86); treatment group 2 (88); control group (87) * 72 patients had an eGFR < 60 mL/min/1.73 m^2 • Mean age ± SD (years)**:** treatment group 1 (58.6 ± 10.4); treatment group 2 (57.5 ± 9.3); control group (60.4 ± 9.7) • Sex (M/F)**:** treatment group 1 (50/36); treatment group 2 (53/35); control group (52/35)

Kaku 2014 *(Continued)*

	• Exclusion criteria: type 1 DM; FBG > 13.3mmol/L; pregnant or breastfeeding women; creatinine kinase >3× ULN; eGFR < 45 mL/min or a SCR >133 µmol/L for men and >124 µmol/L for women; Severe hepatic insufficiency and/or significant abnormal liver function (AST >3 ×ULN and/or ALT >3 × ULN). • NYHA class IV congestive heart failure; unstable or acute congestive heart failure. • Treatment with thiazolidinediones < 6months before enrolment.
Interventions	• The study included a 2-week screening period, and a 4-week, single-blind, placebo lead-in period • These patients would undergo a washout period before study treatments * At enrolment, HbA1c values ≥ 6.5% (48 mmol/mol) and ≤ 10% (86 mmol/mol) were required for patients defined as drug-naive, and HbA1c values ≤ 8% (64 mmol/mol) were required for patients with ongoing treatment. At 1 week before randomisation, HbA1c was required to be ≥ 6.5% (48 mmol/mol) and ≤ 10% (86 mmol/mol) for all patients Treatment group 1 • Oral dapagliflozin: 5 mg once/d for 24 weeks Treatment group 2 • Oral dapagliflozin: 10 mg once/d for 24 weeks Control group • Oral placebo: once/d for 24 weeks
Outcomes	• Change in mean HbA1c from baseline to week 24 • Change from baseline to week 24 in FBG and body weight. • Change from baseline to week 24 in total body weight in patients with baseline BMI ≥ 25 kg/m^2; fasting insulin and C-peptide levels; seated SBP • SBP overall and in patients with baseline seated SBP ≥ 130mmHg • Fasting lipids (total cholesterol, LDL cholesterol, HDL cholesterol, free fatty acid and triglyceride levels) • Proportion of patients achieving a therapeutic glycaemic response (defined as HbA1c < 7% [53 mmol/mol]) after 24 weeks in patients with baseline HbA1c ≥ 7% (53 mmol/mol) • Proportion of patients discontinued for lack of efficacy or rescued for failing to maintain FBG below prespecified rescue criteria after 24 weeks • Evaluated based on reported adverse events (AEs), laboratory values, ECG, heart rate, BP, hypoglycaemic events, calculated CrCl, eGFR and physical examination findings.
Notes	• Funding source: AstraZeneca and Bristol-Myers Squibb

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Reported to be double blind, but method of blinding of participants and personnel was not reported
Blinding of outcome assessment (detection bias)	Unclear risk	Reported to be double blind, but method of blinding of participants and personnel was not reported

Kaku 2014 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	8/87 (9.1%) of placebo group, 5/86 (5.8%) of dapagliflozin 5 mg group and 9/88 (10.2%) of dapagliflozin 10 mg group discontinued
Selective reporting (reporting bias)	Unclear risk	The prespecified outcomes were not available on a clinical trials database
Other bias	High risk	Conflicts of interest: The study was funded by AstraZeneca and Bristol-Myers Squibb the manufacturers of Dapagliflozin. All authors except 3 either received research funding from the sponsoring companies or were employees and share-holders

Kohan 2014

Methods	• Study design: parallel RCT • Study time frame: not reported • Duration of follow-up: 104 weeks
Participants	• Countries: USA, Argentina, Canada, India, Mexico, Peru, Italy, Australia, France, Spain, Denmark, Puerto Rico, Singapore • Setting: multinational (111 sites) • Inclusion criteria: Male and female patients ≥18 years with type 2 DM and inadequate glycaemic control defined as HbA1c ≥ 7.0% (53 mmol/mol) and ≤ 11.0% (97 mmol/mol); eGFR values of 30 to 59 mL/min per 1.73 m^2; BMI ≤ 45.0 kg/m^2. • Number: treatment group 1 (83); treatment group 2 (85); control group (84) • Mean age ± SD (years): treatment group 1 (66 ± 8.9); treatment group 2 (68 ± 7.7); control group (67 ± 8.6) • Sex (M/F): treatment group 1 (55/28); treatment group 2 (56/29); control group (53/31) • Exclusion criteria: AST or ALT > 3.0 times the ULN; serum total bilirubin > 2.8 mmol/L; history of diabetes insipidus or diabetic ketoacidosis or hyperosmolar nonketotic coma; uncontrolled hypertension defined as SBP ≥ 180 mmHg and/or DBP ≥110 mmHg, or specified cardiovascular/vascular diseases within 6 months of enrolment visit; kidney exclusion criteria included the need for HD or RRT, history of rapidly progressing kidney disease, lupus nephritis, renal or systemic vasculitis, renal artery stenosis, kidney transplant; hepatic disease
Interventions	Both groups • A 7-day lead-in period included diet and exercise counselling, which continued throughout the study • Original pre-enrolment antidiabetic regimen Treatment group 1 • Dapagliflozin: 5 mg/d Treatment group 2 • Dapagliflozin: 10 mg/d Control group • Placebo Other information

Kohan 2014 *(Continued)*

	• During the first 24 weeks (short-term period), patients received rescue medication (any approved antidiabetic agent except metformin) if FBG > 15 mmol/L (weeks 4–6), > 13.3 mmol/L (weeks 6–12), or > 11.1 mmol/L (weeks 12–24) • Patients completing the first 24 weeks were eligible to continue into an additional 28-week (long-term) period and were eligible to receive rescue medication if HbA1c > 8.0% (64 mmol/mol) • Patients completing the first 52 weeks (the short-term plus long-term periods) were eligible to continue into the extension period (an additional 52 weeks) and received rescue medication if HbA1c > 7.5% (58 mmol/mol) (weeks 52–76) and > 7.0% (53 mmol/mol) (weeks 76–104)
Outcomes	• Change from baseline in HbA1c with each dose of dapagliflozin versus placebo at 24 weeks • Change from baseline in FBG and weight for each dose of dapagliflozin versus placebo at 24 weeks • Change from baseline in eGFR (MDRD) and CrCl (Cockcroft and Gault method) for each dapagliflozin dose versus placebo at 52 weeks. • Serious and non serious adverse events • Discontinuations owing to adverse events, hypoglycaemia, laboratory abnormalities, ECG, and vital signs (seated BP and heart rate) • UACR and urinary protein:creatinine • UTI and genital infection • All safety analyses included data after glycaemic rescue
Notes	• Funding source: Bristol-Myers Squibb and AstraZeneca

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"On day 1, patients were randomised in a double-blind manner to either placebo, dapagliflozin 5-mg, or dapagliflozin 10-mg daily, in addition to their original pre-enrollment antidiabetic regimen."
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study was labelled as double blind but does not describe how patients were blinded or if they were given placebo medications.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study was labelled as double blind but does not describe how assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	High rates of discontinuation by the end of the study. Dropout rates: At 24 weeks: 5 mg dapagliflozin 11/83 (13.3%); 10 mg dapagliflozin 16/85 (18.8%); Placebo 22/84 (26.2%) At 52 weeks: 5 mg dapagliflozin 19/83 (22.9%); 10 mg dapagliflozin; 21/85 (24.7%); Placebo 30/84 (35.7%) At 104 weeks: 5 mg dapagliflozin 38/83 (45.8%); 10 mg dapagliflozin 34/85 (40.0%); Placebo 41/84 (48.8%)
Selective reporting (reporting bias)	Low risk	There was an error in the study flow diagram - authors missed counting one patient

Kohan 2014 *(Continued)*

Other bias	Low risk	Conflicts of interest: All the authors declared no competing interests. Bristol-Myers Squibb and AstraZeneca-supported the study

Kothny 2015

Methods	• Study design: parallel RCT • Study time frame: not reported • Duration of follow-up: 24 weeks
Participants	• Countries: Brazil, USA • Setting: multinational (87 centres) • Inclusion criteria: patients aged 18 to 85 years, BMI 18 to 42 kg/m^2; HbA1c 6.5–10.0% (48–86 mmol/mol); type 2 DM either untreated (no glucose-lowering medication in the past 8 weeks) or treated with a stable dose of sulphonylureas, thiazolidinedione, meglitinide or insulin, as monotherapy or in combination (for at least 4 weeks); Severe kidney impairment (eGFR (MDRD) < 30 mL/min/1.73 m^2) • Number (randomised/analysed): treatment group 1 (83/81), treatment group 2 (65/63) • Mean age ± SD (years): treatment group 1 (66.7 ± 8.8); treatment group 2 (66.9 ± 9.6) • Sex (M/F): treatment group 1 (42/41); treatment group 2 (29/36) • Exclusion criteria: history of kidney transplant; significant cardiovascular history within 6 months; liver disease; abnormal liver function tests (ALT >2 × ULN, AST > 2 × ULN, or total bilirubin > 2× ULN and/or direct bilirubin > ULN); any treatment that is contraindicated (i.e. metformin) in the severe CKD population
Interventions	Both groups • Patients continued their initial background treatment throughout the study. • 2- week, single-blind, placebo run-in period Treatment group 1 • Vildagliptin: 50 mg once/d for 24 weeks Treatment group 2 • Sitagliptin: 25 mg once/d for 24 weeks Other information • Both medications were used at the doses recommended in the label for patients with severe kidney impairment • Rescue medication (insulin addition or intensification) could be administered on or after week 4 if FBG was > 15 mmol/L, after week 8 if FBG >13.3 mmol/L, and after week 16 if FBG >12.2 mmol/L
Outcomes	• HbA1c • FBG • An analysis of responder rate was also performed to assess the percentage of patients achieving HbA1c ≤6.5% (48 mmol/mol) and < 7.0% (53 mmol/mol). • Routine biochemistry laboratory assessments • Safety, tolerability and all treatment emergent adverse events • Hypoglycaemia was defined as symptoms suggestive of low blood glucose confirmed by a self-monitored blood glucose measurement < 3.1 mmol/L plasma glucose equivalent.
Notes	• The initial protocol excluded patients undergoing any dialysis, but it was subsequently amended to remove this restriction to facilitate recruitment

Kothny 2015 *(Continued)*

- Nearly two-thirds of the patients were white, more than 20% were black and about 12% were Hispanic/Latino
- Funding source: Novartis Pharma AG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Eligible patients were randomised using interactive voice response technology (IVRS) to receive either vildagliptin (50 mg once daily) or sitagliptin (25 mg once daily)"
Allocation concealment (selection bias)	Low risk	"IVRS assigned a randomisation number to the patient, which was used to link the patient to a treatment arm and to specify unique medication numbers for the first package of study drug to be dispensed to the patient"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Patients, investigator staff, persons performing the assessments and data analysts remained blinded to the identity of the treatment from the time of randomisation until database lock"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Patients, investigator staff, persons performing the assessments and data analysts remained blinded to the identity of the treatment from the time of randomisation until database lock"
Incomplete outcome data (attrition bias) All outcomes	Low risk	19/83 (22.9%) of the vildagliptin group and 12/65 (18.5%) of the sitagliptin group discontinued
Selective reporting (reporting bias)	Low risk	The prespecified outcomes were available on a clinical trials database and major outcomes were reported
Other bias	High risk	Conflicts of interest: This study was funded by Novartis Pharma AG, Basel, Switzerland. The sponsor was involved in study design, and collection, analysis and interpretation of data. Four of the authors are employed by and have shares with Novartis. The remaining authors are involved in clinical trials with Novartis. Novartis makes vildagliptin

Laakso 2015

Methods	• Study design: parallel RCT • Study time frame: 17 March 2010 and 18 June 2012 • Duration of follow-up: 12 weeks followed by a 40-week, active-controlled extension
Participants	• Countries: 9 countries including Finland, USA, UK, Germany, Australia • Setting: multinational (52 outpatient clinics) • Inclusion criteria: adults ≥ 18 years with type 2 DM; eGFR < 60 mL/min; HbA1c ≥ 7.0% to ≤ 10% (53 mmol/mol to 86 mmol/mol); BMI ≤ 45 kg/m^2 • Number (randomised/completed week 12/completed week 52): treatment group (113/110/95); control group (122/114/90) • Mean age ± SD: 66.6 ± 9.3 years (data not provided for each group) • Sex (M/F): 149/86 (data not provided for each group) • Exclusion criteria: MI; stroke or TIA within 3 months prior to informed consent.; kidney impairment requiring dialysis; bariatric surgery; impaired hepatic function; treatment with glitazones; GLP-1 ana-

Laakso 2015 *(Continued)*

	logues; DPP-4 inhibitors; treatment with anti-obesity drugs; treatment with sulphonylureas; glinides and metformin 8 weeks prior to informed consent
Interventions	Treatment group • Linagliptin: 5 mg/d for 52 weeks Control group • Placebo for 12 weeks • After 12 weeks placebo patients were then switched to glimepiride 1–4 mg/d, with double blinding maintained using a double dummy design, and treatments continued until week 52. Glimepiride could be up-titrated in 1-mg increments from a 1-mg starting dose to a maximum of 4 mg at 4-week intervals during the first 12 weeks of the extension if patients' self-monitored FBG values were > 6.1 mmol/L
Outcomes	• HbA1c: change from baseline to week 12 in the full-analysis set • Change in HbA1c over time • FBG: change from baseline to week 12 • FBG: change from baseline over time • Percentage of patients with HbA1c < 7.0% (53 mmol/mol) at week 12 and week 52 • Percentage of patients with HbA1c < 6.5% (48 mmol/mol) at week 12 and week 52 • Percentage of patients who have a HbA1c lowering by at least 0.5% (5 mmol/mol) at week 12 and week 52 • Plasma concentration of linagliptin at trough from baseline over time • Adverse events
Notes	• Funding source: Boehringer Ingelheim Pharma GmbH & Co

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients "were randomised 1:1 to double-blind treatment with linagliptin 5 mg/day or placebo for 12 weeks; placebo patients were then switched to glimepiride 1–4 mg/day, with double blinding maintained using a double dummy design, and treatments continued until week 52."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study was reported to be double-blind although the methodology of blinding of outcome assessment was not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Low risk of attrition bias at week 12: 3/113 linagliptin (2.7%) and 8/122 placebo (6.6%) discontinued by week 12. High risk of attrition bias at week 52: 18/113 linagliptin (15.9%) and 32/122 (26.2%) placebo/glimepiride discontinued by week 52
Selective reporting (reporting bias)	Low risk	The prespecified outcomes were available on a clinical trials database and major outcomes were reported
Other bias	High risk	Conflicts of interest: This study was sponsored by Boehringer Ingelheim (BI) Pharma GmbH & Co. KG, the manufacturer of linagliptin. Authors have either

Laakso 2015 *(Continued)*

	served on the scientific advisory board, received grants or research support and/or received speaker honoraria from BI, or are employees of BI

LANTERN 2015

Methods	• Study design: parallel RCT • Study time frame: January 2011 and November 2012 • Duration of follow-up: 24 weeks with open-label 28 week extension
Participants	• Country: Japan • Setting: multicentre (67 institutions) • Inclusion criteria: patients aged 20–74 years; Diagnosed with type 2 DM ≥ 12 weeks before providing informed consent were eligible if they: * Currently on diet/exercise therapy alone or in combination with an alpha-glucosidase inhibitor, a sulphonylureas, or pioglitazone in a constant dosing regimen * Poor glycaemic control despite treatment, defined as a glycated haemoglobin (HbA1c) of 6.9–8.9% (52 to 74 mmol/mol), a change in HbA1c of ≤ 1.0% (11 mmol/mol) between visits 1 and 2, and a FBG concentration of ≥6.99 mmol/L for patients using a sulphonylureas * BMI of 20.0–45.0 kg/$m^{2.}$ * Mild (eGFR ≥ 60 to < 90 mL/min/1.73m^2) or moderate CKD (eGFR ≥30 to <60 mL/min/1.73m^2) • Number: treatment group (119); control group (46) * 81 patients had an eGFR < 60 mL/min/1.73 m^2: treatment group (58); control group (230) • Mean age ± SD (years): treatment group (63.9 ± 6.59); control group (65.7 ± 6.93) • Sex (M/F): treatment group (92/26); control group (36/10) • Exclusion criteria: type 1 DM; proliferative diabetic retinopathy; treatment with insulin within 12 weeks before visit 1; currently using or scheduled to start dialysis; history of clinically significant kidney disease (e.g. renovascular occlusive disease, nephrectomy and/or kidney transplant) or complications of severe kidney disease (e.g. nephrotic syndrome and/or glomerular nephritis); renal tubular dysfunction (e.g. Fanconi syndrome and interstitial nephritis); dysuria caused by a neurogenic bladder or benign prostatic hypertrophy, symptomatic UTI or symptomatic genital infection at visit 1; chronic disease that required the continuous use of adrenocortical steroids, immunosuppressants or loop diuretic; history of cerebral vascular attack, unstable angina, MI, vascular intervention or heart failure (NYHA Class III–IV) within 12 weeks before visit 1, or presence of heart failure or cerebral vascular disease deemed likely to interfere with treatment or evaluation of safety of this study; heart failure or a history of heart failure if treated with pioglitazone; unstable psychiatric disorder; women wishing to become pregnant, were pregnant or were lactating; males or premenopausal females who could not use contraception; severe infection; perioperative or serious trauma; drug addiction or alcohol abuse; presence of a malignant tumour; history of allergy to SGLT2 inhibitor; history of treatment with ipragliflozin; participation in another clinical study, post-marketing study or medical device study within 12 weeks before providing written informed consent; patients who were unable or unwilling to adhere to study procedures, including attending the hospital or following the instructions for drug administration
Interventions	Both groups • The study consisted of a 4-week screening period, a 2-week run-in period in which all patients received placebo • Patients continued their diet/exercise therapy • Patients who had used an oral hypoglycaemic agent for ≥ 12 weeks before the start of the study were permitted to continue the drug at the same dose throughout the study; changes in the dosing regimen or switching to an alternative drug were prohibited • Concomitant use of hypoglycaemic agents other than an alpha--glucosidase inhibitor, a sulphonylureas, or pioglitazone was prohibited Treatment group

LANTERN 2015 *(Continued)*

	• Ipragliflozin: 50 mg once/d before breakfast for 24 weeks Control group • Placebo once daily before breakfast for 24 weeks Other information • At week 24, the ipragliflozin dose to be used in treatment period 2 could be increased to 100 mg in patients who met the following criteria: an HbA1c level of ≥ 7.4% (57 mmol/mol) at week 20 for patients whose HbA1c level was ≥ 7.4% (57 mmol/mol) at week 0; an HbA1c level of ≥ 6.9% (52 mmol/mol) at week 20 for patients whose HbA1c level was < 7.4% (57 mmol/mol) at week 0; and a willingness to use a higher dose. The dose could be reduced to 50mg if there were possible safety concerns, but the dose could not be increased again after the dose reduction. Other patients continued 50 mg ipragliflozin in treatment period 2
Outcomes	• HbA1c • FBG • Fasting serum insulin • Leptin and adiponectin levels • Body weight and waist circumference • Treatment-emergent adverse events, vital signs, laboratory variables, 12-lead ECG and eGFR
Notes	• Funding source: Astellas Pharma Inc. and Kotobuki Pharmaceutical Co., Ltd

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported. Text says: "At the end of the run-in period, patients were randomised at a 2:1 ratio to receive 50mg ipragliflozin or placebo. Randomization was performed after stratifying patients according to RI severity".
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients received placebo or ipragliflozin
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study labelled as double-blind however methodology of blinding of outcome assessment was but not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low rate of discontinuation from the study For the whole cohort 12/119 10.1% treatment group and 4/46 8.7% control group discontinued For those patients with an eGFR < 60 6/58 10.3% treatment group and 3/23 13.0% control group discontinued
Selective reporting (reporting bias)	Low risk	The prespecified outcomes were available on a clinical trials database and major outcomes were reported
Other bias	High risk	Conflicts of interest: ipragliflozin (ASP1941) was developed by Astellas Pharma Inc. and Kotobuki Pharmaceutical Co., Ltd. Authors were either consultants

LANTERN 2015 *(Continued)*

	and received consulting fees/honoraria from Astellas or were employees of Astellas Pharma Inc., Tokyo, Japan

Leiter 2014

Methods	• Study design: phase 3, parallel RCT • Study time frame: 7 May 2010 and 30 May 2012 • Duration of follow-up: 52 weeks
Participants	• Country: 15 countries (countries not reported) • Setting: multinational (134 centres) • Inclusion criteria: male and non-pregnant, non-lactating female patients ≥18 years of age with historical diagnoses of type 2 DM; baseline HbA1c between 7.0 and 10.0% (53–86 mmol/mol); BMI between 20 and 45 kg/m^2; fasting C-peptide level of ≥ 0.8 ng/mL (0.26 nmol/L); GFR ≥ 15 to < 90 mL/min/1.73 m^2; HB ≥ 10 g/dL for male patients and ≥ 9 g/dL for female patients; normal levels of thyroid-stimulating hormone or clinically euthyroid • Number: treatment group 1 (254); treatment group 2 (253) * 239 patients had an eGFR < 60 mL/min/1.73 m^2 • Mean age ± SD (years): treatment group 1 (63.2 ± 8.37); treatment group 2 (63.5 ± 9.02) • Sex (M/F): treatment group 1 (136/113); treatment group 2 (130/116) • Exclusion criteria: malignant disease (except squamous cell or BCC); history of diabetic gastroparesis; current ongoing symptomatic biliary disease or history of pancreatitis; significant GI surgery or surgeries thought to significantly affect upper GI function; recent clinically significant cardiovascular and/or cerebrovascular disease; history of HIV infection, and acute symptomatic hepatitis B or C infection
Interventions	Both groups • All patients continued to receive their prescribed oral antihyperglycaemic medication regimen (metformin, thiazolidinedione, sulphonylureas, or any combination of these oral antihyperglycaemic medications) for the duration of the study with the exception of patients with GFR < 60 mL/min/1.73 m^2, who were washed off their background metformin • Instructions for down-titration of sulphonylureas were also provided to avoid hypoglycaemia Treatment group 1 • SC albiglutide: 30 mg once/wk (with treatment-masked up-titration, if needed, to 50 mg weekly) Treatment group 2 • Sitagliptin: dosed based on the eGFR value at randomisation per the sitagliptin package insert
Outcomes	• Change in HbA1c from baseline at week 26 • HbA1c • FBG • Body weight • Proportion of patients who met prespecified HbA1c treatment targets • Time to hyperglycaemic rescue • Population pharmacokinetics of albiglutide • Adverse and severe adverse events (clinical laboratory parameters, vital sign measurements, ECG readings, and physical examinations) • Immunogenicity
Notes	• We are interested in the 239 patients with an eGFR < 60 mL/min/1.73 m^2 in this systematic review • Funding source: GlaxoSmithKline

Leiter 2014 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"An interactive voice response system was used for the blinded randomisation, which was based on a sequestered fixed randomisation schedule"
Allocation concealment (selection bias)	Low risk	"An interactive voice response system was used for the blinded randomisation, which was based on a sequestered fixed randomisation schedule"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Albiglutide and matching placebo was supplied as a fixed-dose (30 or 50 mg) pen injector system, which was injected subcutaneously into the abdomen. Sitagliptin and matching placebo were provided as overcoated tablets or capsules"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Although the study was described as double-blind the method by which outcome assessment was blinded was not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	High rate of discontinuation, especially in the sitagliptin group 51/254 (20.1%) of the albiglutide and 68/253 (26.9%) of the sitagliptin group discontinued
Selective reporting (reporting bias)	Low risk	The prespecified outcomes were available on a clinical trials database and major outcomes were reported
Other bias	High risk	Conflicts of interest: This study was sponsored by GlaxoSmithKline who manufactures albiglutide. All authors except one are employees and share-holders of GlaxoSmithKline. The remaining author has received research funding from GlaxoSmithKline.

Lewin 2012

Methods	• Study design: phase 3, parallel RCT • Study time frame: December 2008 to January 2010 • Duration of follow-up: 19 weeks
Participants	• Countries: Asia (India, Japan), Europe (Hungary, Poland, Russia), North America (USA), and South America (Argentina). • Setting: multinational (45 centres) • Inclusion criteria: 18 to 80 years; diagnosis of type 2 DM; BMI of ≤ 40 kg/m^2; received either sulphonylurea monotherapy or sulphonylurea plus 1 additional glucose-lowering agent; all agents, including sulphonylurea, were required to have remained unchanged for 10 weeks prior to enrolment; sulphonylurea dose had to be at least half the maximum dose (or less if documented as the maximum tolerated dose for ≥ 12 weeks).HbA1c ≥ 7.0% (53 mmol/L) to ≤ 9.0% (75 mmol/mol) for patients undergoing washout and ≥ 7.5% (58 mmol/mol) to ≤ 10.0% (86 mmol/mol) for patients on sulphonylurea monotherapy • Number: treatment group (161); control group (84) * 6.9% of population (17) had an eGFR < 60 mL/min/1.73 m^2 • Mean age ± SD (years): treatment group (57.2 ± 9.8); control group (56.2 ± 10.2) • Sex (M/F): treatment group (77/84); control group (52/32) • Exclusion criteria: previous treatment with thiazolidinedione, GLP-1 analogues, long-term daily use of insulin or anti-obesity drugs in the previous 3 months; treatment with systemic corticosteroids or a change in dosage of thyroid hormones in the previous 6 weeks; experience of a MI, stroke, or TIA

Lewin 2012 *(Continued)*

	in the previous 6 months; unstable or acute congestive heart failure; kidney failure, severe kidney impairment, or impaired hepatic function (defined as elevated serum levels of either ALT, AST or ALP > 3-fold the ULN, or elevated serum total bilirubin levels > 3-fold ULN; hypersensitivity or allergy to linagliptin or its excipients, the prescribed sulphonylurea drug, or placebo; history of alcohol or drug abuse in the previous 3 months; hereditary galactose intolerance; premenopausal women who were nursing or pregnant
Interventions	Run-in period • Patients taking 1 oral glucose-lowering agent in addition to sulphonylureas at screening underwent a 4-week drug washout period followed by a 2-week placebo run-in period, whereas patients on sulphonylurea monotherapy were entered directly into the 2-week placebo run-in Treatment group • Linagliptin: 5 mg once daily for 18 weeks Control group • Placebo for 18 weeks Both groups • The background sulphonylurea therapy was administered at an unchanged dosage throughout the entire study duration (including the washout and placebo run-in periods), with the exception that down-titration of sulphonylurea was permitted for safety reasons
Outcomes	• Change in HbA1c from baseline to week 18 • Mean change in FBG from baseline • Mean change from baseline in HbA1c and FBG over time • Proportion of patients achieving a reduction in HbA1c ≥ 0.5% (5 mmol/mol) • Proportion of patients achieving HbA1c < 7% (53 mmol/mol) • Mean change in body weight from baseline • Proportion of patients requiring rescue therapy or discontinuing due to lack of efficacy • Tolerability data were collected at every visit and included incidence of AE, serious AEs, discontinuation due to AEs, 12-lead ECG, vital signs, and clinical laboratory parameters. • Hypoglycaemic episodes
Notes	• Funding source: Boehringer Ingelheim

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomised using the interactive voice response system (IVRS; Almac Clinical Technologies, Yardley, Pennsylvania) to ensure that the investigator did not know to which of the 2 treatment groups the next patient would belong"
Allocation concealment (selection bias)	Low risk	"Patients were randomised using the interactive voice response system (IVRS; Almac Clinical Technologies, Yardley, Pennsylvania) to ensure that the investigator did not know to which of the 2 treatment groups the next patient would belong"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was labelled as double-blind. Patients were given either linagliptin or placebo

Lewin 2012 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Although the study was labelled as double-blind, the method through which outcome assessment was blinded was not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	10/161 (6.21%) in the linagliptin plus sulphonylurea group versus 7/84 (1.19%) in the sulphonylurea group discontinued
Selective reporting (reporting bias)	Low risk	The prespecified outcomes were available on a clinical trials database and major outcomes were reported
Other bias	High risk	Conflicts of interest: The study was initiated and supported by Boehringer Ingelheim, the manufacturer of linagliptin. Boehringer Ingelheim financially supported the medical writing and editorial assistance. Authors were either employees of Boehringer Ingelheim or received honoraria for attending meetings, consultancy fees, speaker fees and/or travel grants from Boehringer Ingelheim

LIRA-RENAL 2016

Methods	• Study design: parallel RCT • Study time frame: June 2012 to August 2013 • Duration of follow-up: 26 weeks
Participants	• Countries: France (4 sites), Poland (8 sites), Russian Federation (15 sites), Ukraine (6 sites), UK (9 sites), USA (36 sites) • Inclusion criteria: 18 to 80 years, previously diagnosed with type 2 DM.HbA1c 7% to 10% (53 to 86 mmol/mmol inclusive); on stable diabetes treatment for > 90 days before screening; the following background diabetes treatments were allowed: monotherapy or dual-therapy combinations of metformin and/or sulphonylurea and/or pioglitazone, monotherapy with basal or premix insulin, or any combination of basal or premix insulin with metformin and/or pioglitazone; moderate CKD (eGFR 30 to 59 mL/min/1.73 m^2) > 90 days before screening (confirmed at screening); BMI of 25 to 45 kg/m^2 (inclusive). • Number: treatment group (140); control group (139) • Mean age ± SD (years): treatment group (68 ± 8.3); control group (66.3 ± 8.0) • Sex (M/F): treatment group (75/65); control group (65/72) • Exclusion criteria: hypoglycaemic unawareness and/or recurrent severe hypoglycaemia as judged by the investigator; impaired liver function (ALT ≥ 2.5 x ULN; history of chronic pancreatitis or idiopathic acute pancreatitis; NYHA Functional Classification IV heart failure; episode of unstable angina, acute coronary event, cerebral stroke/TIA, or other significant cardiovascular event within the past 180 days; SBP ≥ 180 mmHg or a DBP ≥ 100 mmHg; screening calcitonin value ≥ 50 ng/L; personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2
Interventions	Treatment group • Liraglutide: initiated at 0.6 mg/d with subsequent weekly dose escalations of 0.6 mg/d until the maintenance dose of 1.8 mg/d was reached. Dose escalation could be extended for up to 4 weeks in case of GI adverse effects Control group • Placebo: initiated at 0.6 mg/d with subsequent weekly dose escalations of 0.6 mg/d until the maintenance dose of 1.8 mg/d was reached. Dose escalation could be extended for up to 4 weeks in case of GI adverse effects Both groups

LIRA-RENAL 2016 *(Continued)*

	• If the patient was on insulin with an HbA1c ≤ 8% (64 mmol/mol) at screening, the pretrial insulin dose was reduced by 20% at day 0 and kept fixed until the liraglutide/placebo dose escalation was complete. Titration to pretrial insulin dose was allowed at the discretion of the investigators. Patients were to maintain their background diabetes medications during the study and were allowed to dose reduce insulin or sulphonylureas doses if hypoglycaemic episodes occurred
Outcomes	• Change in HbA1c from baseline to week 26. Responder end points at week 26 for HbA1c < 7.0% (< 53 mmol/mol) and HbA1c < 7.0% (< 53 mmol/mol) with no hypoglycaemic episodes were determined • Change from baseline to week 26 in FBG, body weight, BMI, SBP and DBP, fasting lipids, and selected cardiovascular bio markers, total prescribed daily insulin dose • Adverse events, change from baseline in eGFR , UACR, amylase, lipase and pulse rate • Hypoglycaemic episodes
Notes	• Funding source: Novo Nordisk

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised using a sponsor-provided telephone or Web-based randomisation system.
Allocation concealment (selection bias)	Low risk	Randomised using a sponsor-provided telephone or Web-based randomisation system.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	“Trial site personnel, patients, and the sponsor remained blinded until trial completion”.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	“Trial site personnel, patients, and the sponsor remained blinded until trial completion”.
Incomplete outcome data (attrition bias) All outcomes	High risk	Discontinuation rates were moderately high: 35/140 (25%) from the liraglutide group versus 34/137 (24.8%) in the control group
Selective reporting (reporting bias)	Low risk	The prespecified outcomes were available on a clinical trials database and major outcomes were reported
Other bias	High risk	Conflicts of interest: The study was sponsored by Novo Nordisk who developed and sells liraglutide. All authors have either been on the advisory panel for Novo Nordisk, received research support or educational grants from Novo Nordisk or work for Novo Nordisk

Lukashevich 2011

Methods	• Study design: parallel RCT • Study time frame: not reported • Duration of follow-up: 52-week clinical study – 24 weeks with extension to 1 year
Participants	• Country: international (countries not reported) • Setting: multicentre (108 sites)

Lukashevich 2011 *(Continued)*

- Inclusion criteria: Adults aged 18 to 85 years with type 2 DM; moderate or severe CKD (eGFR by the MDRD formula ≥ 30 to < 50 mL/min/1.73 m^2 and < 30 mL/min/1.73 m^2, respectively) either untreated (no therapy in previous 8 weeks) or treated with an sulphonylurea, alpha glucosidase inhibitor, thiazolidinedione, insulin, meglitinide or a combination of agents was permitted provided that their dosages were stable for the previous 4 weeks; HbA1C was between 6.5% (48 mmol/mol) and 10% (86 mmol/mol); BMI was between 18 and 42 kg/m^2
- Number (randomised)
  * Moderate CKD: treatment group (165); control group (129)
  * Severe CKD: treatment group (124); control group (97)
- Mean age ± SD (years)
  * Moderate CKD: treatment group (67.7 ± 8.8); control group (69.7 ± 7.3)
  * Severe CKD: treatment group (64.1 ± 9.2); control group (64.5 ± 10.8)
- Sex (M/F)
  * Moderate CKD: treatment group (96/69); control group (80/49)
  * Severe CKD: treatment group (65/59); control group (44/53)
- Exclusion criteria: FBG ≥15 mmol/L; history of kidney transplant; significant cardiovascular history within 6 months; active liver disease or abnormal liver tests (ALT, AST or bilirubin 2× ULN)

Interventions	Run-in period • 2-week single-blind, placebo run-in period Treatment group • Vildagliptin: 50 mg once/d Control group • Placebo once daily Both group • Rescue medication (insulin addition or intensification) was administered after Week 4 if the FBG was 15 mmol/L, at Week 8 if the FBG was 13.3 mmol/L and at Week 16, if the FBG was 12.2 mmol/L.
Outcomes	• FBG and HbA1c • Percentage of patients achieving HbA1c < 7.0% • Adverse events • Particular attention was paid to safety areas considered to be of potential concern for DPP-4 inhibitors (i.e. hepatic, infections, skin, pancreatitis) as well as oedema and cardiovascular safety, which were considered of interest in this renally impaired population and which were previously analysed in patients with normal kidney function or mild CKD. • Hypoglycaemia was defined as symptoms suggestive of low blood glucose confirmed by self-monitored blood glucose measurement < 3.1 mmol/L plasma glucose equivalent • Severe hypoglycaemia was defined as any episode requiring assistance of another party (whether or not a confirmatory self-monitoring blood glucose measure was available)
Notes	• The initial protocol excluded patients undergoing any dialysis, but this was subsequently amended to remove that restriction • Funding source: Novartis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported

Lukashevich 2011 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	“The investigators and patients remained blinded to the identity of the treatment”.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	“The investigators and patients remained blinded to the identity of the treatment”.
Incomplete outcome data (attrition bias) All outcomes	High risk	High rate of discontinuation across both treatment groups in those with moderate CKD (52/165 (31.5%) from the vildagliptin group and 40/129 (31.0%) from the placebo group) and severe CKD (41/124 (33.1%) from the vildagliptin group and 41/97 (42.3%) from the placebo group).
Selective reporting (reporting bias)	Unclear risk	The prespecified outcomes were not available on a clinical trials database
Other bias	High risk	"P.-H. G. has served on advisory boards for Novartis, Boehringer Ingelheim and Cebix, has received honoraria for speaking engagements from Novartis, Boehringer Ingelheim, Novo-Nordisk, Eli Lilly, Genzyme and MSD Finland and received research support from Eli Lilly. V. L., Q. S., A. S.and W. K. are employed by and own shares in Novartis."

McGill 2013

Methods	• Study design: parallel RCT • Study time frame: not reported • Duration of follow-up: 52-week double-blind treatment period, and a 1-week follow-up period
Participants	• Countries: international (Australia, Hong Kong, Israel, New Zealand, Ukraine, USA) • Setting: multicentre (53 sites) • Inclusion criteria: women (non-fertile or using a medically approved birth control method) and men aged 18 to 80 years; previously diagnosed with type 2 DM, who were treated with glucose-lowering agents, including insulin, sulphonylureas, glinides, pioglitazone, and alpha-glucosidase inhibitors; existing glucose-lowering therapy must have remained unchanged for ≥ 8 weeks before study entry; severe CKD (CKD stage 4/5) at screening, having an eGFR < 30 mL/min/1.73 m^2 (while not receiving chronic dialysis); HbA1c > 7 and ≤ 10% (> 53 and ≤ 86 mmol/mol); BMI ≤ 45 kg/m^2 • Number (randomised/completed): treatment group (68/49); control group (65/48) • Mean age ± SD (years): treatment group (64.0 ± 10.9); control group (64.9 ± 9.6) • Sex (M/F): treatment group (45/23); control group (35/30) • Exclusion criteria: MI, stroke, or TIA within the previous 6 months; any requirement for acute dialysis within the previous 3 months; kidney transplantation; impaired hepatic function; use of any other DPP-4 inhibitor or anti-obesity drug within the previous 3 months
Interventions	Run-in period • 2-week, open-label placebo run-in period Treatment group • Linagliptin: 5 mg/d in addition to their glucose-lowering background therapy for 52 weeks. To assess the glucose-lowering effect of adding linagliptin, stable doses of existing background therapy were maintained

McGill 2013 *(Continued)*

	• During the first 12 weeks of treatment (unless dose adjustment was required for safety reasons) • During the following 40-week treatment period, background therapy could be adjusted according to glucose parameters Control group • Placebo in addition to their glucose-lowering background therapy for 52 weeks Both groups • Rescue therapy (any changes in treatment or doses of glucose-lowering background therapy during weeks 1–12 and/or addition of insulin during weeks 1–52) could be initiated based on failure to meet prespecified glycaemic response criteria: a confirmed FBG level > 13.3 mmol/L during weeks 1–12, a confirmed FBG level > 11.1 mmol/L during weeks 12–52, or a randomly determined glucose level > 22.2 mmol/L at any time. Patients who failed to meet these criteria despite rescue therapy were discontinued from the study

Outcomes	• Change from baseline to week 12 in HbA1c
	• Changes from baseline to week 52 in HbA1c, FBG, glucose-lowering background therapy, and body weight
	• Frequency and intensity of AEs, withdrawals because of AEs, physical examinations, 12-lead electrocardiograms, vital signs, and clinical laboratory assessments throughout the 52 weeks
	  * Hypoglycaemic events and severe hypoglycaemic episodes
	  * Treatment-emergent fatal events and suspected cardiovascular events (cardiovascular death, stroke, MI, and hospitalisation for unstable angina.

Notes	• Stratified by HbA1c and glucose-lowering background therapy • Funding source: Boehringer Ingelheim

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Study investigators and participants were blinded to treatment assignment for the duration of the study and to results of interim analyses"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Study investigators and participants were blinded to treatment assignment for the duration of the study and to results of interim analyses"
Incomplete outcome data (attrition bias) All outcomes	High risk	Moderately large discontinuation rate across both groups: 19/68 (27.9%) of the linagliptin group and 17/65 (26.2%) of the placebo group
Selective reporting (reporting bias)	Unclear risk	The prespecified outcomes were not available on a clinical trials database
Other bias	High risk	The study was sponsored by Boehringer Ingelheim. Authors were either employees of Boehringer Ingelheim or have spoken for or served as a consultant for Boehringer Ingelheim

Mohideen 2005

Methods	• Study design: open-label, parallel RCT • Study time frame: not reported • Duration of follow-up: 6 months
Participants	• Country: USA • Setting: single centre • Inclusion criteria: men and women ≥ 18 years; physician-diagnosed diabetes mellitus type 2; ESKD treated with either HD or PD; treated with insulin or a sulphonylureas or if not taking insulin, had HbA1c > 7% • Number: treatment group (6); control group (6) • Mean age ± SD (years): treatment group (58.8 ± 6.2); control group (52.0 ± 5.5) • Sex (M/F): treatment group (2/4); control group (2/4) • Exclusion criteria: known liver disease or cirrhosis; ALT or AST > 3 times ULN; congestive heart failure or cardiomyopathy; sensitivity to troglitazone or components of troglitazone
Interventions	Treatment group • Troglitazone: started on 200 mg/d and titrated to a maximum dose 600 mg/d • Continuing previous diabetes medications (insulin or sulphonylureas) Control group • Continued to receive their current diabetes medication regimen (insulin or sulphonylureas)
Outcomes	• HbA1c levels • Blood glucose profiles (blood glucose values were averaged for the week prior to study visit) • Insulin and sulphonylureas dosage • Safety measures
Notes	• Control subjects were eligible to “cross-over” into the troglitazone treatment group after completing 6 months of the protocol • Written to authors to get first phase data on 6th February 2017 to include in the meta-analysis. No data available • Funding source: Pfizer

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“Eligible subjects were randomised to either with troglitazone or without troglitazone (control) group using a table of random numbers assigned by an independent investigator”
Allocation concealment (selection bias)	Unclear risk	“Eligible subjects were randomised to either with troglitazone or without troglitazone (control) group using a table of random numbers assigned by an independent investigator”. But for second phase, subjects were given the option of crossing over into the Troglitazone arm. This give a risk of selection bias. The risk is removed if we analyse first phase data only as per the protocol
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study

Mohideen 2005 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	High risk	3/6 (50%) of the troglitazone arm and 1/6 (16.7%) of the control arm discontinued
Selective reporting (reporting bias)	Unclear risk	The prespecified outcomes were not available on a clinical trials database
Other bias	High risk	Conflicts of interest: The study was supported in part by Pfizer, Inc

Mori 2016

Methods	• Study design: open-label, parallel RCT • Study time frame: 6 July 2012 to 8 July 2014 • Duration of follow-up: 12 weeks
Participants	• Country: Japan • Setting: multicentre (15 sites) • Inclusion criteria: men and women with type 2 DM undergoing stable maintenance HD, aged ≥ 20 years; HbA1c level ≥ 4.6% (27 mmol/mol) and ≤ 10% (86 mmol/mol) or a GA level ≥ 18% and ≤ 30%; GA level was adopted as an inclusion criterion because HbA1c level is often underestimated in this population as a result of renal anaemia and/or the use of ESA • Number: treatment group 1 (38); treatment group 2 (40) • Mean age ± SD (years): treatment group 1 (69.2 ± 9.5); treatment group 2 (66.7 ± 9.5) • Sex (M/F): treatment group 1 (31/7); treatment group 2 (30/10) • Exclusion criteria: treatment with any type of insulin; impaired hepatic function (AST ≥ 100 IU/L or ALT ≥ 100 IU/L); malignant tumours; untreated diabetic retinopathy
Interventions	Treatment group 1 • Linagliptin: 5 mg/d Treatment group 2 • Voglibose 0.2 mg 3 times/d
Outcomes	• Change in HbA1c level between baseline and week 12. • Changes in GA and casual plasma glucose levels between baseline and week 12 • Adverse events, clinical laboratory tests • Hypoglycaemia episodes: defined as any hypoglycaemia symptoms or a casual blood glucose level < 2.8 mmol/L as evaluated by finger-stick blood testing
Notes	• Funding source: KM, ME, TS and MI received unrestricted research grants from Mitsubishi Tanabe Pharma Corporation, Daiichi Sankyo Co., Astellas Pharma, Asahi Kasei Pharm Corporation, Kyowa Hakko Kirin Co., Chugai Pharmaceutical Co., Teijin Pharma, Takeda Pharmaceutical Company, and Ono Pharmaceutical Co

Risk of bias

Bias	Authors' judgement	Support for judgement

Mori 2016 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	High risk	There was higher discontinuation in voglibose compared to the linagliptin group: 6/38 (15.8%) in the voglibose group and 3/40 (7.5 %) in the linagliptin group. Data were analysed using the full analysis set with the last observation carried forward
Selective reporting (reporting bias)	Unclear risk	Prespecified outcomes were available on a public database and were reported
Other bias	High risk	The authors received unrestricted research grants from Mitsubishi Tanabe Pharma Corporation, Daiichi Sankyo Co., Astellas Pharma, Asahi Kasei Pharm Corporation, Kyowa Hakko Kirin Co., Chugai Pharmaceutical Co., Teijin Pharma, Takeda Pharmaceutical Company, and Ono Pharmaceutical Co. All but one of the authors received honorarium for lecturing from Nippon Boehringer Ingelheim. Takeda produces voglibose, and Nippon Boehringer Ingelheim linagliptin

Nakamura 2001

Methods	• Study design: parallel RCT • Study time frame: not reported • Duration of follow-up: 3 months
Participants	• Country: Japan • Setting: not reported • Inclusion criteria: dialysis patients with type 2 DM, dyslipidaemia without lipid lowering drugs • Number: treatment group (10); control group (10) • Mean age: 54.5 years (age not reported for each group) • Sex (M/F): 12/8 (sex not reported for each group) • Exclusion criteria: not reported
Interventions	Treatment group • Pioglitazone: 30 mg/d Control group • Placebo
Outcomes	• HbA1c levels • Fasting serum triglyceride levels

Nakamura 2001 *(Continued)*

	• Fasting HDL cholesterol levels • Fasting total cholesterol levels
Notes	• Written to authors for data for inclusion in the meta-analysis. No data available • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients were given a placebo tablet
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients discontinued
Selective reporting (reporting bias)	Unclear risk	The prespecified outcomes were not available on a clinical trials database
Other bias	Unclear risk	Conflicts of interest were not reported

Nowicki 2011

Methods	• Study design: parallel RCT • Study time frame: January 2008 to March 2010 • Duration of follow-up: 52 weeks; 12-week double-blind treatment period followed by a 40-week double-blind controlled extension with continuation of treatment
Participants	• Country: international (countries not reported) • Setting: multicentre (number of sites not reported) • Inclusion criteria: adults with a diagnosis of type 2 DM; CrCl < 50 mL/min within the past 3 months; inadequate glycaemic control (HbA1c 7% to 11% [53 to 97 mmol/mol]).C-peptide ≥ 0.33 nmol/L • Number (randomised/completed week 12): treatment group (85/61); control group (85/68) • Mean age ± SD (years): treatment group (66.8 ± 8.3); control group (66.2 ± 9.1) • Sex (M/F): treatment group (32/53); control group (41/44) • Exclusion criteria: current or anticipated need for PD or expected kidney transplant within 3 months after enrolment; AST, ALT and/or total bilirubin > 1.5 times ULN; creatine kinase ≥ 3 times ULN; treatment with metformin within 4 weeks before enrolment; previous or current treatment with any DPP-4 inhibitor or GLP-1 agonist
Interventions	Run-in period

Nowicki 2011 *(Continued)*

	• 2-week, single-blind, placebo lead-in period Treatment group • Oral saxagliptin: 2.5 mg once/d taken immediately before or with a meal Control group • Oral placebo: once/d taken immediately before or with a meal Both groups • For patients with ESKD receiving HD, study medication was taken after completion of the HD treatment on the days that scheduled HD treatment occurred, with the exception of week 12 when patients took one dose for pharmacokinetic (PK) sampling and a second dose after HD treatment • Patients were provided with a glucometer and diary, and instructed to monitor their plasma glucose at least every other day throughout the study, and record plasma glucose values and information about any hypoglycaemic events in their diaries • Counselling on dietary and lifestyle modifications was provided according to usual clinical practice during the lead-in period, and reinforced at all subsequent visits • Oral antihyperglycaemic drugs and/or insulin therapy present at enrolment were continued throughout the study; discontinuation or down titration of these medications was allowed only if needed to prevent hypoglycaemia
Outcomes	• Absolute HbA1c change from baseline to week 12 • Assessment of efficacy at 52 weeks using absolute change from baseline in HbA1c and FBG and changes from baseline in the type and/or daily doses of background oral glucose-lowering therapy and insulin. • AEs, treatment-related AEs, AEs leading to discontinuation of study medication and serious AEs • Laboratory values, including estimated glomerular filtration rate using the Cockcroft-Gault and MDRD equations and the urinary albumin:creatinine ratio • Electrocardiograms, measurement of body weight and vital signs and physical examinations were performed at predetermined intervals, incidence of doubling of SCr concentration and shifts in CKD category, including progression to ESKD
Notes	• Patients were stratified based on degree of CKD (moderate, severe or ESKD), and randomised (1:1) • Patients were to be discontinued from the study if they did not meet progressively stringent glycaemic control criteria. These prespecified glycaemic goals included confirmed FBG > 15.0 mmol/L at weeks 2 or 4; > 13.3 mmol/L at weeks 6 or 9 and > 12.2 mmol/L at week 12. Study discontinuation criteria also included confirmed lymphopenia (≤ 400 cells/μL), thrombocytopenia (< 75,000 cells/μL) or clinical symptoms of poorly controlled DM. Glycaemic parameters were assessed at each visit to determine if criteria for discontinuation were met • Funding source: "This study was funded, designed and supervised by scientists at Bristol-Myers Squibb and AstraZeneca."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“Using CrCl estimated by the Cockcroft-Gault equation (23), patients were stratified by degree of renal impairment: moderate (CrCl ≥ 30 and < 50 mL/min), severe (CrCl < 30 mL/min and not receiving dialysis) or end-stage renal disease (ESRD) on haemodialysis at baseline. Patients were randomised 1 : 1 via an interactive voice response system in balanced blocks within each renal impairment category to once-daily double-blind treatment with saxagliptin 2.5 mg or placebo”
Allocation concealment (selection bias)	Unclear risk	“Using CrCl estimated by the Cockcroft-Gault equation (23), patients were stratified by degree of renal impairment: moderate (CrCl ≥30 and < 50 mL/min), severe (CrCl < 30 mL/min and not receiving dialysis) or end-stage renal

Nowicki 2011 *(Continued)*

		disease (ESRD) on haemodialysis at baseline. Patients were randomised 1 : 1 via an interactive voice response system in balanced blocks within each renal impirment category to once-daily double-blind treatment with saxagliptin 2.5 mg or placebo".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Blinding was ensured using a single-dummy technique".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study labelled as a double-blind study. Otherwise, method of blinding was not described
Incomplete outcome data (attrition bias) All outcomes	High risk	There was high discontinuation in both groups: 43/85 (50.6%) in the saxagliptin group and 35/85 (41.2%) in the control group
Selective reporting (reporting bias)	Low risk	The prespecified outcomes were available on a clinical trials database and major outcomes were reported
Other bias	High risk	Conflicts of interest: The study was funded, designed and supervised by scientists at Bristol-Myers Squibb and AstraZeneca. Three of the authors were employees of Astra Zeneca, the maker of saxagliptin. Two of the authors are either study investigators for Astra Zeneca or have received speaking honoraria.

Pfutzner 2011

Methods	• Study design: phase 2, parallel RCT • Study time frame: not reported • Duration of follow-up: 6 months
Participants	• Country: Germany • Setting: multicentre (12 sites) • Inclusion criteria: patients with type 2 DM (WHO criteria); HbA1c ≥ 48 mmol/mol (6.5%); persistent albuminuria (≥ 30 mg/g (3.39 mg/mmol) in at least 2 out of 3 consecutive morning spot urine samples) and who were receiving stable RAS-blocking treatment • Number (randomised/completed): treatment group (20/15); control group (19/11) • Mean age ± SD (years): treatment group (68.9 ± 6.8); control group (69.6 ± 9.4) • Sex (M/F): treatment group (14/6); control group (13/6) • Exclusion criteria: diagnosis of clinical heart failure; eGFR ≤ 30 mL/min/1.73 m^2
Interventions	Treatment group • Pioglitazone: 1 x 30 mg/d at breakfast for 6 months. Advice for insulin dosage adaptation and choice of insulin was at the discretion of the investigator. At the discretion of the investigator, the initial insulin dose was reduced by 10% at the randomisation visit. Insulin was titrated to target a FBG level of 4.44 to 6.67 mmol/L. Patients were allowed to use any further concomitant medications that they required as far as they did not belong to those representing exclusion criteria. If medically acceptable, all concomitant medications had to be kept constant during the investigation. Control group • Placebo for 6 months Both groups

Pfutzner 2011 *(Continued)*

	• Advice for insulin dosage adaptation and choice of insulin was at the discretion of the investigator. At the discretion of the investigator, the initial insulin dose was reduced by 10% at the randomisation visit. Insulin was titrated to target a FBG level of 4.44 – 6.67 mmol/L. Patients were allowed to use any further concomitant medications that they required as far as they did not belong to those representing exclusion criteria. If medically acceptable, all concomitant medications had to be kept constant during the investigation.
Outcomes	• The change in the daily insulin dose (basal and prandial) after 6 months of treatment with either pioglitazone or placebo given in addition to insulin. The total daily insulin dose was defined as the mean of the daily insulin dose on 3 consecutive days before the respective visits • The number of patients with a reduction of the daily insulin dose of ≥ 30% • Laboratory parameters such as HbA1c, glucose, C-peptide, intact proinsulin, adiponectin, relaxin, fetuin A, carbonyl protein, angiotensin, high-sensitivity CRP, calcification markers (MPO, matrix Gla protein), lipids (cholesterol, HDL, LDL, triglycerides), matrix metallopeptidase 9 (MMP-9), monocyte chemotactic protein-1 (MCP-1), soluble E-selectin, oxidized LDL (ox LDL), PIO in serum, iPTH, and N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP) • Laboratory efficacy parameters were measured using blood collected prior to dialysis at visit 2 (baseline), visit 5 (12 weeks later), and visit 7 (6 months later) • The influence of the treatment on cardiac function was furthermore evaluated as the change in the ultrafiltrate volumes during the course of the study. Another objective was the safety surveillance including assessment of adverse events (AE) and safety laboratory parameters.
Notes	• Funding source: The study was sponsored by TAKEDA Pharma GmbH, Aachen, Germany

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"After written informed consent was obtained from each participant, patients were randomised to either receive an additional treatment with pioglitazone (1 x 30 mg/day at breakfast) or placebo for 6 months". Also the study was reported to be a double-blind study.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	There was greater discontinuation in the control group compared to the pioglitazone group: 4/19 (21.1%) pioglitazone versus 6/17 (35.3%) control group.
Selective reporting (reporting bias)	Unclear risk	The prespecified outcomes were not available on a clinical trials database
Other bias	High risk	Conflicts of interest: The study was sponsored by TAKEDA Pharma GmbH, Aachen, Germany.

Ruggenenti 2003a

Methods	• Study design: cross-over RCT • Study time frame: not reported • Duration of follow-up: two 10 hour periods separated by a 2-week washout period
Participants	• Country: Italy • Setting: single centre • Inclusion criteria: type 2 DM; continued treatment with oral antidiabetic argents and/or insulin for at least 1 year; SCr < 176.8 µmol/L and an albuminuria persistently ≥ 200 µg/min in 2 of 3 urinary collections for at least 6 months were asked to submit within 2 weeks three consecutive timed overnight urine collections for the centralised measurement of UAER ≥ 200 µg/min in 2 of the 3 urinary samples entered the study • Number: 11 • Median age (range): 59.3 years (42 to 72) • Sex (M/F): 7/4 • Exclusion criteria: any evidence of nondiabetic kidney disease; renovascular disease; urinary tract obstruction; incomplete bladder voiding; UTI; stroke, acute MI or unstable angina in the last 6 months; severe liver or haematological disease; collagen vascular disease; cancer; treatment with cimetidine; steroidal or NSAIDs over the last 2 months; any condition that in the investigator's judgement might prevent study completion or affect data interpretation were not included; pregnancy or childbearing potential
Interventions	Treatment group • After an insulin clamp to maintain BGL between 4.44 to 6.66 mmol/L for 2 hours, baseline bloods were done and subjects were then given insulin lispro. Five minutes after insulin administration, subjects were given a standard meal made of pasta, turkey, bread, fresh tomatoes, an apple, and olive oil, containing 692 kcal (54.2% CHO, 17.l4% proteins and 28.4% lipids), with the broad aim to achieve postprandial BGL > 13.88 mmol/L after the SC injection of a standard dose (0.1 U/kg) of regular insulin. Patients voided at the beginning of the meal and six consecutive 1 hour urine collections were made for postprandial evaluations. Blood was sampled at the beginning and end of each postprandial urine collection. Urine and plasma samples were collected for the measurement of inulin, PAH and albumin which were used to calculate GFR. At completion of the clearance studies, patients were discharged and asked to continue their previous antidiabetic and antihypertensive therapy. No change was introduced in diet or pharmacological treatments. 2 weeks later, they attended the clinical research centre for a second clearance study, and given regular SC insulin half an hour before the meal, with exactly the same procedure as described previously. Control group • Same procedure as in active arm, except regular insulin given half an hour before the meal, and 2 weeks later, given insulin lispro.
Outcomes	• The percent change in postprandial GFR achieved by lispro versus regular insulin – 2 and 4 hour change in GFR • Albumin concentration • Amino acid plasma concentration • Inulin and PAH clearance samples. • Blood glucose and plasma amino acid areas under the curve, mean GFR, renal plasma flow, filtration fraction, renal vascular resistance, albumin fractional clearances
Notes	• Funding source: sponsored partially by Eli Lilly Florence Italy

Risk of bias

Bias	Authors' judgement	Support for judgement

Ruggenenti 2003a *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no discontinuations
Selective reporting (reporting bias)	Unclear risk	The prespecified outcomes were not available on a clinical trials database
Other bias	High risk	Conflicts of interest: The study was sponsored partially by Eli Lilly Florence Italy

SAVOR-TIMI 53 2011

Methods	• Study design: parallel RCT • Study time frame: May 2010 to December 2011 • Duration of follow-up: median duration 2.1 years
Participants	• Country: 26 countries (included Europe, Russia, South-east Asia, China, South and North America, Israel, Australia) • Setting: multicentre (788 sites) • Inclusion criteria: documented type 2 DM; HbA1c from 6.5% to 12.0%; history of established CVD or multiple risk factors for vascular disease; eGFR was determined according to the MDRD formula • Number: treatment group (8280); control group (8212) * 2576 patients had an eGFR < 50 mL/min/1.73 m^2: treatment group (1294); control group (1282) • Mean age ± SD (years): treatment group (65.1 ± 8.5); control group (65.0 ± 8.6) • Sex (M/F): treatment group (5512/2768); control group (5525/2687) • Exclusion criteria: currently receiving or had received within the previous 6 months an incretin-based therapy; ESKD and undergoing long-term dialysis; undergone a kidney transplant; SCr level > 6.0 mg/dL (530 µmol/L)
Interventions	Treatment group • Saxagliptin: 5 mg/d (or 2.5 mg/d in patients with an eGFR ≤ 50 mL/min) Control group • Placebo Both groups

SAVOR-TIMI 53 2011 *(Continued)*

	• All other therapy for the management of the patient's diabetes and CVD - including adding, discontinuing, or changing the dose of concomitant anti hyperglycaemic drugs - was at the discretion of the responsible physician • Concomitant use of other DPP-4 inhibitors or glucagon-like peptide 1 agonists was not allowed
Outcomes	• A composite of cardiovascular death, nonfatal MI, or nonfatal ischaemic stroke • The primary composite end point plus hospitalisation for heart failure, coronary revascularization, or unstable angina • Hypoglycaemic events, pancreatitis, thrombocytopenia, lymphocytopenia, infections, cancers, hypersensitivity or skin reactions, bone fractures, kidney abnormality and liver abnormalities.
Notes	• For this systematic review, we are interested in those patients with an eGFR < 60 mL/min/1.73 m^2 • Written to authors for further data for patients with an eGFR < 50 for the meta-analysis. No further data available • Funding source: AstraZeneca and Bristol-Myers Squibb

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomised via a central computerized telephone or Web-based system in blocks of 4, with stratification according to the qualifying CVD state and kidney function
Allocation concealment (selection bias)	Low risk	Patients were randomised via a central computerized telephone or Web-based system in blocks of 4, with stratification according to the qualifying CVD state and kidney function
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Saxagliptin or placebo was administered in a blinded fashion until the end of the follow-up period"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"No member of the study delivery team at AstraZeneca or BMS or representative, personnel at study centres or any clinical research organisation (CRO) handling data will have access to the randomisation scheme during the conduct of the study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low rate of attrition:- 202/8280 (2.4%) in the Saxagliptin group; 214/8212 (2.6%) in the placebo group
Selective reporting (reporting bias)	Low risk	The prespecified outcomes were available on a clinical trials database and all major outcomes were reported
Other bias	High risk	Conflicts of interest: The study was sponsored by AstraZeneca and Bristol-Myers Squibb and designed by the TIMI Study Group and Hadassah Medical Organization in conjunction with the sponsors, who provided monitoring support and donated the drug. All authors except one author either received grant support, consulting fees and/or lecture fees from AstraZeneca and Bristol-Myers Squibb or are employees of AstraZeneca or Bristol-Myers Squibb

Scarpioni 1994

Methods	• Study design: cross-over RCT • Study time frame: not reported

Scarpioni 1994 *(Continued)*

	• Duration of follow-up: not reported
Participants	• Country: Italy • Setting: single centre • Inclusion criteria: insulin-dependent patients with DM receiving CAPD • Number: 6 • Mean age ± SD: 52.4 ± 5.2 years • Sex (M/F): 5/1 • Exclusion criteria: not reported
Interventions	Treatment group • IP insulin: 4 injections of regular insulin in every dialysis bag immediately before the IP infusion of the last 200mL of dialysate Control group • SC insulin: 3 daily injections of regular insulin at 7:00/12:00/17:00 and 1 injection of mixture of regular and intermediate acting insulin at 21:00 Both groups • Isocaloric diet (126 kJ/kg body weight plus 33.6 kJ/kg from the dialysate) containing, as a percentage of the total calories, 20% from proteins (1.4 g/kg body weight), 50% from carbohydrates and 30% from fats, divided in four meals taken immediately after the exchanges. Also patients received tolrestat (aldose-reductase inhibitor) and nifedipine or an ACEi
Outcomes	• Blood glucose, free insulin, lactate, glycerol, β -hydroxybutyrate at each hour following treatment
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No discontinuations occurred
Selective reporting (reporting bias)	Unclear risk	The prespecified outcomes were not available on a clinical trials database. All outcomes were reported

Scarpioni 1994 *(Continued)*

Other bias	High risk	No washout period documented, therefore potential for carryover effect. No conflicts of interest documented

TECOS 2013

Methods	• Study design: parallel RCT • Study time frame: December 2008 to July 2012 • Duration of follow-up: median follow-up 3.0 years
Participants	• Country: 38 countries (Europe, North and South America, Asia, Oceania and Israel) • Setting: multicentre (673 sites) • Inclusion criteria: Type 2 DM with established CVD, defined as a history of major coronary artery disease, ischaemic cerebrovascular disease, or atherosclerotic peripheral arterial disease; at least 50 years of age; HbA1c of 6.5 to 8.0% when treated with stable doses of one or two oral antihyperglycaemic agents (metformin, pioglitazone, or sulphonylureas) or insulin (with or without metformin) • Number: treatment group (); control group () * eGFR < 60 mL/min/1.73m^2: treatment group (1667); control group (1657) • Mean age ± SD: 68.8 ± 7.9 years (not reported for groups) • Sex (M/F): 2060/1263 (not reported for groups) • Exclusion criteria: taken a DPP-4 inhibitor, glucagon-like peptide-1 receptor agonist, or thiazolidinedione (other than pioglitazone) during the preceding 3 months; history of two or more episodes of severe hypoglycaemia (defined as requiring third party assistance) during the preceding 12 months; eGFR < 30 mL/min/1.73 m^2 at baseline
Interventions	Treatment group • Sitagliptin: 100 mg/d (or 50 mg/d if the baseline eGFR was ≥ 30 and < 50 mL/min/1.73 m^2) Control group • Placebo
Outcomes	• Composite cardiovascular outcome" defined as the first confirmed event of cardiovascular death, nonfatal MI, nonfatal stroke, or hospitalisation for unstable angina • The secondary composite cardiovascular outcome was the first confirmed event of cardiovascular death, nonfatal MI, or nonfatal stroke. Other secondary outcomes included the occurrence of the individual components of the primary composite cardiovascular outcome, fatal and nonfatal MI, fatal and nonfatal stroke, death from any cause, and hospitalisation for heart failure • Changes in the glycated haemoglobin level and the eGFR, initiation of additional antihyperglycaemic agents or long-term insulin therapy, and frequency of severe hypoglycaemia, adverse events, severe hypoglycaemia, and expected diabetes-related complications.
Notes	• Written to authors for further data for the subgroup analysis for those patients with an eGFR < 60. Authors reported that data not available currently as they will publish the subgroup analysis. • Funding source: Merck

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"An interactive voice-response system assigned the study medication in a double-blind manner, blocked within each site"

TECOS 2013 *(Continued)*

Allocation concealment (selection bias)	Low risk	"An interactive voice-response system assigned the study medication in a double-blind manner, blocked within each site"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"An interactive voice-response system assigned the study medication in a double-blind manner, blocked within each site"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"A clinical events committee (CEC), blinded to treatment allocation and independent of the sponsor, will adjudicate events including cardiovascular-related death, non-fatal MI, nonfatal stroke, unstable angina requiring hospitalization, congestive heart failure requiring hospitalization, and acute pancreatitis"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low rate of discontinuation for the whole population (not just eGFR < 60) in both sitagliptin arm (360/7332; 4.9%) and placebo arm (434/7339; 5.9%)
Selective reporting (reporting bias)	Low risk	The prespecified outcomes were available on a clinical trials database and all major outcomes were reported
Other bias	High risk	Conflicts of interest: The study was supported by Merck, the manufacturer of sitagliptin. All authors except 2, either received research grants, consulting fees, travel reimbursements and/or speaker fees from Merck or were employees of Merck with shares in the company

Wong 2005

Methods	• Study design: open-label, parallel RCT • Study time frame: 2001 to 2002 • Duration of follow-up: 24 weeks
Participants	• Country: Hong Kong • Setting: single centre • Inclusion criteria: insulin-treated patients with type 2 DM; on CAPD therapy; stable glycaemic control (defined as HbA1c < 8% while insulin dosage is maintained at the same dose in the past 6 weeks) • Number: treatment group 1 (26); treatment group 2 (26) • Mean age ± SD (years): treatment group 1 (62.9 ± 7.3); treatment group 2 (61.6 ± 9.7) • Sex (M/F): not reported • Exclusion criteria: deranged liver function at baseline (ALT level > 2.5 times ULN); decompensated congestive heart failure
Interventions	Treatment group • Rosiglitazone: 4 mg daily • Insulin: intermediate acting insulin. Insulin dosage was reduced by 10% at the start of the study to minimize the risk for hypoglycaemia Control group • Insulin alone: intermediate acting insulin Both groups • PD prescription was kept unchanged during the study period except during episodes of fluid overload as a temporary change.

Wong 2005 *(Continued)*

Outcomes	• Change in insulin dosage at the end of the study compared with baseline dosage • Change in C-peptide, HbA1c, lipid, and high-sensitivity CRP levels and adverse events • Adverse events: defined as liver function derangement, fluid overload, and need for blood transfusion
Notes	• Funding source: GLaxoSmithKline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer generalized list was used for randomisation
Allocation concealment (selection bias)	Low risk	"Investigators were unaware of the randomisation schedule when recruiting patients"
Blinding of participants and personnel (performance bias) All outcomes	High risk	"investigators and patients were not blinded during the follow-up period"
Blinding of outcome assessment (detection bias) All outcomes	High risk	"investigators and patients were not blinded during the follow-up period"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No discontinuations were reported
Selective reporting (reporting bias)	Unclear risk	The prespecified outcomes were available on a clinical trials database
Other bias	Low risk	Conflicts of interest: Rosiglitazone was provided by GLaxoSmithKline UK, with no other funding involved

Yale 2013

Methods	• Study design: phase 3, parallel RCT • Study time frame: not reported • Duration of follow-up: 52 weeks (26-week core period and a 26-week extension)
Participants	• Country: 19 countries • Setting: multicentre (89 sites) • Inclusion criteria: patients with type 2 DM aged ≥ 25 years; HbA1c ≥ 7.0% (53 mmol/mol) and ≤ 10.5% (91 mmol/mol); eGFR ≥30 and <50 mL/min/1.73 m^2: either not on glucose-lowering therapy or were on stable glucose-lowering therapy monotherapy or combination therapy with any approved agent • Number: treatment group 1 (89); treatment group 2 (90); control group (90) • Mean age ± SD (years): treatment group 1 (67.9 ± 8.2); treatment group 2 (69.5 ± 8.2); control group (68.2 ± 8.4) • Sex (M/F): treatment group 1 (48/41); treatment group 2 (58/32); control group (57/33) • Exclusion criteria: repeated FBG > 15.0 mmol/L (270 mg/dL) during the pretreatment phase; history of type 1 DM; kidney disease that required immunosuppressive therapy, dialysis or transplant; nephrotic syndrome or inflammatory kidney disease; MI, unstable angina, revascularization procedure or cerebrovascular accident within 3 months prior to screening

Yale 2013 *(Continued)*

Interventions	Treatment group 1 • Canagliflozin: 300 mg Treatment group 2 • Canagliflozin: 100 mg Control group • Placebo All groups • During the double blind treatment period, glycaemic rescue therapy (up-titration of current antihypertensive agents or step-wise addition of oral or non-oral antihypertensive agents) was initiated if protocol-specified glycaemic criteria were met. Patients were to remain on their stable glucose-lowering regimens through completion of the 52-week period unless glycaemic rescue criteria were met
Outcomes	• Change from baseline in HbA1c, FBG and SBP, and percent change from baseline in body weight and fasting plasma lipids • AE reports, safety laboratory tests, vital sign measurements, physical examinations and 12-lead electrocardiograms • Selected AEs of interest, including genital mycotic infections, UTI and AEs related to osmotic diuresis and volume depletion, hypoglycaemia episode, were assessed • Measures of kidney function, including eGFR, SCr, (BUN) and UACR were also assessed
Notes	• Funding source: Janssen

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	An Interactive Voice Response System/Interactive Web Response System was used for randomisation
Allocation concealment (selection bias)	Low risk	An Interactive Voice Response System/Interactive Web Response System was used for randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients received canagliflozin at 100 or 300 mg or placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study was labelled as a double-blind placebo controlled study, but the methodology for the blinding of outcome assessment was not described
Incomplete outcome data (attrition bias) All outcomes	High risk	23/90 (25.6%) from the canagliflozin 100 mg; 13/89 (14.6%) from the canagliflozin 300 mg group; and 26/90 (28.9%) from the placebo group did not complete the study
Selective reporting (reporting bias)	Low risk	All major outcomes were reported and the prespecified outcomes were available on a clinical trials database
Other bias	High risk	Conflicts of interest: All authors except one are either employees of Janssen or have received research support, served on the advisory panels for, and/or served as a lecturer for Janssen or Johnson and Johnson. Janssen, a division of Johnson and Johnson markets canagliflozin

Yki-Järvinen 2013

Methods	• Study design: parallel RCT • Study time frame: August 2009 to September 2011 • Duration of follow-up: 52 weeks
Participants	• Country: 9 countries (Argentina, Belgium, Brazil, Canada, Czech Republic, Finland, Germany, Greece, Italy, Korea, Mexico, the Netherlands, Norway, Peru, Russia, Slovakia, Spain, Taiwan, and the USA) • Setting: multicentre (167 sites) • Inclusion criteria: ≥ 18 years; diagnosis of type 2 DM; inadequate glycaemic control (HbA1c ≥ 7.0% (53 mmol/mol) to ≤ 10.0% (86 mmol/mol)); BMI of ≤ 45 kg/m^2; receiving treatment with basal insulin, alone or in combination with metformin and/or pioglitazone, for ≥ 12 weeks.; acceptable basal insulins were insulin glargine, insulin detemir, and neutral protamine Hagedorn insulin; total prescribed insulin dose must not have changed by > 10% of the baseline value during the 12 weeks before randomisation • Number (randomised/completed study): treatment group (631/543); control group (630/520) * eGFR < 60: 127 participants • Mean age ± SD (years): treatment group (65.8 ± 7.4); control group (68.0 ± 9.1) • Sex (M/F): treatment group (33/26); control group (33/35) • Exclusion criteria: uncontrolled fasting hyperglycaemia (glucose > 13.3 mmol/L during placebo run in); MI, stroke, or TIA within 6 months before informed consent; impaired hepatic function (either ALT, ASP, or ALP > 3 times ULN); previous gastric bypass surgery; any medical history of cancer (except BCC) in the 5 years before screening; hypersensitivity or allergy to the investigational products; contraindications to metformin or pioglitazone; treatment with rosiglitazone, sulphonylureas, glucagon-like peptide 1 analogs, DPP-4 inhibitors, or anti-obesity drugs within the 3 months before informed consent; history of alcohol or drug abuse in the previous 3 months; current treatment with systemic steroids or change in dosage of thyroid hormones within 6 weeks before informed consent; premenopausal women who were nursing, pregnant, or not practicing an acceptable method of birth control
Interventions	Run-in period • Patients underwent a 2-week, open-label placebo run-in period to confirm their eligibility after the initial screening and to exclude those who were non-adherent Treatment group • Linagliptin: 5 mg once/d for 52 weeks • Basal insulin Control group • Placebo: 52 weeks • Basal insulin Both groups • During the first 24 weeks of treatment, the doses of basal insulin (within 10% of baseline dose) and oral glucose-lowering agents were kept unchanged. After week 24, adjustments to the dose of basal insulin (but not oral glucose-lowering agents) were allowed according to the medical judgment of the investigator, with a treatment target for FBG of 6.1 mmol/L • Rescue therapy could be initiated during randomised treatment if a patient met the following criteria: confirmed FBG (after overnight fast) > 13.3 mmol/L during the first 12 weeks, FBG > 11.1 mmol/L from weeks 12 to 24, or FBG > 10.0 mmol/L or HbA1c > 8.0% (64 mmol/mol) after week 24. For initiation of rescue medication, these criteria had to be confirmed by two measurements on separate days. Patients were withdrawn from the study if the FBG remained above this threshold despite rescue therapy
Outcomes	• Change from baseline in HbA1c after 24 weeks of treatment • Changes from baseline in HbA1c and FBG with time, change from baseline in FBG after 52 weeks of treatment, the proportion of patients achieving HbA1c < 7% (53 mmol/mol), the proportion of patients

Yki-Järvinen 2013 *(Continued)*

	achieving ≥ 0.5% (5.5 mmol/mol) reduction in HbA1c, and the change from baseline in mean basal insulin dose after 52 weeks of treatment, use of rescue medication and mean change in body weight to the end of treatment • The frequency and intensity of AEs, including hypoglycaemia and clinically relevant new or worsening findings in physical examination, 12-lead electrocardiogram, vital signs, lipid parameters, and clinical laboratory assessments • Also treatment-emergent fatal events and suspected events of stroke or cardiac ischaemia (including MI), hospitalisation for heart failure, stent thrombosis, and revascularization procedures
Notes	• As part of the unique study design, after the 24-week period, free insulin titration was allowed up to at least week 52 at the investigators' discretion • Funding source: Boehringer Ingelheim

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Treatment assignment was determined by computer-generated random sequence with an interactive voice response system"
Allocation concealment (selection bias)	Low risk	"Treatment assignment was determined by computer-generated random sequence with an interactive voice response system"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was reported to be double-blind, and patients received placebo medication if they were not prescribed linagliptin
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	88/631 (13.9%) of the linagliptin group and 110/630 (17.5%) of the control group discontinued
Selective reporting (reporting bias)	Low risk	The prespecified outcomes were available on a clinical trials database and major outcomes were reported
Other bias	High risk	Conflicts of interest: The study was sponsored by Boehringer Ingelheim. Authors either received research support, received consulting fees and/or served on scientific advisory committee and received honoraria, or were employees of Boehringer Ingelheim

Zambrowicz 2015

Methods	• Study design: parallel RCT • Study time frame: 31 October 2012 to 14 August 2013 • Duration of follow-up: 7 days
Participants	• Country: USA • Setting: single centre • Inclusion criteria: patients with type 2 DM; moderate to severe CKD (defined by an eGFR < 60 mL/min/1.73 m^2) • Number: treatment group (16); control group (15)

Zambrowicz 2015 *(Continued)*

- Mean age ± SD (years): treatment group (64.8 ± 8.53); control group (68.1 ± 7.33)
- Sex (M/F): treatment group (8/8); control group (9/6)
- Exclusion criteria: Type 1 DM; diabetes due to a pancreatic disorder; secondary diabetes (e.g. from Acromegaly or Cushing's disease); received a kidney allograft; expecting to require dialysis or undergo kidney transplantation within 3 months of Day 1; active hepatic disease; history of MI or stable angina or coronary revascularisation within 6 months prior to start of study; clinically significant arrhythmia; congestive heart failure; uncontrolled hypertension; history of 2 or more emergency or doctor visits due to hypoglycaemia within 6 months of study or hypoglycaemia unawareness; history of alcohol or illicit drug use; any bowel condition affecting gastric emptying or malabsorptive disorder or bowel resection; history of active infection within 2 weeks of recruitment; history of major surgery within 6 months of recruitment or imminent surgery during study; history of malignancy within 5 years of recruitment; pregnant; previous reaction to SGLT2 inhibitor; previous exposure to LX4211

Interventions	Treatment group • LX4211 400 mg/d Control group • Placebo
Outcomes	• Effect of LX4211 therapy on post-prandial glucose levels, measured as the change from baseline to day 7 • Tolerability, pharmacodynamic effects on FBG and GLP-1 levels from baseline to day 7, and pharmacokinetics effects of single and multiple doses. including 24-hour urine glucose excretion, BP, mean finger-stick BGL, fractional excretion of calcium and phosphate, serum uric acid levels and fractional excretion of uric acid, fasting triglyceride levels, tumour necrosis factor α levels, leptin levels, and exogenous insulin dose • Monitoring of AEs, clinical laboratory tests (chemistry, haematology, lipid profile, and urinalysis), vital signs (BP, heart rate, respiratory rate, and oral temperature), 12-lead electrocardiograms, physical examinations, and BGL
Notes	• Funding source: Lexicon Pharmaceuticals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants received LX4211 or placebo. study also described as double blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Although the study was described as double blind, the methodology behind outcome assessment blinding was not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 patient 1/16 (6.3%) of the LX4211 group discontinued. No patients discontinued from the placebo arm
Selective reporting (reporting bias)	Low risk	Protocol available. All major outcomes reported

Zambrowicz 2015 *(Continued)*

Other bias	High risk	Conflicts of interest: All authors were employees of Lexicon Pharmaceuticals who funded the study and was responsible for the study design, interpretation of the data, writing of the manuscript, and the decision to submit the manuscript

ABPM - ambulatory blood pressure monitoring; AE - adverse event/s; AKI - acute kidney injury; ALT - alanine aminotransferase; ALP - alkaline phosphatase; AST - aspartate aminotransferase; BCC - basal cell carcinoma; BGL - blood glucose level/s; BMI - body mass index; BP - blood pressure; BUN - blood urea nitrogen; CAPD - continuous ambulatory peritoneal dialysis; CrCl - creatinine clearance; CRP - C-reactive protein; CTR - cardiothoracic ratio; CVD - cardiovascular disease; DBP - diastolic blood pressure; DKD - diabetic kidney disease; DM - diabetes mellitus; eGFR - estimated glomerular filtration rate; ESA - erythropoietin stimulating agent/s; ESKD - end-stage kidney disease; FBG - fasting blood glucose; GI - gastrointestinal; GA - glycated albumin; Hb - haemoglobin; HbA1c - haemoglobin A1c (glycated); HD - haemodialysis; HDL - high-density lipoprotein; HIV - human immunodeficiency virus; HOMA-IR - homeostasis model assessment for insulin resistance; IP - intraperitoneal; iPTH - intact parathyroid hormone; LDH - lactate dehydrogenase; LDL - low-density lipoprotein; MDRD - Modification of Diet in Renal Disease; M/F - male/female; MI - myocardial infarction; NYHA - New York Heart Association; NSAID - nonsteroidal anti-inflammatory drugs; PAH - paraminohippuric acid; PD - peritoneal dialysis; RBC - red blood cell/s; RCT- randomised controlled trial; RRT - renal replacement therapy; SBP - systolic blood pressure; SC- subcutaneous; SCr - serum creatinine; SD - standard deviation; SEM - standard error of the mean; TIA - transient ischaemic attack; UACR - urinary albumin/creatinine ratio; UAER - urinary albumin excretion ratio; ULN - upper limit of normal; UTI - urinary tract infection

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

Study	Reason for exclusion
ACCORD 2007	Wrong intervention: comparing intensive versus less intensive glucose targets
ADOPT 2011	Wrong study population: not in patients with diabetes and an eGFR < 60
ADVANCE 2001	Wrong intervention: comparing intensive versus less intensive glucose targets
Agarwal 2005	Inadequate information: data for subgroup of patients with an eGFR < 60 not available from authors
Aljabri 2004	Wrong study population: not in patients with diabetes and an eGFR < 60
Amador-Licona 2000	Wrong study population: not in patients with diabetes and an eGFR < 60
Aoki 1995	Wrong intervention: insulin is not being used as glucose-lowering agent
APRIME 2011	Wrong study population: not in patients with diabetes and an eGFR < 60
Bakris 2006	Wrong study population: not in patients with diabetes and an eGFR < 60
Bangstad 1992	Wrong study population: not in patients with diabetes and an eGFR < 60
BARI 2D 2011	Wrong intervention: not comparing specific glucose-lowering agents but comparing insulin sensitiser versus insulin provision therapy
Barnett 1984	Wrong intervention: intervention was not a glucose-lowering agent
CANTATA-SU 2016	Wrong study population: not in patients with diabetes and an eGFR < 60
Cao 2005	Wrong study population: not in patients with diabetes and an eGFR < 60
Chacra 2009	Wrong study population: not in patients with diabetes and an eGFR < 60

Study	Reason for exclusion
Chen 2004b	Wrong study population: no information concerning whether patients had an eGFR < 60
Chen 2006h	Wrong study population: no information concerning whether patients had an eGFR < 60
Christensen 1986	Wrong study population: not in patients with diabetes and an eGFR < 60
Christensen 2001c	Wrong intervention: intervention was not a glucose-lowering agent
Chu 2006	Wrong intervention: intervention was not a glucose-lowering agent
Ciavarella 1985	Wrong study population: not in patients with diabetes and an eGFR < 60
Dailey 2000	Wrong intervention: insulin is not being used as glucose-lowering agent
Davidson 2007	Wrong study population: no information concerning whether patients had an eGFR < 60
DCCT 1986	Wrong study population: not in patients with diabetes and an eGFR < 60
de Boer 2013	Wrong intervention: intervention was not a glucose-lowering agent.
DeFronzo 2009	Wrong study population: not in patients with diabetes and an eGFR < 60
Derosa 2004	Wrong study population: not in patients with diabetes and an eGFR < 60
Di Mauro 2001	Wrong intervention: intervention was not a glucose lowering-agent
Didjurgeit 2002	Wrong intervention: intervention was not a glucose-lowering agent
DNETT Japan 2010	Wrong intervention: intervention was not a glucose-lowering agent
Einhorn 2000	Wrong study population: not in patients with diabetes and an eGFR < 60
Fadini 2016	No relevant outcomes (looks at progenitor cells and monocyte phenotypes)
Fang 2007	Wrong study population: no information concerning whether patients had an eGFR < 60
Feldt-Rasmussen 1986	Wrong study population: not in patients with diabetes and an eGFR < 60
Frederich 2012	Wrong study population: not in patients with diabetes and an eGFR < 60
Gadallah 2000b	Wrong study population: not in patients with diabetes and an eGFR < 60
Gan 2007	Wrong study population: no information concerning whether patients had an eGFR < 60
Gao 2006a	Wrong study population: no information concerning whether patients had an eGFR < 60
Gao 2007a	Wrong study population: no information concerning whether patients had an eGFR < 60
Gao 2007b	Wrong study population: no information concerning whether patients had an eGFR < 60
GEMINI 2005	Wrong intervention: intervention was not a glucose-lowering agent
Goicolea 2002	Wrong intervention: intervention was not a glucose-lowering agent
He 2004	Wrong study population: no information concerning whether patients had an eGFR < 60

Study	Reason for exclusion
Hollander 2009	Wrong study population: not in patients with diabetes and an eGFR < 60
Holman 1983	Wrong study population: not in patients with diabetes and an eGFR < 60
Hu 2007	Wrong study population: no information concerning whether patients had an eGFR < 60
Hu 2010	Wrong study population: not in patients with diabetes and an eGFR < 60
Huang 2004	Wrong study population: no information concerning whether patients had an eGFR < 60
Huang 2006	Wrong study population: no information concerning whether patients had an eGFR < 60
Huang 2007	Wrong study population: no information concerning whether patients had an eGFR < 60
Imano 1998	Wrong study population: no information concerning whether patients had an eGFR < 60
Inagaki 2014	No relevant outcomes (pharmacokinetic and pharmacodynamic study)
Jerums 1987	Wrong study population: not in patients with diabetes and an eGFR < 60
Kadhim 2006	Wrong intervention: intervention was not a glucose-lowering agent
Kadowaki 2014	Wrong study population: not in patients with diabetes and an eGFR < 60
Karalliedde 2006	Wrong intervention: intervention was not a glucose-lowering agent
Katavetin 2006	Inadequate information: unable to get information about patients with an eGFR < 60
Kim 2003	Wrong study population: no information concerning whether patients had an eGFR < 60
Kirk 1999	Wrong study population: not in patients with diabetes and an eGFR < 60
KUMAMOTO 1995	Wrong study population: no information concerning whether patients had an eGFR < 60
Lebovitz 2001	Wrong study population: no information concerning whether patients had an eGFR < 60
Leslie 2008	Wrong study population: not in patients with diabetes and an eGFR < 60
Li 2004a	Wrong study population: no information concerning whether patients had an eGFR < 60
Li 2006e	Wrong study population: no information concerning whether patients had an eGFR < 60
Li 2008f	Wrong study population: no information concerning whether patients had an eGFR < 60
Li 2008g	Wrong study population: not in patients with diabetes and an eGFR < 60
Lu 2010	Wrong intervention: intervention was not a glucose-lowering agent
Matthews 2005	Wrong study population: no information concerning whether patients had an eGFR < 60
MEMO 2011	Wrong intervention: intervention was not a glucose-lowering agent
Miyazaki 2007	Wrong study population: not in patients with diabetes and an eGFR < 60
Nakamura 2000b	Wrong study population: not in patients with diabetes and an eGFR < 60

Study	Reason for exclusion
Nakamura 2001b	Wrong study population: not in patients with diabetes and an eGFR < 60
Nakamura 2004	Wrong study population: not in patients with diabetes and an eGFR < 60
Nakamura 2006a	Wrong study population: not in patients with diabetes and an eGFR < 60
NCT00708981	Wrong intervention: intervention was not a glucose-lowering agent
NCT01245166	Wrong study population: no information concerning whether patients had an eGFR < 60
Nishimura 2015	Wrong study population: not in patients with diabetes and an eGFR < 60
OSLO 1986	Wrong study population: no information concerning whether patients had an eGFR < 60
Ostman 1998	Wrong intervention: intervention was not a glucose-lowering agent
Pan 2012	Wrong study population: not in patients with diabetes and an eGFR < 60
Petrica 2009	Wrong study population: not in patients with diabetes and an eGFR < 60
Pistrosch 2004	Wrong study population: no information concerning whether patients had an eGFR < 60
Pistrosch 2005	Wrong study population: not in patients with diabetes and an eGFR < 60
Pistrosch 2012	Wrong study population: not in patients with diabetes and an eGFR < 60
PIVIT 2010	Wrong intervention: insulin was not being used as a glucose-lowering agent
Pomerleau 1993	Wrong intervention: intervention was not a glucose-lowering agent
QUARTET 2004	Wrong study population: no information concerning whether patients had an eGFR < 60
Reinhard 2013	Wrong intervention: intervention looking at bioactive IGF-I and inflammatory biomarkers
Rosenstock 2009	Wrong study population: not in patients with diabetes and an eGFR < 60
SDIS 1988	Wrong study population: not in patients with diabetes and an eGFR < 60
Seino 2015	Inadequate information: unable to get information about patients with an eGFR < 60 from authors
SESTA R 2011	Wrong study population: not in patients with diabetes and an eGFR < 60
Shata'er 2007	Wrong study population: no information concerning whether patients had an eGFR < 60
SPEAD-A 2013	Wrong study population: not in patients with diabetes and an eGFR < 60
Stein 2014	Wrong study population: not in patients with diabetes and an eGFR < 60
STENO-2 1999	Wrong intervention: intervention was not a glucose-lowering agent
Strojek 2011	Wrong study population: not in patients with diabetes and an eGFR < 60
Su 2006	Wrong study population: no information concerning whether patients had an eGFR < 60
Sun 2006	Wrong study population: no information concerning whether patients had an eGFR < 60

Study	Reason for exclusion
Tan 2006	Wrong study population: no information concerning whether patients had an eGFR < 60
Tang 2007	Wrong study population: no information concerning whether patients had an eGFR < 60
Thrasher 2012	Wrong study population: no information concerning whether patients had an eGFR < 60
UKPDS 1991	Wrong intervention - examining "more intensive" versus "less intensive" glucose targets
UKPDS-HD 1998	Wrong intervention: examining "more intensive" versus "less intensive" glucose targets
VA-CSDM 1992	Wrong intervention: examining "more intensive" versus "less intensive" glucose targets
Viswanathan 1990	Inadequate information: unable to get information about patients with an eGFR < 60 from authors
Vos 2011	Wrong study population: not in patients with diabetes and an eGFR < 60
Wang 2004	Wrong study population: no information concerning whether patients had an eGFR < 60
Wang 2005b	Wrong study population: no information concerning whether patients had an eGFR < 60
Wang 2005c	Wrong study population: no information concerning whether patients had an eGFR < 60
Wang 2006	Wrong study population: no information concerning whether patients had an eGFR < 60
Wang 2008e	Wrong study population: no information concerning whether patients had an eGFR < 60
Wiseman 1985	Wrong study population: not in patients with diabetes and an eGFR < 60
Xu 2005	Wrong study population: no information concerning whether patients had an eGFR < 60
Yang 2011a	Wrong study population: no information concerning whether patients had an eGFR < 60
Yokoyama 2009	No relevant outcomes (serum cystatin C levels)
Zhang 2007c	Wrong study population: no information concerning whether patients had an eGFR < 60
Zhang 2012a	Wrong study population: not in patients with diabetes and an eGFR < 60
Zhao 2007	Wrong study population: no information concerning whether patients had an eGFR < 60
Zheng 2006	Wrong study population: no information concerning whether patients had an eGFR < 60
Zhou 2003	Wrong study population: no information concerning whether patients had an eGFR < 60
Zhou 2007	Wrong study population: no information concerning whether patients had an eGFR < 60
Zhu 2007	Wrong study population: no information concerning whether patients had an eGFR < 60
Zou 2005	Wrong study population: no information concerning whether patients had an eGFR < 60

eGFR - estimated glomerular filtration rate

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

AWARD-7 2017

Methods	Open-label, parallel RCT over 26 weeks
Participants	• Number: 576 patients • Inclusion criteria: men and non-pregnant women aged ≥18 years; HbA1c ≥7.5% (58 mmol/mol) and ≤ 10.5% (91 mmol/mol); type 2 DM on insulin or insulin + oral glucose-lowering medications; participants with presumed DKD with or without hypertensive nephrosclerosis diagnosed with moderate or severe CKD with eGFR of ≥15 to <60 mL/min/1.73 m^2; able and willing to perform multiple daily injections; BMI between 23 and 45 kg/m^2 • Exclusion criteria: stage 5 CKD as defined by eGFR < 15 mL/min/1.73 m^2 OR having required dialysis; rapidly progressing kidney dysfunction likely to require RRT; history of a transplanted organ, type 1 DM; at screening a SBP of ≥ 150 mmHg or a DBP of ≥ 90 mmHg with or without antihypertensive medication; an episode of ketoacidosis or hyperosmolar state/coma in the past 6 months or a history of severe hypoglycaemia in the past 3 months prior to the screening visit; cardiovascular conditions within 12 weeks prior to randomisation: acute MI, NYHA class III or class IV heart failure, or cerebrovascular accident (stroke); acute or chronic hepatitis; signs and symptoms of chronic or acute pancreatitis, or were in the past diagnosed with pancreatitis; serum calcitonin ≥ 35 pg/mL at screening visit; self or family history of medullary C-cell hyperplasia, focal hyperplasia, or carcinoma; known history of untreated proliferative retinopathy
Interventions	Treatment group 1 • Insulin glargine Treatment group 1 • Dulaglutide: 0.75 mg and 1.5 mg
Outcomes	• Change from baseline in HbA1c • Percentage of participants whose HbA1c was < 7.0% (53 mmol/mol) • Percentage of participants whose HbA1c was < 8.0% (64 mmol/mol) • Change from baseline in 8-Point SMPG • Change from baseline in mean daily Insulin Lispro dose • Percentage of participants with estimated average glucose < 8.5 mmol/L. • Change from baseline in SCr • Change from baseline in eGFR • Change from baseline in estimated CrCl • Change from baseline in UACR • Percentage of participants with self-reported hypoglycaemic events • Rate of hypoglycaemic event • Change from baseline in FBG • Change from baseline in body weight • Percentage of participants with allergic/hypersensitivity reactions
Notes	• Awaiting full publication. More information is required from the authors

Chacra 2017

Methods	This was a randomised, placebo-controlled, parallel-group, double-blind, multicentre, multinational study. Study duration was up to 69 weeks, including a 1-week screening period, an 8-week "wash-off" period (for patients on oral glucose-lowering agents at screening), a 2-week single-blind placebo run-in period, a 54-week double-blind treatment period consisting of a 24-week placebo-controlled period (Phase A) and a 30-week active-controlled period (Phase B) and a post-trial phone follow-up 28 days after final dose

Chacra 2017 *(Continued)*

Participants	• Number: 213 patients • Setting: multinational; 109 centres in Australia, North America, Europe, Asia, Israel and Russia • Inclusion criteria: male or female ≥ 30 years with type 2 DM; moderate kidney impairment (eGFR ≥ 30 to < 60 mL/min/1.73 m^2) or severe CKD (eGFR < 30 mL/min/1.73 m^2), as determined by the MDRD formula, or ESKD on dialysis for at least 6 months; eligible patients were either (1) not on a glucose lowering agent (naive or off therapy for ≥ 12 weeks) with HbA1c ≥ 7.0% (53 mmol/mol) and ≤ 10.0% (86 mmol/mol); (2) on a single oral glucose lowering agent or low-dose dual oral combination glucose lowering agents (i.e. at ≤ 50% of maximum labelled dose of each agent) with an HbA1c of ≥ 6.5% (48 mmol/mol) and ≤ 9.0% (75 mmol/mol); or (3) on a stable insulin regimen, at a dose of at least 15 U/d, for ≥ 10 weeks, with no oral glucose lowering agent and HbA1c ≥ 7.5% (58 mmol/mol) and ≤ 10.0% (86 mmol/mol) and FBG > 7.22 mmol/L, subjects on oral glucose lowering agents therapy had their medication discontinued ("washed-off") • Exclusion criteria: type 1 DM; history of ketoacidosis; C-peptide level < 0.7 ng/mL; active liver disease; significant CVD; a haematological disorder; a history of malignancy; treated with any incretin mimetic or thiazolidinedione within the prior 12 weeks of screening, or with omarigliptin at any time prior to signing informed consent
Interventions	Treatment group • Omarigliptin Control group • Matching placebo.
Outcomes	• Changes from baseline in HbA1c and FBG • Percentages of subjects at HbA1c goal of <7.0% (53 mmol/mol)
Notes	

Chan 2011

Methods	Randomised double-blind placebo-controlled study over 8 weeks
Participants	• Country: Australia • Setting: multi-centre, from the Perth Renal Units • Inclusion criteria: CKD stages 3 and 4 (eGFR 20 to 60 mL/min/1.73 m^2 by the MDRD equation; 18 to 75 years; non-diabetic and non-insulin requiring type 2 DM patients; patients who were current smokers, and on antiplatelet and antihypertensive agents were included • Number: treatment group (36); control group (35) * 16 patients had both DM and CKD (eGFR < 60 mL/min/1.73 m^2) • Mean age ± SD (years)**:** treatment group (62 ± 10); control group (62 ± 10) • Sex (M/F)**:** treatment group (24/11); control group (26/9) • Exclusion criteria: Type 1 DM; nephrotic-range proteinuria; liver enzymes > 2 times ULN; alcohol consumption > 3 standard drinks/d; cardiovascular event or unstable CVD; symptomatic or NYHA Stage 3 or 4 heart failure; Hb < 100 g/L; significant psychiatric disorder; active infection or inflammation; pregnancy or planning a pregnancy; currently receiving a glucagon-like peptide-1 analogue for glycaemic control of type 2 DM at screening
Interventions	Treatment group • Rosiglitazone: 4 mg/d Control group • Matching placebo

Chan 2011 *(Continued)*

Outcomes	• Endothelial function as assessed by post-ischaemic flow mediated dilatation of the brachial artery • Systemic arterial compliance as assessed by small artery compliance (C1) and large artery compliance (C2) • Arterial stiffness as assessed by augmentation index • Pulse wave velocity • Insulin resistance as measured by the HOMA score • Lipid and lipoprotein profile (cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), apolipoprotein B and A-I) adipocytokine (adiponectin); in vivo markers of inflammation; high-sensitivity CRP, high-sensitivity interleukin 6 and endothelial function; 24 hour ambulatory BP monitoring
Notes	Awaiting data from authors for patients with an eGFR < 60 mL/min/1.73m^2 and with DM

DEVOTE 2017

Methods	Multinational, treat-to-target, randomised, double-blind, active comparator–controlled cardiovascular outcomes trial
Participants	• Country: 20 countries in North America, South America, Europe, Asia, and South Africa • Setting: multicentre (438 sites) • Inclusion criteria: type 2 DM treated with ≥ 1 oral or injectable antihyperglycaemic therapy, HbA1c ≥ 7.0% (53 mmol/mol) or HbA1c < 7.0%, if treated with ≥ 20 U/d of basal insulin; 2 cohorts were eligible for recruitment into the trial: * Prior CVD or history of moderate CKD cohort: ☐ ≥ 50 years and had a history of CVD or moderate CKD. Prior CVD was defined by any 1 of the following: MI; stroke or TIA (TIA); coronary, carotid, or peripheral revascularization; > 50% diameter stenosis found on angiography or other imaging modality of the coronary, carotid, or lower extremity arteries; history of symptomatic coronary heart disease documented by positive non-invasive stress test or unstable angina pectoris with ECG changes; asymptomatic cardiac ischaemia; NYHA class II to III congestive heart failure; OR * Moderate CKD (stage 3) defined as eGFR 30 to 59 mL/min per 1.73 m^2 using the CKD-EPI equation • No prior CVD cohort: * ≥ 60 years and did not have a history of CVD; OR * Moderate CKD but did have at least one of the following: microalbuminuria or proteinuria; hypertension with left ventricular hypertrophy; left ventricular systolic and diastolic dysfunction as defined by the investigator; or an abnormal ankle-brachial index of < 0.9 • Number: treatment group (2701); control group (2679) * eGFR < 60 mL/min/1.73 m^2: treatment group (772); control group (793) • Exclusion criteria: acute coronary or cerebrovascular event in the previous 60 days; planned coronary, carotid or peripheral artery revascularization; chronic heart failure NYHA class IV.; current HD or PD or eGFR < 30 mL/min per 1.73 m^2 per CKD-EPI; end-stage liver disease, defined as the presence of acute or chronic liver disease and recent history of 1 or more of the following: ascites, encephalopathy, variceal bleeding, bilirubin ≥ 34.2 mmol/L; albumin ≤ 3.5 g/dL, prothrombin time ≥ 4 s prolonged, international normalized ratio ≥ 1.7 or prior liver transplant; known or suspected hypersensitivity to trial products or related products; female of child-bearing potential who is pregnant, breastfeeding or intends to become pregnant, or is not using adequate contraceptive methods as required by local law or practice; expected simultaneous participation in any other clinical trial of an investigational medicinal product; receipt of any investigational medicinal product within 30 days before randomisation
Interventions	Treatment group 1 • Insulin degludec: 100 U/mL

DEVOTE 2017 *(Continued)*

	Treatment group 2 • Insulin glargine: 100 U/mL Identical 100 U/mL, 10 mL vials
Outcomes	• Time from randomisation to the first occurrence of a 3-component MACE consisting of cardiovascular death, nonfatal MI, or nonfatal stroke • Severe hypoglycaemia, defined according to contemporary ADA criteria, as an episode requiring assistance from another person or an episode temporally associated with an accident, convulsion, or death • Time from randomisation to all-cause death, the frequency of serious adverse events, and the frequency of adverse events leading to discontinuation of the investigational product. • The change from baseline to the final assessment of HbA1c, FBG, BP, pulse rate, lipid profile, weight, BMI, eGFR, as well as basal and bolus insulin dose at the end of the trial
Notes	Information for the subgroup of patients with an eGFR < 60 mL/min/1.73 m^2 is required from the authors

EXAMINE 2011

Methods	Multicenter, prospective, randomised, double-blind trial over 4.75 years
Participants	• Country: 49 countries in North America, South America, Europe, Asia, and South Africa • Setting: multicentre (898 sites) • Inclusion criteria: diagnosis of type 2 DM; receiving monotherapy or combination antidiabetic therapy with a glycosylated haemoglobin level between 6.5% and 11.0%, inclusive, at screening (between 7.0 and 11.0%, inclusive, if the participant's antidiabetic regimen includes insulin); diagnosis of acute coronary syndrome within 15 to 90 days prior to randomisation • Number: treatment group (2701); control group (2679) * eGFR < 60 mL/min/1.73 m^2: treatment group (772); control group (793) • Median age: treatment group (61.0); control group (61.0) • Sex (M/F): treatment group (1828/873); control group (1823/856) • Exclusion criteria: signs of type 1 DM; currently receiving a glucagon-like peptide-1 analogue for glycaemic control of type 2 DM at screening; received a dipeptidyl peptidase-4 inhibitor for either more than 14 days total or within the 3 months prior to screening
Interventions	Treatment group • Oral alogliptin: 25 mg once/d for participants with normal or mildly impaired kidney function as defined by eGFR ≥ 60 mL/min) • Oral alogliptin 12.5 mg once/d for participants with moderately impaired kidney function (eGFR ≥ 30 and < 60 mL/min) • Oral alogliptin 6.25 mg once/d for participants with severely impaired kidney function or ESKD (eGFR < 30 mL/min) • Participants continued to receive standard care for CVD and DM according to regional guidelines. Control group • Oral alogliptin placebo matching tablets: once/d • Participants continued to receive standard care for CVD and DM according to regional guidelines.
Outcomes	• Composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke • Primary composite outcome with the addition of urgent revascularization due to unstable angina within 24 hours after hospital admission • Death from cardiovascular causes and death from any cause

EXAMINE 2011 *(Continued)*

	• Angioedema, hypoglycaemia, pancreatitis, cancer, and the results of laboratory testing
Notes	Further data for those patients with an eGFR < 60 mL/min/1.73 m^2 were not available at the moment but will be published

LEADER 2017

Methods	Multicenter, randomised double-blind, placebo-controlled trial with a median follow-up of 3.8 years
Participants	• Countries: 32 countries • Setting: Multi-national (410 sites) • Inclusion criteria: patients with type 2 DM who had HbA1c of 7.0% or more if they either had not received drugs for this condition previously or had been treated with one or more oral antihyperglycaemic agents or insulin (human neutral protamine Hagedorn, long-acting analogue, or premixed) or a combination of these agents; aged ≥ 50 years with at least one cardiovascular coexisting condition (coronary heart disease, cerebrovascular disease, peripheral vascular disease, CKD of stage 3 or greater, or chronic heart failure of NYHA class II or III); OR age ≥ 60 years with at least one cardiovascular risk factor, as determined by the investigator (microalbuminuria or proteinuria, hypertension and left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction, or an ankle–brachial index (the ratio of the SBP at the ankle to the SBP in the arm) of less than 0.9) • Number: 9340; 2158 patients had an eGFR < 60 mL/min/1.73 m^2 • Exclusion criteria: type 1 DM; use of GLP-1–receptor agonists, dipeptidyl peptidase 4 (DPP-4) inhibitors, pramlintide, or rapid-acting insulin; familial or personal history of multiple endocrine neoplasia type 2 or medullary thyroid cancer; acute coronary or cerebrovascular event within 14 days before screening and randomisation
Interventions	Treatment group • Liraglutide Control group • Placebo
Outcomes	• Composite outcome in the time-to-event analysis of the first occurrence of death from cardiovascular causes, nonfatal (including silent) MI, or nonfatal stroke • An expanded composite cardiovascular outcome (death from cardiovascular causes, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalisations for unstable angina pectoris or heart failure) • Death from any cause • A composite kidney and retinal microvascular outcome (nephropathy defined as the new onset of macroalbuminuria or a doubling of the SCr level and an eGFR of ≤ 45 mL/min/1.73 m^2), the need for continuous RRT, or death from kidney disease; retinopathy defined as the need for retinal photocoagulation or treatment with intravitreal agents, vitreous haemorrhage, or the onset of diabetes-related blindness) • HbA1c • Neoplasms • Pancreatitis
Notes	

Li 2012b

Methods	Randomised cross-over trial. Randomly assigned to receive either oral pioglitazone 15 mg once daily or no pioglitazone for 12 weeks then, after a 4-week washout, the patients were switched to the alternative regimen
Participants	• Country: China • Setting: single centre • Inclusion criteria: > 20 years; DM (HbA1c > 10% (86 mmol/mol)) or no diagnosis of DM; never received glitazones; serum triglyceride (> 1.8 mmol/L); > 1 month of treatment of regular continuous ambulatory PD • Number: 36 • Mean age ± SD: 64 ± 11 years • Sex (M/F): 12/24 • Exclusion criteria: not reported
Interventions	Treatment group • Oral pioglitazone 15 mg once daily for 12 weeks, and then after a washout period of 4 weeks, they received no pioglitazone for 12 weeks. Control group • No pioglitazone for 12 weeks, and then after a washout period of 4 weeks, they received pioglitazone for 12 weeks Both groups • Food intake was recorded in a continuous self-completed 3-day food diary every 6 weeks • All patients were under the direction of a dietitian and were instructed to eat a low-lipid diet and to take more exercise
Outcomes	• Change in serum triglycerides • Changes in serum cholesterol, LDL, HDL, HOMA-IR, adipocytokines, and CRP
Notes	Awaiting reply to authors for patients with both DM and on PD (n = 10). Wrote to the authors on 6/2/17

MARLINA-T2D 2015

Methods	Randomised, double-blind parallel group trial
Participants	• Inclusion criteria: diagnosis of type 2 DM; HbA1c between 6.5 and 10% (48 and 86 mmol/mol); current therapy with ACEi or ARB at stable dose for 10 weeks; UACR 30-3000 mg/g creatinine 3.39-339 mg/mmol to documented in the previous 12 months or detected at screening; eGFR > 30 mL/min; 18 and 80 years • Exclusion criteria: dual or triple blockade of the RAS; uncontrolled hyperglycaemia; MAP > 110 mmHg; known hypersensitivity or allergy to the investigational product, or their excipients (including matching placebos); treatment with a glitazone within 6 months prior to informed consent; treatment with a DPP-4 inhibitor, a glucagon-like peptide-1 agonist, a sodium/glucose cotransporter 2 inhibitor, a dopamine-agonist, a bile-acid sequestrant a short acting (prandial) insulin or premixed insulin within 10 weeks prior to informed consent; treatment with anti-obesity drugs 10 weeks prior to informed consent; alcohol or drug abuse within 3 months prior to informed consent that would interfere with trial participation or any ongoing condition leading to a decreased compliance to study procedures or study drug intake in the opinion of the investigator; current treatment with systemic steroids (glucocorticoids) at time of informed consent or change in dosage of thyroid hormones within 6 weeks prior to informed consent; participation in another trial with an investigational drug within 2 months prior to informed consent

MARLINA-T2D 2015 *(Continued)*

Interventions	Treatment group • Linagliptin: 5 mg/d Control group • Matching placebo
Outcomes	Change from baseline in HbA1c at 24 weeks Time weighted average of percentage change from baseline in UACR at 24 weeks
Notes	Information for the subgroup of patients with an eGFR < 60 mL/min/1.73 m^2 is required from the authors

NCT00846716

Methods	Randomised, open-label parallel group trial of pioglitazone added on to a sulphonylurea or biguanide versus a sulphonylurea or biguanide
Participants	• Inclusion criteria: Type 2 DM; HbA1c < 8.0%(64 mmol/mol); creatinine < 300 mg/g (33.9 mg/mmol) of urinary albumin level; concomitant therapy with sulphonylurea and/or biguanide; untreated hypertension and hypertension treated with ARB or ACEi • Exclusion criteria: history of heart failure and concomitant heart failure; history of administration of thiazolidinedione agent; severe hepatic dysfunction with more than 3 times higher than ULN range of GOT, GPT or rGPT; severe kidney dysfunction creatinine > 221 µmol/L; history of AE with thiazolidinedione agent; insulin treatment; concomitant UTI
Interventions	Treatment group 1 • Pioglitazone • Sulphonylurea or biguanide Treatment group 2 • Sulphonylurea or biguanide
Outcomes	• Onset or progression of DKD • Progression of DM; change in HbA1c; change in UACR change in GFR; change in cystatin C
Notes	The recruitment status of this study is unknown. The completion date has passed and the status has not been verified in more than two years. The study is not published. Written to authors 3 March 2017. Awaiting response.

Neff 2016

Methods	RCT
Participants	• Inclusion criteria: type 2 DM with a HbA1c of 42-75 mmol/mol (6-9% DCCT); Male or female aged > 30 years; negative pregnancy test at screening (women of child bearing potential only); BMI ≥ 25 kg/m^2 on a RAS antagonist, at a stable dose, for at least 8 weeks before inclusion into the study; established microalbuminuria; eGFR ≥ 30 mL/min/1.73m^2 MDRD formula. • Exclusion criteria: any cognitive impediment that preclude the patient from giving free and informed consent; DPP-4 inhibitors or thiazolidinedione treatment; stage 4-5 CKD, defined as an eGFR ≤ 30 mL/min/1.73m^2; used a GLP-1 agent in the last 6 months; female patients of child

Neff 2016 *(Continued)*

	bearing potential who are pregnant, breastfeeding, or unwilling to practice an acceptable barrier and/or hormonal method of contraception or abstinence during participation in the study; previous pancreatitis; hypersensitivity to Glucagon-like peptide-1 analogues; proliferative diabetic retinopathy; any other contraindications, as per the summary of product characteristics for liraglutide; any other clinical condition or prior therapy that, in the opinion of the investigator, would make the patient unsuitable for the study or unable to comply with the dosing requirements.; on current treatment with an investigational drug or participation in another clinical trial; use of an investigational drug within 4 weeks or 5 half-lives, whichever is longer, preceding the first dose of investigational medicinal product
Interventions	Treatment group • Liraglutide: 0.6 mg/d Control group • Standard diabetes care including renin angiotensin aldosterone inhibitor or antagonist
Outcomes	• Monocyte chemoattractant protein-1:creatinine ratio in urine up to 26 weeks • UACR up to 26 weeks; other bio markers including sCD163 in serum • Safety in all participants as measured by adverse event rate
Notes	Further details are required from the authors. The complete manuscript has not been published yet.

Ott 2016

Methods	Double-blind, parallel-group, investigator-initiated RCT
Participants	• Inclusion criteria: Type 2 DM; males and females (female participants had to have a negative pregnancy test before and during the study period); aged 18 and 65 years • Exclusion criteria: use of insulin, thiazolidinedione or DPP-4 inhibitor within the last 3 months or use of any other oral glucose-lowering drug that could not be discontinued for the study period; HbA1c > 10% (86 mmol/mol); UACR > 11.3 mg/mmol (> 100 mg/g); eGFR < 45 mL/min/1.73m^2; cardio- and cerebrovascular event within the previous 6 months
Interventions	Treatment group • Linagliptin: 5 mg/d Control group • Placebo
Outcomes	The primary objective was to assess endothelial function of the renal vasculature, by constant-infusion input clearance and UACR, both before and after blockade of nitric oxide synthase with NG-monomethyl-L-arginine
Notes	Further details regarding the subpopulation of patient with an eGFR < 60 mL/min/1.73m^2 are required from the authors

SUSTAIN-6 2016

Methods	Multi-national, double-blind, placebo-controlled, parallel-group RCT

SUSTAIN-6 2016 *(Continued)*

Participants	• Country: 20 countries • Setting: multinational (230 sites) • Inclusion criteria: patients with type 2 DM and a HbA1c ≥ 7% were eligible if they had not been treated with a glucose-lowering agent or had been treated with no more than 2 oral antihyperglycaemic agents, with or without basal or premixed insulin; aged ≥ 50 years with established CVD (previous cardiovascular, cerebrovascular, or peripheral vascular disease), chronic heart failure (NYHA class II or III), or CKD of stage 3 or higher OR aged ≥ 60 years with at least one cardiovascular risk factor • Number: 3297 randomised; 2358 patients had an eGFR < 60 mL/min/1.73m^2 • Exclusion criteria: treatment with a DPP-4 inhibitor within 30 days before screening or with a glycogen-like peptide-1 receptor agonist or insulin other than basal or premixed within 90 days before screening; history of an acute coronary or cerebrovascular event within 90 days before randomisation; planned revascularization of a coronary, carotid, or peripheral artery; long-term dialysis
Interventions	Treatment group • Semaglutide: 0.5 mg or 1.0 mg once/week for 104 weeks Control group • Placebo
Outcomes	• First occurrence of death from cardiovascular causes, nonfatal MI (including silent), or nonfatal stroke • First occurrence of an expanded composite cardiovascular outcome (death from cardiovascular causes, nonfatal MI, nonfatal stroke, revascularization (coronary or peripheral), and hospitalisation for unstable angina or heart failure), an additional composite outcome (death from all causes, nonfatal MI, or nonfatal stroke), the individual components of the composite outcomes, retinopathy complications, and new or worsening nephropathy. • Serious and non serious adverse events and hypoglycaemic episodes, which were defined as severe (according to ADA criteria 6) or as confirmed on analysis of plasma glucose (with symptomatic hypoglycaemia defined as < 56 mg/dL (3.1 mmol/L • Neoplasm and pancreatitis events
Notes	Further details regarding the subpopulation of patient with an eGFR < 60 mL/min/1.73m^2 are required from the authors

von Scholten 2017

Methods	Double-blind, placebo-controlled, cross-over RCT running for 28 weeks.
Participants	• Country: Denmark • Setting: single centre • Inclusion criteria: patients with type 2 DM (WHO criteria); HbA1c ≥ 48 mmol/mol (6.5%); persistent albuminuria (≥ 30 mg/g creatinine (3.39 mg/mmol) in at least 2 out of 3 consecutive morning spot urine samples) and who were receiving stable RAS-blocking treatment • Number (randomised/completed): 32/27 • Mean age ± SD: 65 ± 7 years • Sex (M/F): 22/5 • Exclusion criteria: diagnosis of clinical heart failure; eGFR ≤ 30 mL/min/1.73 m^2
Interventions	Treatment group • Liraglutide

von Scholten 2017 *(Continued)*

	• Standard therapy Control group • Placebo • standard therapy After 12 weeks of treatment, patients underwent a 4-week washout period prior to crossing over to the other treatment group for 12 weeks. Participants attended a baseline examination visit and were instructed in SC injection of the study drug. Participants were treated with liraglutide/placebo 0.6 mg/d for 7 days, escalated to 1.2 mg/d for 7 days and lastly to 1.8 mg/d for the remaining 10 weeks or matching placebo
Outcomes	• Change in UAER after 12 weeks of liraglutide treatment compared with placebo treatment • The effect of liraglutide treatment on measured GFR (51Cr-EDTA) and RAS hormones in plasma (renin, renin activity, angiotensin II and aldosterone) • 24-hour SBP, 24-hour DBP, 24-hour heart rate and fractional albumin clearance
Notes	Written to authors for the subgroup analysis for those patients with an eGFR < 60. There were 11 patients with an eGFR < 60. We are awaiting reply from authors for the sub-analysis

Xie 2006

Methods	No details available
Participants	No details available
Interventions	No details available
Outcomes	No details available
Notes	Unable to obtain a copy of the study

ACEi - angiotensin-converting enzyme inhibitor; ADA - American Diabetes Association; AE - adverse event/s; ARB - angiotensin receptor blocker; BMI - body mass index; BP - blood pressure; CKD - chronic kidney disease; CKD-EPI - CKD-Epidemiology Collaboration; CrCl - creatinine clearance; CRP - C-reactive protein; CVD - cardiovascular disease; DBP - diastolic blood pressure; DKD - diabetic kidney disease; DM - diabetes mellitus; DPP-4 - dipeptidyl-peptidase 4; ECG - electrocardiogram; (e)GFR - (estimated) glomerular filtration rate; ESKD - end-stage kidney disease; FBG - fasting blood glucose; GOT - glutamic oxaloacetic transaminase; GPT - glutamic pyruvic transaminase; Hb - haemoglobin; HbA1c - haemoglobin A1c (glycated); HD - haemodialysis; HOMA - homoeostasis model assessment; MACE - Major Adverse Cardiac Events; MAP - mean arterial pressure; MI - myocardial infarction; NYHA - New York Heart Association; PD - peritoneal dialysis; RAS - renin-angiotensin system; RCT - randomised controlled trial; RRT - renal replacement therapy; SBP - systolic blood pressure; SCr - serum creatinine; SMPG - self-monitored plasma glucose; UACR - urinary albumin-creatinine ratio; UAER - urinary albumin excretion rate; ULN - upper limit of normal; UTI - urinary tract infection

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

CARMELINA 2017

Trial name or title	Cardiovascular and renal microvascular outcome study with linagliptin in patients with type 2 diabetes mellitus (CARMELINA)
Methods	Parallel group, double-blind RCT
Participants	Inclusion criteria • Type 2 DM

CARMELINA 2017 *(Continued)*

- Male or female patients who are drug-naive or pre-treated with any antidiabetic background medication, excluding treatment with glycogen-like peptide-1 receptor agonists, DPP-4 inhibitors or sodium-glucose co-transporter-2 inhibitors if ≥ consecutive 7 days
- Stable antidiabetic background medication (unchanged daily dose) for at least 8 weeks prior to randomisation. If insulin is part of the background therapy, the average daily insulin dose should not have changed by more than 10% within the 8 weeks prior to randomisation compared with the daily insulin dose at randomisation
- HbA1c of ≥ 6.5% (48 mmol/mol) and ≤ 10.0% (86 mmol/mol) at visit 1 (screening)
- Age ≥ 18 years at visit 1(screening); for Japan only: age ≥ 20 years at visit 1
- BMI ≤ 45 kg/m^2 at visit 1 (screening)
- Signed and dated written informed consent by date of visit 1(screening) in accordance with Good Clinical Practice and local legislation prior to any study related procedure
- High risk of cardiovascular events defined by: 1) albuminuria (micro or macro) and previous macrovascular disease and/or 2) impaired kidney function with albuminuria

Exclusion criteria

- Type 1 DM
- Treatment (≥ 7 consecutive days) with glycogen-like peptide-1 receptor agonists, other DPP-4 inhibitors or sodium-glucose co-transporter-2 inhibitors prior to informed consent. Note: This also includes clinical trials where these glucose-lowering agents have been provided to the patient
- Active liver disease or impaired hepatic function, defined by serum levels of either ALT, AST, or ALP ≥ 3 x ULN as determined at visit 1
- eGFR < 15 mL/min/1.73 m^2 (severe CKD or ESKD, MDRD formula), as determined during screening at Visit 1 and/or the need for maintenance dialysis
- Any previous (or planned within next 12 months) bariatric surgery (open or laparoscopic) or intervention (gastric sleeve)
- Pre-planned coronary artery revascularisation or any previous ≤ 2 months prior informed consent
- Known hypersensitivity or allergy to the investigational products or its excipients
- Any previous or current alcohol or drug abuse that would interfere with trial participation in the opinion of the investigator
- Participation in another trial with an investigational drug ongoing or within 2 months prior to visit 1 (screening)
- Pre-menopausal women (last menstruation = 1 year prior to informed consent) who are nursing or pregnant, are of child-bearing potential and were not practicing an acceptable method of birth control (acceptable methods of birth control include tubal ligation, transdermal patch, intra uterine devices/systems (IUDs/IUSs), oral, implantable or injectable contraceptives, sexual abstinence (if allowed by local authorities), double barrier method and vasectomised partner) or do not plan to continue using acceptable method of birth control throughout the study and do not agree to submit to periodic pregnancy testing during participation in the trial
- Patients considered unreliable by the investigator concerning the requirements for follow up during the study and/or compliance with study drug administration, have a life expectancy less than 5 years for non-cardiovascular causes, or have cancer other than non-melanoma skin cancer within last 3 years, or has any other condition than mentioned which in the opinion of the investigator, would not allow safe participation in the study
- Acute coronary syndrome, diagnosed ≤ 2 months prior to visit 1 (screening).
- Stroke or TIA ≤ 3 months prior to visit 1 (screening)

Interventions	Treatment group • Linagliptin Control group • Placebo

CARMELINA 2017 *(Continued)*

Outcomes	• Time to the first occurrence of any of the following by adjudication confirmed components of the primary composite endpoint (3-point MACE): cardiovascular death, non-fatal MI, or non-fatal stroke (time frame: 54 months) • Time to the first occurrence of any of the following by adjudication confirmed components: composite kidney endpoint (death due to kidney disease, sustained ESKD, sustained decrease of 40% or more in eGFR) (time frame: 54 months)
Starting date	July 10 2013
Contact information	Boehringer Ingelheim
Notes	

NCT02547935

Trial name or title	An exploratory phase II/III, randomised, double-blind, placebo controlled, parallel design study to evaluate the efficacy, safety and pharmacodynamics of dapagliflozin and dapagliflozin in combination with saxagliptin in CKD patients with type 2 diabetes mellitus and albuminuria treated With ACEi or ARB
Methods	Double-blind randomised parallel group trial.
Participants	Inclusion criteria • Provision of informed consent prior to any study specific procedures • Female or male aged ≥ 18 years • History of type 2 DM for more than 12 months • HbA1c ≥ 7.0% (53 mmol/mol) and ≤11.0% (97 mmol/mol) • Stable antidiabetic treatment during the last 12 weeks up to randomisation • eGFR 25 to 75 mL/min/1.73 m^2, inclusive • Micro or macroalbuminuria (UACR 30 to 3500 mg/g (3.39 to 395.5 mg/mmol)) • Treatment with ACEi or an ARB for at least 3 months prior to screening • BMI between 20 and 45 kg/m^2 Exclusion criteria • Any of the following cardiovascular/vascular diseases within 3 month prior to signing the consent at Visit 1: MI, cardiac surgery or revascularization, unstable angina, unstable heart failure, NYHA Class III-IV, TIA or significant cerebrovascular disease unstable or previously undiagnosed arrhythmia • Significant hepatic disease, including, but not limited to, chronic active hepatitis and/or severe hepatic insufficiency • AST or ALT > 3 x ULN • Total bilirubin >2 mg/dL (34.2 µmol/L) • History of AKI requiring RRT (dialysis or ultrafiltration) or any biopsy or imaging verifying intercurrent kidney disease other than DKD or DKD with nephrosclerosis. • Ongoing treatment with a Sodium-glucose co-transporter-2 inhibitor, glycogen-like peptide-1 agonist or DPP-4 inhibitors • Any condition which, in the judgment of the Investigator, may render the patient unable to complete the study or which may pose a significant risk to the patient or patient suspected or with confirmed poor protocol or medication compliance
Interventions	Treatment group 1 • Dapagliflozin: 10 mg/d

NCT02547935 *(Continued)*

	Treatment group 2 • Dapagliflozin: 10 mg/d • Saxagliptin 2.5 mg/d Control group • Placebo tablets
Outcomes	• Change in HbA1c (dapagliflozin 10 mg + saxagliptin 2.5 mg) (time frame: up to 24 weeks of treatment); to compare the mean change from baseline to week 24 in HbA1c between dapagliflozin 10 mg plus saxagliptin 2.5 mg and placebo • Percent change in Urine albumin to creatinine ratio (UACR) (dapagliflozin 10 mg + saxagliptin 2.5 mg) (time frame: up to 24 weeks of treatment) • Mean percent change from baseline to week 24 in UACR between dapagliflozin 10 mg plus saxagliptin 2.5 mg and placebo • Percent change in UACR) (dapagliflozin 10 mg) (time frame: up to 24 weeks of treatment); to compare the mean percent change from baseline to week 24 in UACR between dapagliflozin 10 mg and placebo. • Percent change in total body weight (time frame: up to 24 weeks of treatment); to compare the mean percent change from baseline in total body weight between dapagliflozin 10 mg with and, separately, without saxagliptin 2.5 mg and placebo • Change in FBG (time frame: up to 24 weeks of treatment); to compare the mean change from baseline in FBG between dapagliflozin 10 mg with and, separately, without saxagliptin 2.5 mg and placebo • Proportion of patients that achieve 30% reduction in UACR (time frame: up to 24 weeks of treatment); to compare the proportion of patients achieving a 30% reduction in UACR between dapagliflozin 10 mg with and, separately, without saxagliptin 2.5 mg and placebo • Proportion of patients which achieve HbA1c < 7% (53 mmol/mol) (time frame: up to 24 weeks of treatment); to compare the proportion of patients achieving a reduction in HbA1c <7.0% (53 mmol/mol) between dapagliflozin 10 mg with and, separately, without saxagliptin 2.5 mg and placebo • Change in seated SBP (time frame: up to 24 weeks of treatment); to compare the mean change from baseline in seated SBP between dapagliflozin 10 mg with and, separately, without saxagliptin 2.5 mg and placebo • Change in HbA1c (time frame: up to 24 weeks of treatment); to compare the mean change from baseline in HbA1c between dapagliflozin 10 mg and placebo
Starting date	September 21, 2015
Contact information	AstraZeneca Clinical Study Information centre: 1-877-240-9479; information.center@astrazeneca.com
Notes	Currently recruiting participants.

NCT02608177

Trial name or title	Continuous glucose monitoring to assess glycaemia in chronic kidney disease - Changing glucose management (CANDY-CANE)
Methods	Interventional cross-over RCT
Participants	Inclusion criteria • Type 2 DM • eGFR 15 to 59 mL/min/1.73 m^2

NCT02608177 *(Continued)*	• HbA1c < 8% • Age ≥ 18 years • Current use of sulphonylureas Exclusion criteria • BMI > 40 kg/m^2 • Actively using continuous glucose monitoring for clinical care • ESKD needing dialysis • Kidney transplant • Pregnant or nursing • Unable to provide informed consent
Interventions	Linagliptin/glipizide • 4 weeks of study drug linagliptin followed by 4 weeks of glipizide Glipizide/linagliptin • 4 weeks of study drug glipizide followed by 4 weeks linagliptin
Outcomes	• Glucose time in range (time frame: 28 days) • Glycaemic variability (time frame: 28 days) • Hypoglycaemia (time frame: 28 days) • Biomarkers of systemic inflammation (time frame: 28 days). Measured by plasma C-reactive protein • Biomarkers of systemic inflammation (time frame: 28 days). Measured by plasma interleukin-6 • Biomarkers of oxidative stress (time frame: 28 days). Measured by plasma F2-isoprostanes • Biomarkers of oxidative stress (time frame: 28 days). Measured by urine F2-isoprostanes • Biomarkers of albuminuria (time frame: 28 days). Measured by UACR
Starting date	November 2015
Contact information	Ian de Boer, Associate Professor, Medicine/Nephrology, University of Washington
Notes	Currently recruiting participants

ACEi - angiotensin-converting enzyme inhibitor; AKI - acute kidney injury; ALT - alanine aminotransferase; ALP - alkaline phosphatase; ARB - angiotensin receptor blocker; AST - aspartate aminotransferase; BMI - body mass index; BP - blood pressure; CKD - chronic kidney disease; DKD - diabetic kidney disease; DM - diabetes mellitus; DPP-4 - dipeptidyl-peptidase 4; eGFR - estimated glomerular filtration rate; ESKD - end-stage kidney disease; HbA1c - haemoglobin A1c (glycated); MDRD - Modification of Diet in Renal Disease; MACE - Major Adverse Cardiac Events; MI - myocardial infarction; NYHA - New York Heart Association; RCT - randomised controlled trial; RRT - renal replacement therapy; SBP - systolic blood pressure; TIA - transient ischaemic attack; UACR - urinary albumin-creatinine ratio; ULN - upper limit of normal

DATA AND ANALYSES

Comparison 1. SGLT2 inhibitors versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 HbA1c	7	1092	Mean Difference (IV, Random, 95% CI)	-0.29 [-0.38, -0.19]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2 Fasting blood glucose	5	855	Mean Difference (IV, Random, 95% CI)	-0.48 [-0.78, -0.19]
3 Death (all causes)	5	2933	Risk Ratio (IV, Random, 95% CI)	0.78 [0.60, 1.02]
4 All cardiovascular death	4	2788	Risk Ratio (IV, Random, 95% CI)	0.78 [0.56, 1.10]
5 Myocardial infarction	4	2788	Risk Ratio (IV, Random, 95% CI)	0.63 [0.30, 1.34]
6 Stroke	5	2933	Risk Ratio (IV, Random, 95% CI)	0.96 [0.63, 1.48]
7 Heart failure	3	2519	Risk Ratio (IV, Random, 95% CI)	0.59 [0.41, 0.87]
8 Weight	5	1029	Mean Difference (IV, Random, 95% CI)	-1.41 [-1.80, -1.02]
9 eGFR [mL/min/1.73 m^2]	4	848	Mean Difference (IV, Random, 95% CI)	-1.85 [-2.76, -0.94]
10 Systolic blood pressure	7	1198	Mean Difference (IV, Random, 95% CI)	-4.68 [-6.69, -2.68]
11 Diastolic blood pressure	6	1142	Mean Difference (IV, Random, 95% CI)	-1.72 [-2.77, -0.66]
12 Serum creatinine	4	848	Mean Difference (IV, Random, 95% CI)	3.82 [1.45, 6.19]
13 Urinary albumin/creatinine ratio	5	1153	Mean Difference (IV, Random, 95% CI)	-8.14 [-14.51, -1.77]
14 Serum potassium	4	2443	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.05, 0.02]
15 Total cholesterol	2	529	Mean Difference (IV, Random, 95% CI)	0.09 [-0.05, 0.24]
16 HDL cholesterol	4	918	Mean Difference (IV, Random, 95% CI)	0.04 [0.01, 0.07]
17 LDL cholesterol	4	917	Mean Difference (IV, Random, 95% CI)	0.04 [-0.06, 0.14]
18 Triglyceride	4	918	Mean Difference (IV, Random, 95% CI)	0.01 [-0.11, 0.14]
19 Hypoglycaemia	7	3086	Risk Ratio (IV, Random, 95% CI)	0.88 [0.73, 1.07]
20 Discontinuation of medication due to adverse events	4	917	Risk Ratio (IV, Random, 95% CI)	0.86 [0.56, 1.32]
21 End-stage kidney disease	2	700	Risk Ratio (IV, Random, 95% CI)	0.71 [0.10, 4.98]
22 Hyperkalaemia	4	2788	Risk Ratio (IV, Random, 95% CI)	0.58 [0.42, 0.81]

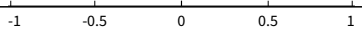
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
23 Hypoglycaemia requiring third party assistance	3	845	Risk Ratio (IV, Random, 95% CI)	0.47 [0.17, 1.28]
24 Hypovolaemia	6	3005	Risk Ratio (IV, Random, 95% CI)	1.07 [0.63, 1.84]
25 Fracture	5	2860	Risk Ratio (IV, Random, 95% CI)	0.81 [0.31, 2.10]
26 Diarrhoea	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
27 Diabetic ketoacidosis	2	1962	Risk Ratio (IV, Random, 95% CI)	1.00 [0.09, 11.02]
28 Upper respiratory tract infection	2	593	Risk Ratio (IV, Random, 95% CI)	0.79 [0.43, 1.44]
29 Urinary tract infection	7	3086	Risk Ratio (IV, Random, 95% CI)	1.09 [0.82, 1.43]
30 Genital infection	7	3086	Risk Ratio (IV, Random, 95% CI)	2.50 [1.52, 4.11]
31 Acute kidney injury	4	2788	Risk Ratio (IV, Random, 95% CI)	0.78 [0.61, 1.00]
32 Doubling of serum creatinine	2	700	Risk Ratio (IV, Random, 95% CI)	0.96 [0.49, 1.88]

Analysis 1.1. Comparison 1 SGLT2 inhibitors versus placebo, Outcome 1 HbA1c.

Study or subgroup	SGLT2i N	SGLT2i Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Kohan 2014	18	-0.9 (0.9)	8	-0.7 (0.8)		1.98%	-0.28[-0.95,0.39]
EMPA-REG BP 2015	34	-0.4 (0.6)	22	0.1 (0.6)		9.13%	-0.54[-0.85,-0.23]
Kaku 2014	47	-0.4 (0.6)	24	-0.1 (0.6)		11.65%	-0.28[-0.56,-0]
LANTERN 2015	58	-0.3 (0.6)	23	-0.1 (0.5)		13.45%	-0.19[-0.45,0.07]
Yale 2013	178	-0.3 (1)	87	0.1 (1)		14.29%	-0.33[-0.58,-0.08]
Haneda 2016	95	-0.1 (0.5)	50	0.1 (0.7)		17.7%	-0.2[-0.42,0.02]
EMPA-REG RENAL 2014	224	-0.2 (0.9)	224	0 (0.9)		31.81%	-0.29[-0.46,-0.12]
Total * **	**654**		**438**			**100%**	**-0.29[-0.38,-0.19]**

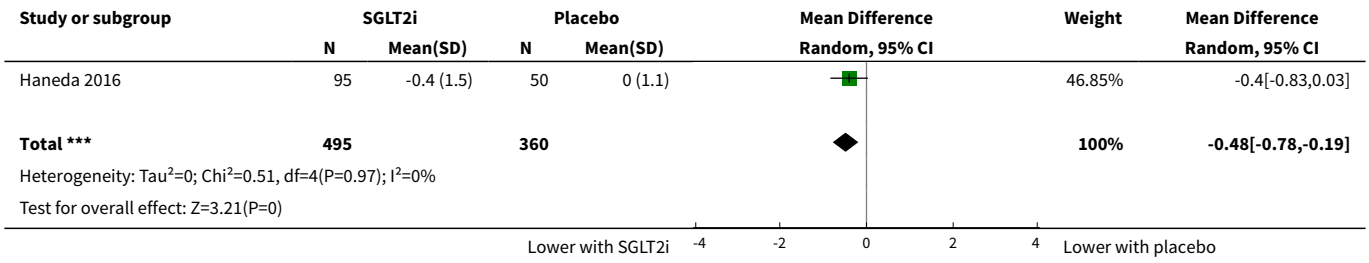
Heterogeneity: Tau^2=0; Chi^2=3.79, df=6(P=0.7); I^2=0%

Test for overall effect: Z=6(P<0.0001)

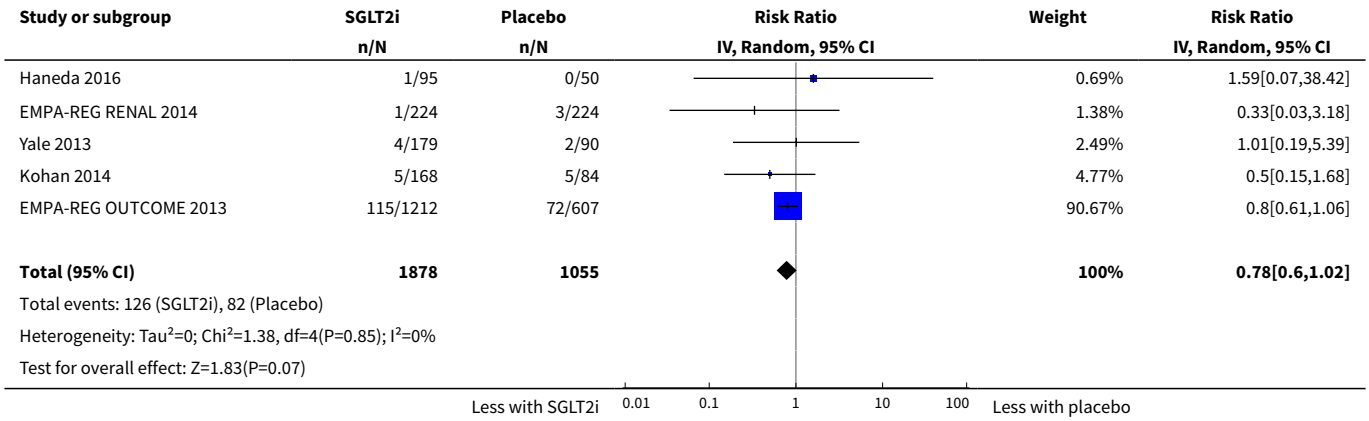


Analysis 1.2. Comparison 1 SGLT2 inhibitors versus placebo, Outcome 2 Fasting blood glucose.

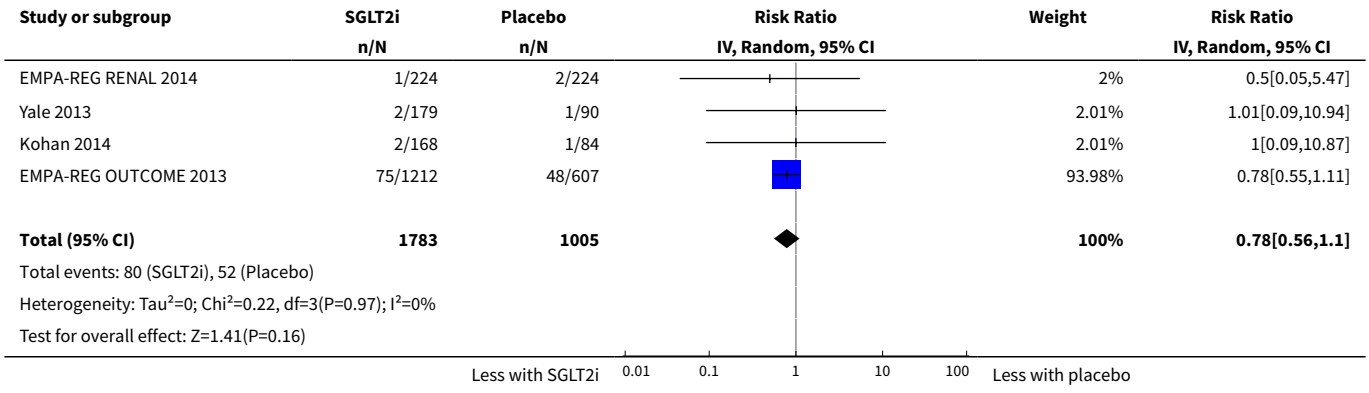
Study or subgroup	SGLT2i N	SGLT2i Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Kohan 2014	18	-1.4 (1.7)	8	-1 (3.8)		1.17%	-0.44[-3.17,2.29]
Zambrowicz 2015	14	-1.5 (1.6)	15	-1.1 (2.3)		4.31%	-0.39[-1.81,1.03]
Yale 2013	144	-0.1 (3.3)	63	0.3 (3.3)		9.41%	-0.39[-1.35,0.57]
EMPA-REG RENAL 2014	224	-0.3 (2.6)	224	0.3 (2.6)		38.25%	-0.62[-1.1,-0.14]



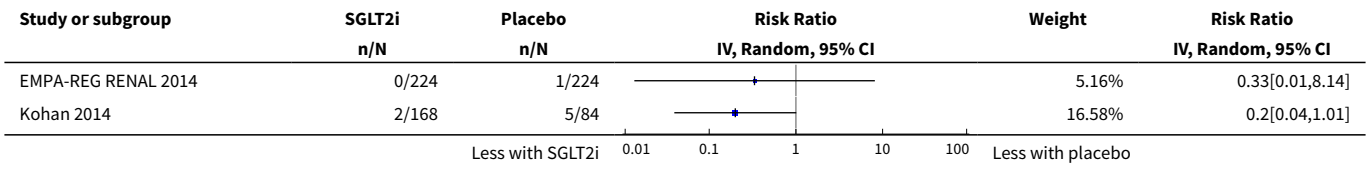
Analysis 1.3. Comparison 1 SGLT2 inhibitors versus placebo, Outcome 3 Death (all causes).

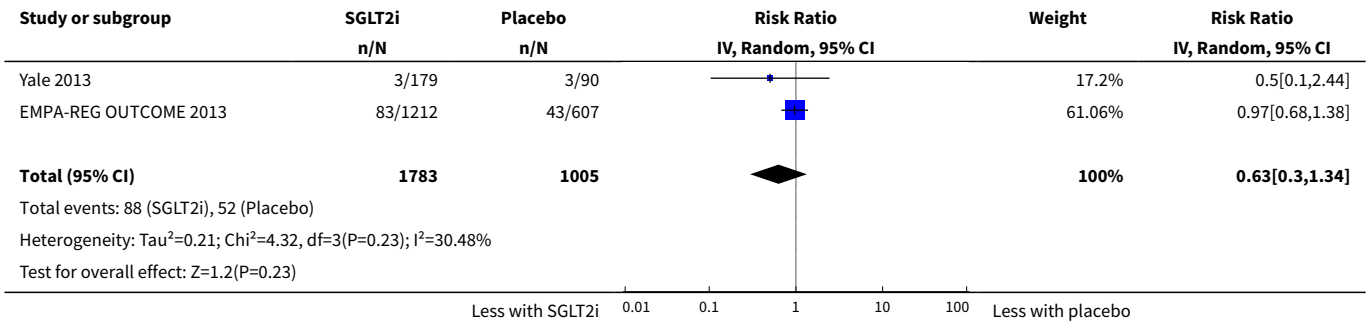


Analysis 1.4. Comparison 1 SGLT2 inhibitors versus placebo, Outcome 4 All cardiovascular death.

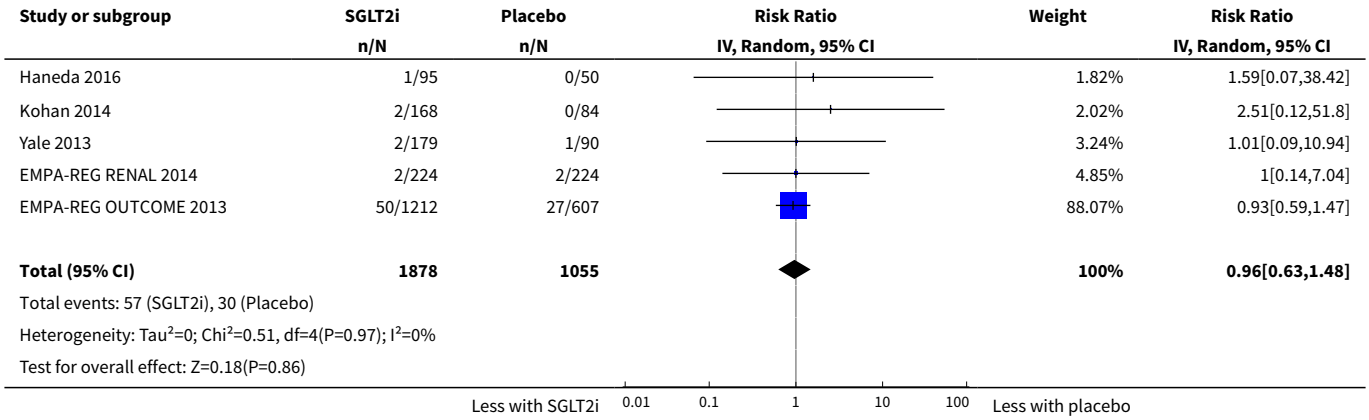


Analysis 1.5. Comparison 1 SGLT2 inhibitors versus placebo, Outcome 5 Myocardial infarction.

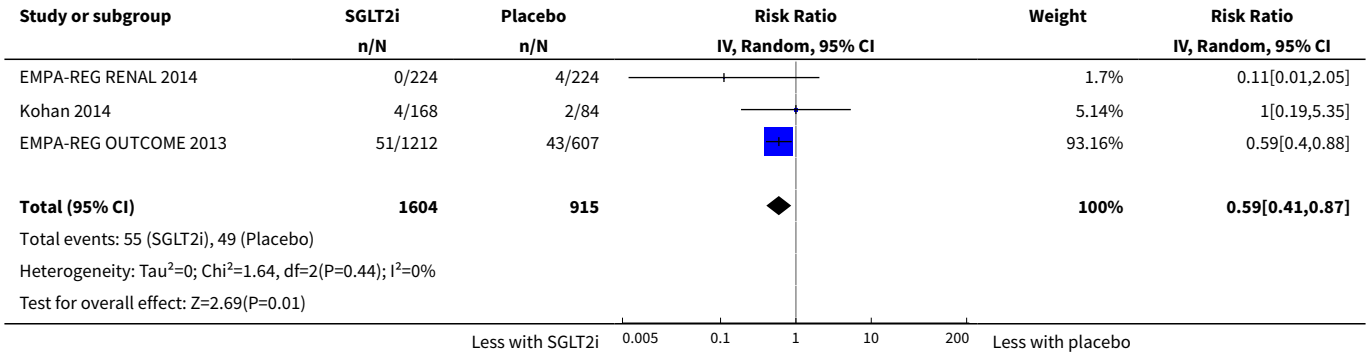




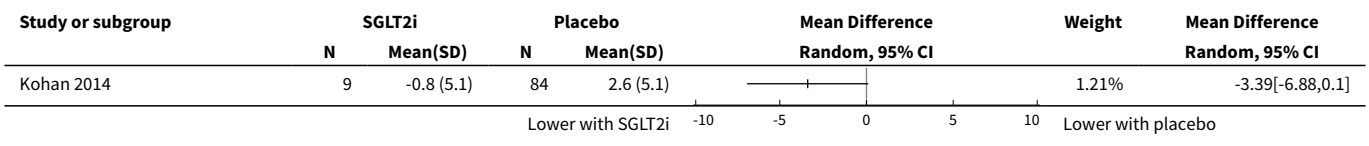
Analysis 1.6. Comparison 1 SGLT2 inhibitors versus placebo, Outcome 6 Stroke.

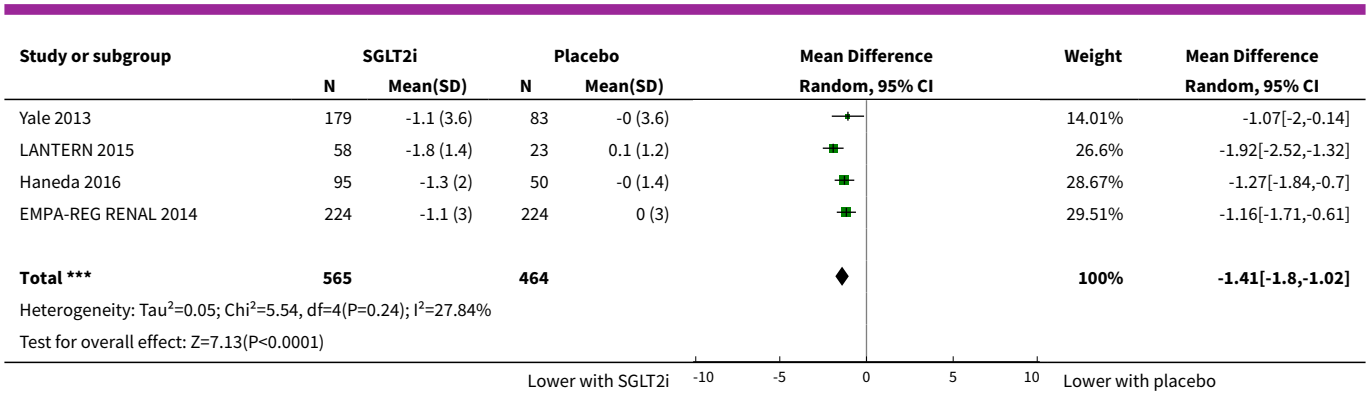


Analysis 1.7. Comparison 1 SGLT2 inhibitors versus placebo, Outcome 7 Heart failure.

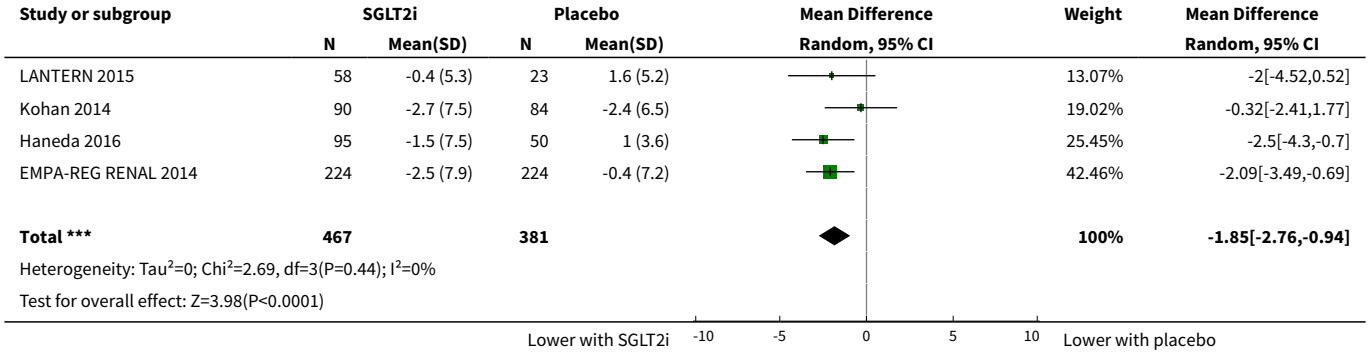


Analysis 1.8. Comparison 1 SGLT2 inhibitors versus placebo, Outcome 8 Weight.

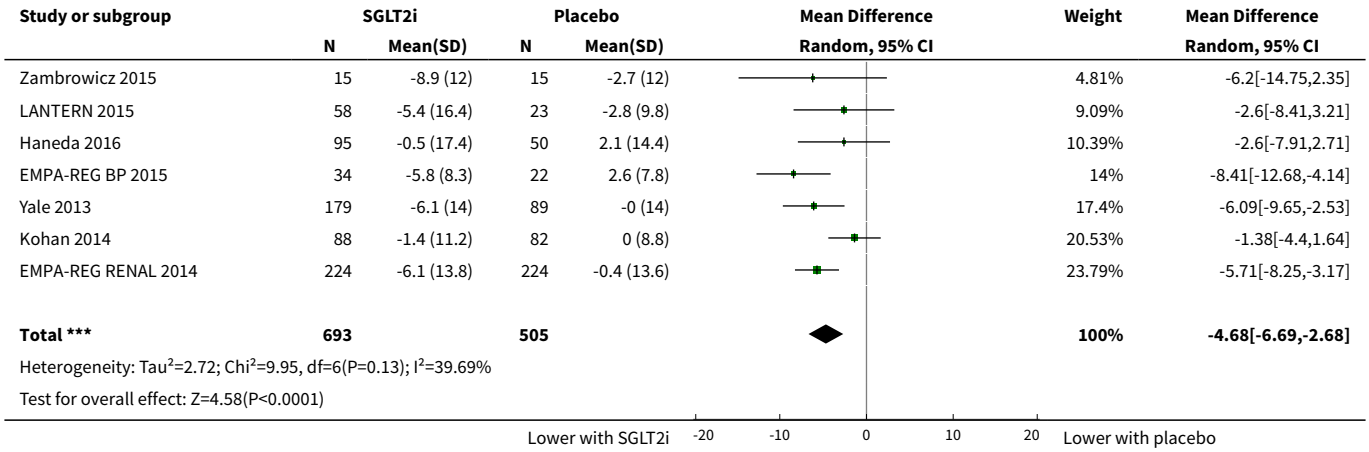




Analysis 1.9. Comparison 1 SGLT2 inhibitors versus placebo, Outcome 9 eGFR [mL/min/1.73 m^2].



Analysis 1.10. Comparison 1 SGLT2 inhibitors versus placebo, Outcome 10 Systolic blood pressure.



Analysis 1.11. Comparison 1 SGLT2 inhibitors versus placebo, Outcome 11 Diastolic blood pressure.

Study or subgroup	SGLT2i N	SGLT2i Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Kohan 2014	88	0.3 (19.3)	82	4.1 (15.6)		4.04%	-3.75[-9.01,1.51]
Zambrowicz 2015	15	-4.5 (6.6)	15	-1.9 (6.6)		4.98%	-2.6[-7.34,2.14]
LANTERN 2015	58	-1.6 (10.2)	23	-1.4 (9)		5.51%	-0.2[-4.71,4.31]
Haneda 2016	95	-0.9 (10)	50	-1.2 (10.8)		8.6%	0.3[-3.31,3.91]
Yale 2013	179	-2.2 (9.2)	89	-1.4 (9.1)		20.73%	-0.82[-3.14,1.5]
EMPA-REG RENAL 2014	224	-2.2 (7.6)	224	0 (7.6)		56.15%	-2.28[-3.69,-0.87]
Total ***	**659**		**483**			**100%**	**-1.72[-2.77,-0.66]**
Heterogeneity: Tau^2=0; Chi^2=3.53, df=5(P=0.62); I^2=0%							
Test for overall effect: Z=3.18(P=0)							

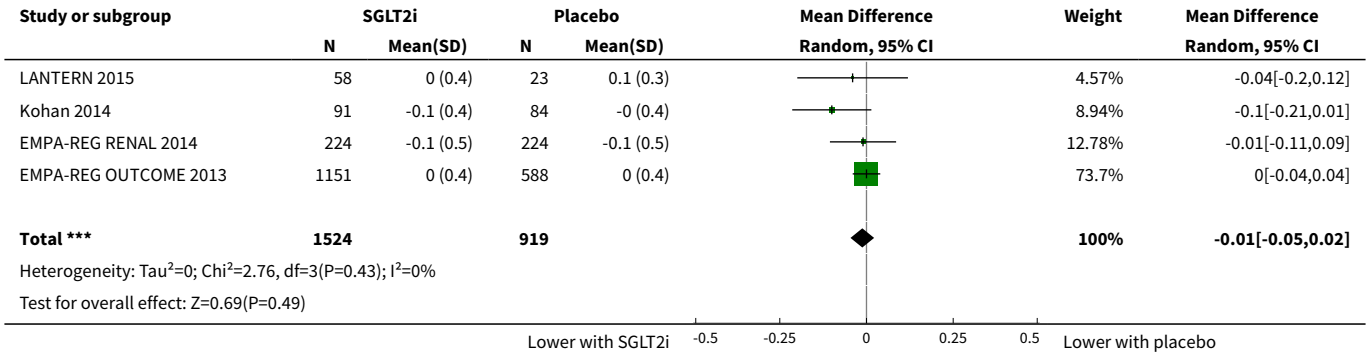
Analysis 1.12. Comparison 1 SGLT2 inhibitors versus placebo, Outcome 12 Serum creatinine.

Study or subgroup	SGLT2i N	SGLT2i Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Kohan 2014	90	8 (23.9)	84	8 (23)		10.74%	0[-6.96,6.96]
EMPA-REG RENAL 2014	224	11.5 (27.4)	224	2.7 (40.7)		12.46%	8.84[2.42,15.26]
LANTERN 2015	58	1.2 (10.4)	23	-2.3 (6.9)		29.48%	3.54[-0.36,7.44]
Haneda 2016	95	2.7 (8.8)	50	-0.9 (8)		47.32%	3.53[0.7,6.36]
Total ***	**467**		**381**			**100%**	**3.82[1.45,6.19]**
Heterogeneity: Tau^2=1; Chi^2=3.56, df=3(P=0.31); I^2=15.79%							
Test for overall effect: Z=3.16(P=0)							

Analysis 1.13. Comparison 1 SGLT2 inhibitors versus placebo, Outcome 13 Urinary albumin/creatinine ratio.

Study or subgroup	SGLT2i N	SGLT2i Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Kohan 2014	168	3.7 (136.6)	168	7.9 (82.7)		6.67%	-4.2[-28.35,19.95]
EMPA-REG RENAL 2014	224	-26.5 (103.6)	224	0.2 (105.3)		10.17%	-26.7[-46.04,-7.36]
Haneda 2016	95	4.8 (43.7)	50	7.7 (32.8)		22.01%	-2.9[-15.54,9.74]
Yale 2013	73	-0.7 (38.5)	70	8.7 (38)		22.33%	-9.4[-21.94,3.14]
LANTERN 2015	58	-4.2 (31.5)	23	2 (9.3)		38.82%	-6.2[-15.15,2.75]
Total ***	**618**		**535**			**100%**	**-8.14[-14.51,-1.77]**
Heterogeneity: Tau^2=6.31; Chi^2=4.51, df=4(P=0.34); I^2=11.36%							
Test for overall effect: Z=2.51(P=0.01)							

Analysis 1.14. Comparison 1 SGLT2 inhibitors versus placebo, Outcome 14 Serum potassium.

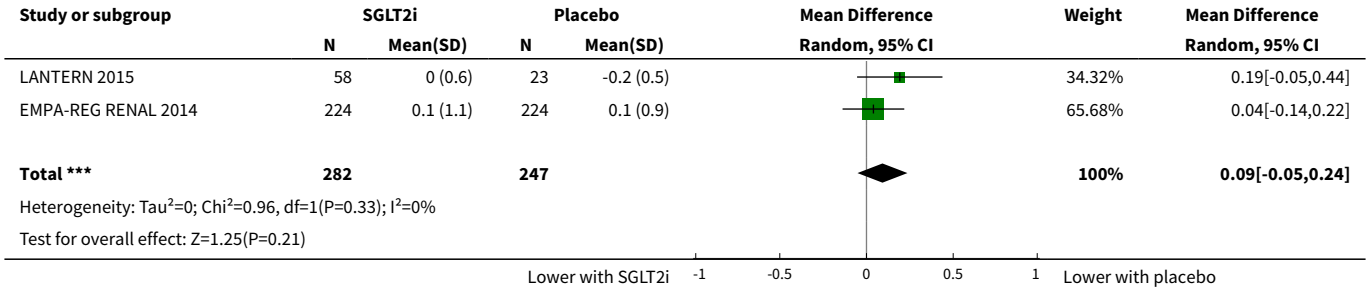


Study or subgroup	SGLT2i N	SGLT2i Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
LANTERN 2015	58	0 (0.4)	23	0.1 (0.3)		4.57%	-0.04[-0.2,0.12]
Kohan 2014	91	-0.1 (0.4)	84	-0 (0.4)		8.94%	-0.1[-0.21,0.01]
EMPA-REG RENAL 2014	224	-0.1 (0.5)	224	-0.1 (0.5)		12.78%	-0.01[-0.11,0.09]
EMPA-REG OUTCOME 2013	1151	0 (0.4)	588	0 (0.4)		73.7%	0[-0.04,0.04]
Total ***	**1524**		**919**			**100%**	**-0.01[-0.05,0.02]**

Heterogeneity: $Tau^2=0$; $Chi^2=2.76$, df=3(P=0.43); $I^2=0\%$

Test for overall effect: Z=0.69(P=0.49)

Analysis 1.15. Comparison 1 SGLT2 inhibitors versus placebo, Outcome 15 Total cholesterol.

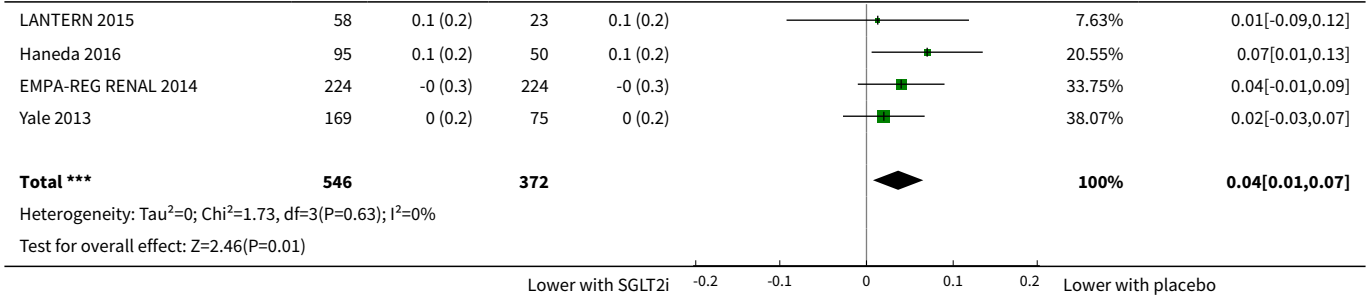


Study or subgroup	SGLT2i N	SGLT2i Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
LANTERN 2015	58	0 (0.6)	23	-0.2 (0.5)		34.32%	0.19[-0.05,0.44]
EMPA-REG RENAL 2014	224	0.1 (1.1)	224	0.1 (0.9)		65.68%	0.04[-0.14,0.22]
Total ***	**282**		**247**			**100%**	**0.09[-0.05,0.24]**

Heterogeneity: $Tau^2=0$; $Chi^2=0.96$, df=1(P=0.33); $I^2=0\%$

Test for overall effect: Z=1.25(P=0.21)

Analysis 1.16. Comparison 1 SGLT2 inhibitors versus placebo, Outcome 16 HDL cholesterol.

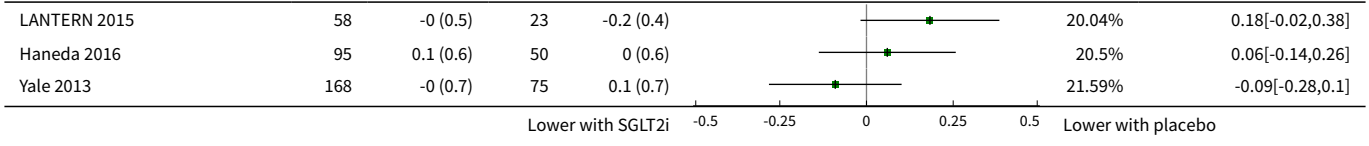


Study or subgroup	SGLT2i N	SGLT2i Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
LANTERN 2015	58	0.1 (0.2)	23	0.1 (0.2)		7.63%	0.01[-0.09,0.12]
Haneda 2016	95	0.1 (0.2)	50	0.1 (0.2)		20.55%	0.07[0.01,0.13]
EMPA-REG RENAL 2014	224	-0 (0.3)	224	-0 (0.3)		33.75%	0.04[-0.01,0.09]
Yale 2013	169	0 (0.2)	75	0 (0.2)		38.07%	0.02[-0.03,0.07]
Total ***	**546**		**372**			**100%**	**0.04[0.01,0.07]**

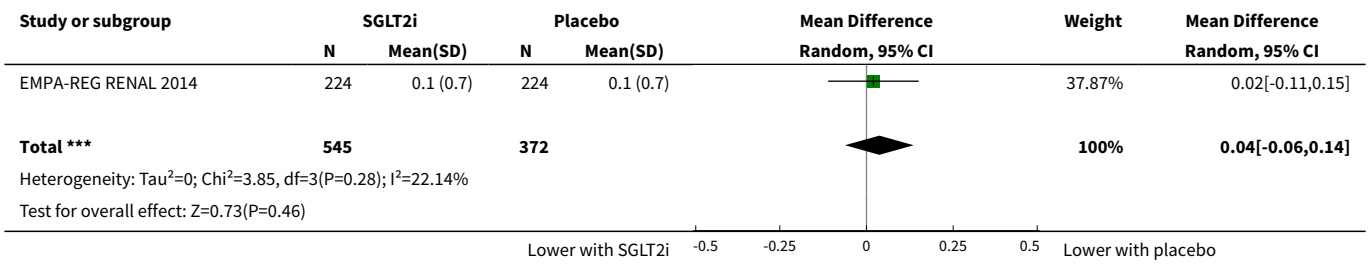
Heterogeneity: $Tau^2=0$; $Chi^2=1.73$, df=3(P=0.63); $I^2=0\%$

Test for overall effect: Z=2.46(P=0.01)

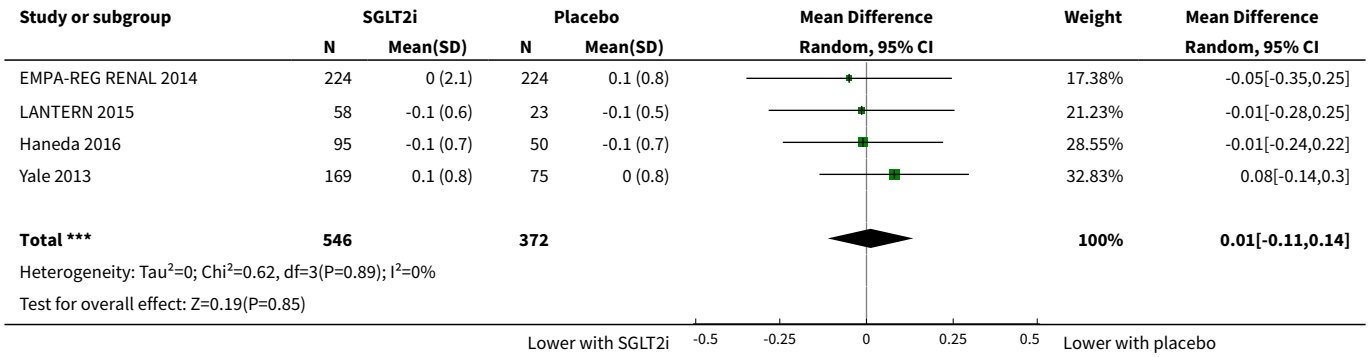
Analysis 1.17. Comparison 1 SGLT2 inhibitors versus placebo, Outcome 17 LDL cholesterol.



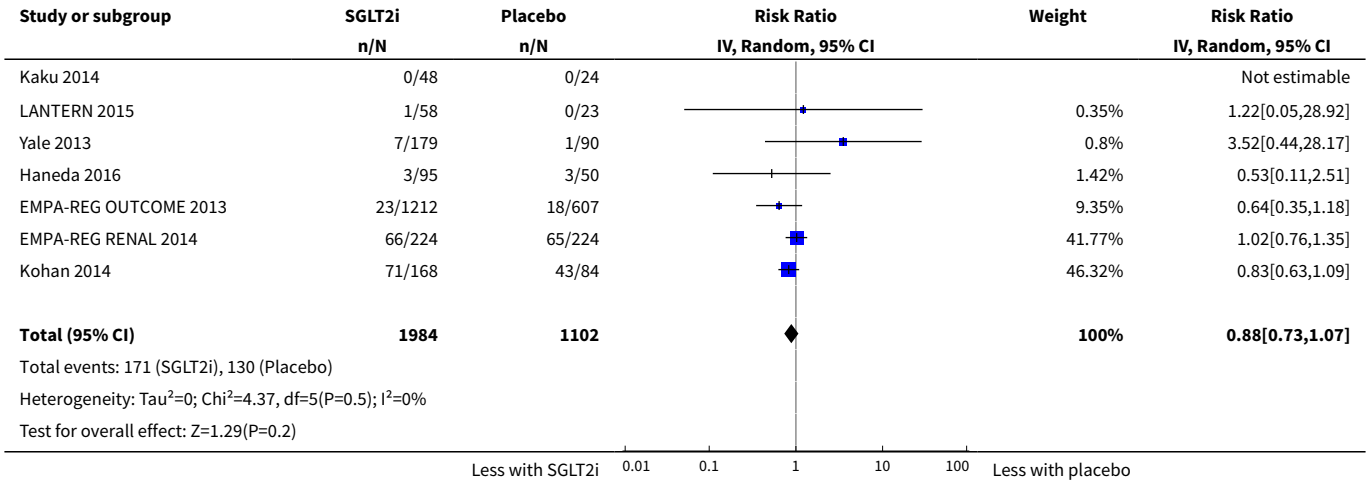
Study or subgroup	SGLT2i N	SGLT2i Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
LANTERN 2015	58	-0 (0.5)	23	-0.2 (0.4)		20.04%	0.18[-0.02,0.38]
Haneda 2016	95	0.1 (0.6)	50	0 (0.6)		20.5%	0.06[-0.14,0.26]
Yale 2013	168	-0 (0.7)	75	0.1 (0.7)		21.59%	-0.09[-0.28,0.1]



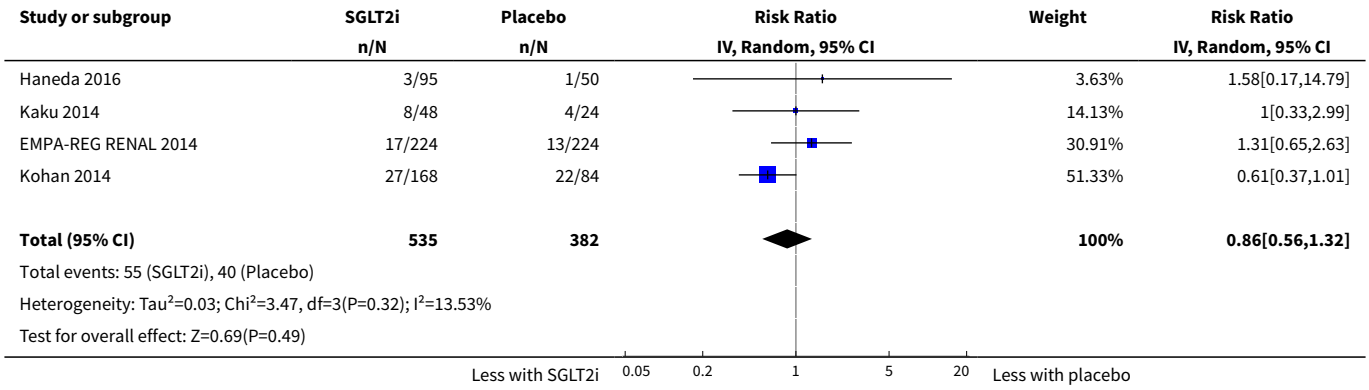
Analysis 1.18. Comparison 1 SGLT2 inhibitors versus placebo, Outcome 18 Triglyceride.



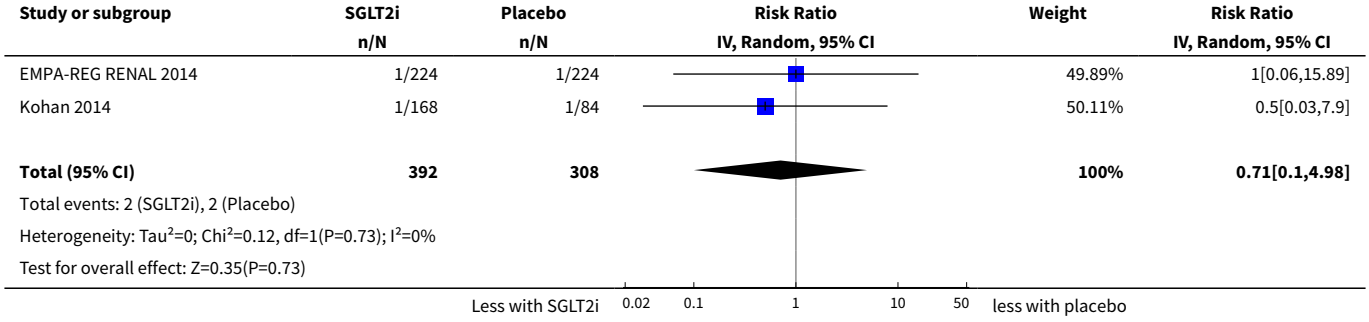
Analysis 1.19. Comparison 1 SGLT2 inhibitors versus placebo, Outcome 19 Hypoglycaemia.



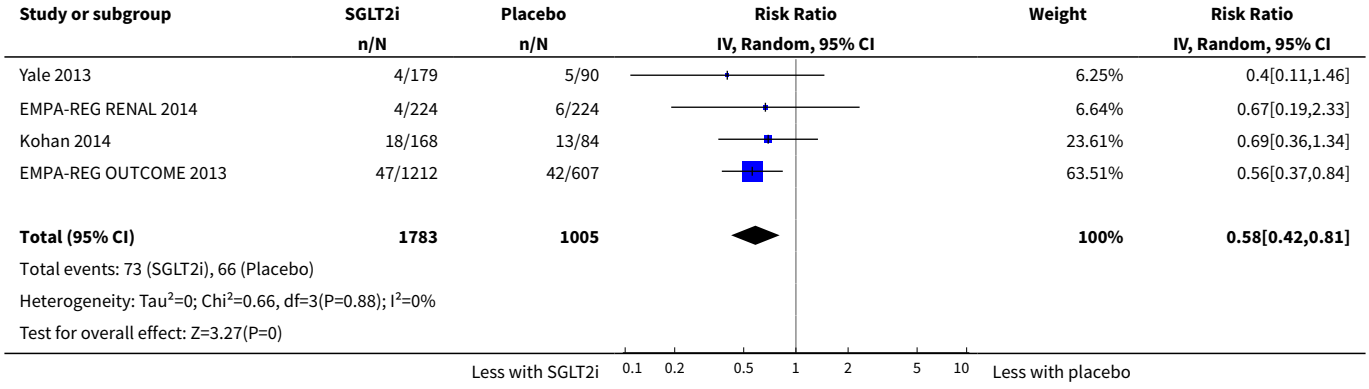
Analysis 1.20. Comparison 1 SGLT2 inhibitors versus placebo, Outcome 20 Discontinuation of medication due to adverse events.



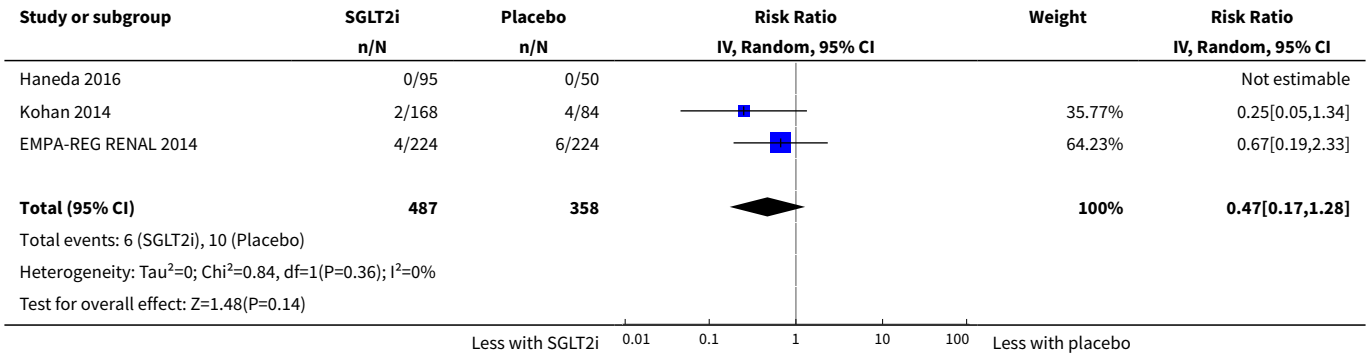
Analysis 1.21. Comparison 1 SGLT2 inhibitors versus placebo, Outcome 21 End-stage kidney disease.



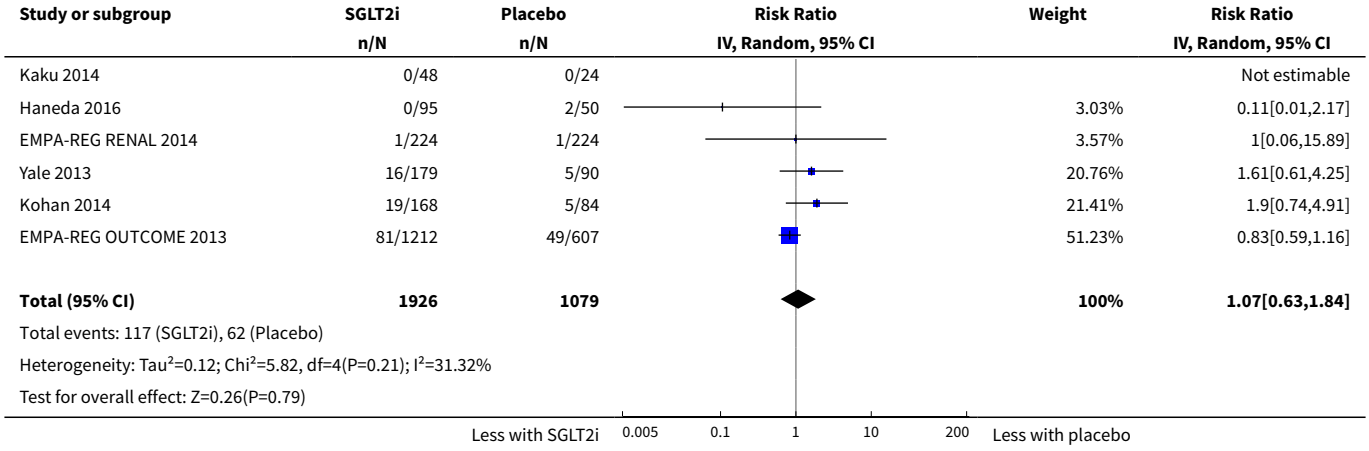
Analysis 1.22. Comparison 1 SGLT2 inhibitors versus placebo, Outcome 22 Hyperkalaemia.



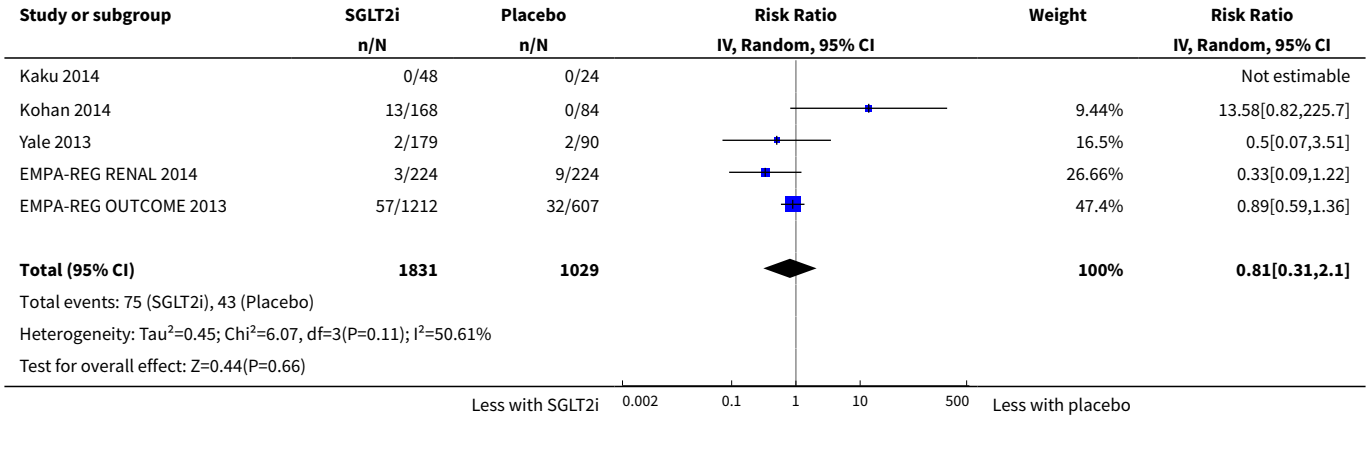
Analysis 1.23. Comparison 1 SGLT2 inhibitors versus placebo, Outcome 23 Hypoglycaemia requiring third party assistance.



Analysis 1.24. Comparison 1 SGLT2 inhibitors versus placebo, Outcome 24 Hypovolaemia.

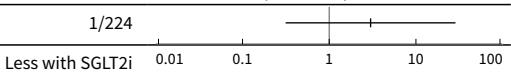


Analysis 1.25. Comparison 1 SGLT2 inhibitors versus placebo, Outcome 25 Fracture.



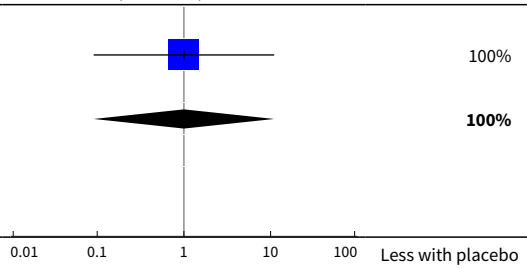
Analysis 1.26. Comparison 1 SGLT2 inhibitors versus placebo, Outcome 26 Diarrhoea.

Study or subgroup	SGLT2i n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
EMPA-REG RENAL 2014	3/224	1/224		3[0.31,28.62]



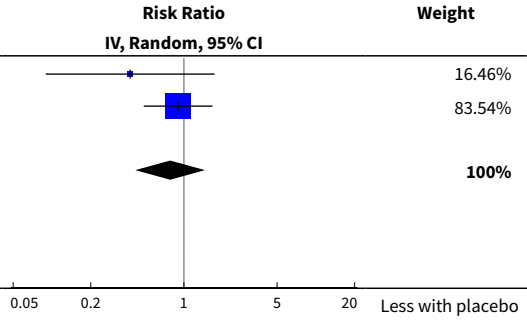
Analysis 1.27. Comparison 1 SGLT2 inhibitors versus placebo, Outcome 27 Diabetic ketoacidosis.

Study or subgroup	SGLT2i n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Haneda 2016	0/95	0/48			Not estimable
EMPA-REG OUTCOME 2013	2/1212	1/607		100%	1[0.09,11.02]
Total (95% CI)	**1307**	**655**		**100%**	**1[0.09,11.02]**
Total events: 2 (SGLT2i), 1 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0(P=1)					



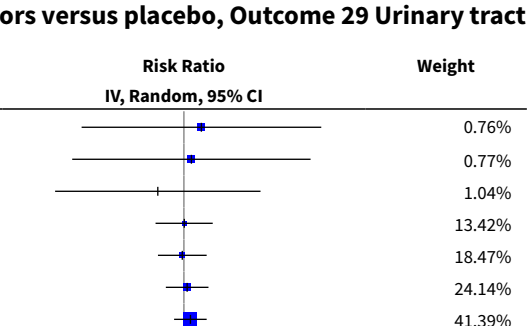
Analysis 1.28. Comparison 1 SGLT2 inhibitors versus placebo, Outcome 28 Upper respiratory tract infection.

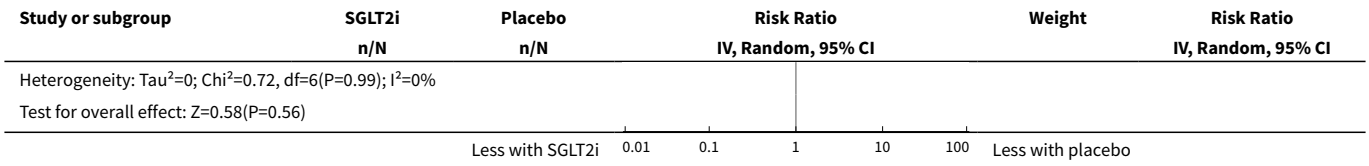
Study or subgroup	SGLT2i n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Haneda 2016	3/95	4/50		16.46%	0.39[0.09,1.7]
EMPA-REG RENAL 2014	19/224	21/224		83.54%	0.9[0.5,1.64]
Total (95% CI)	**319**	**274**		**100%**	**0.79[0.43,1.44]**
Total events: 22 (SGLT2i), 25 (Placebo)					
Heterogeneity: Tau^2=0.02; Chi^2=1.07, df=1(P=0.3); I^2=6.38%					
Test for overall effect: Z=0.77(P=0.44)					



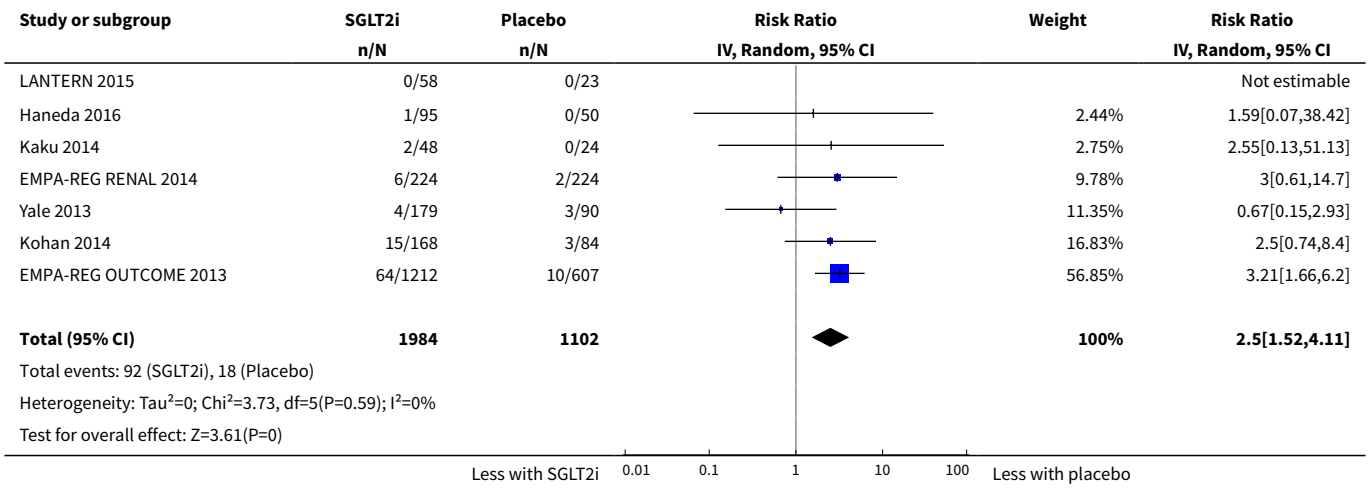
Analysis 1.29. Comparison 1 SGLT2 inhibitors versus placebo, Outcome 29 Urinary tract infection.

Study or subgroup	SGLT2i n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Haneda 2016	1/95	0/50		0.76%	1.59[0.07,38.42]
LANTERN 2015	1/58	0/23		0.77%	1.22[0.05,28.92]
Kaku 2014	1/48	1/24		1.04%	0.5[0.03,7.65]
Yale 2013	18/179	9/90		13.42%	1.01[0.47,2.15]
Kohan 2014	23/168	12/84		18.47%	0.96[0.5,1.83]
EMPA-REG OUTCOME 2013	37/1212	17/607		24.14%	1.09[0.62,1.92]
EMPA-REG RENAL 2014	38/224	32/224		41.39%	1.19[0.77,1.83]
Total (95% CI)	**1984**	**1102**		**100%**	**1.09[0.82,1.43]**
Total events: 119 (SGLT2i), 71 (Placebo)					

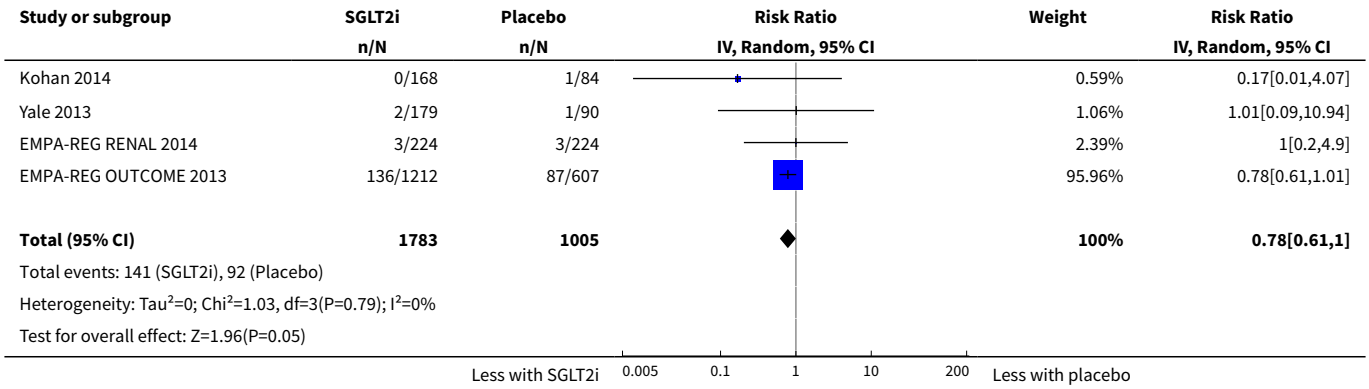




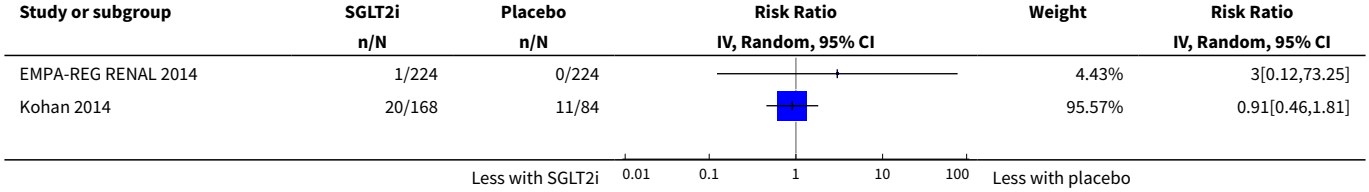
Analysis 1.30. Comparison 1 SGLT2 inhibitors versus placebo, Outcome 30 Genital infection.

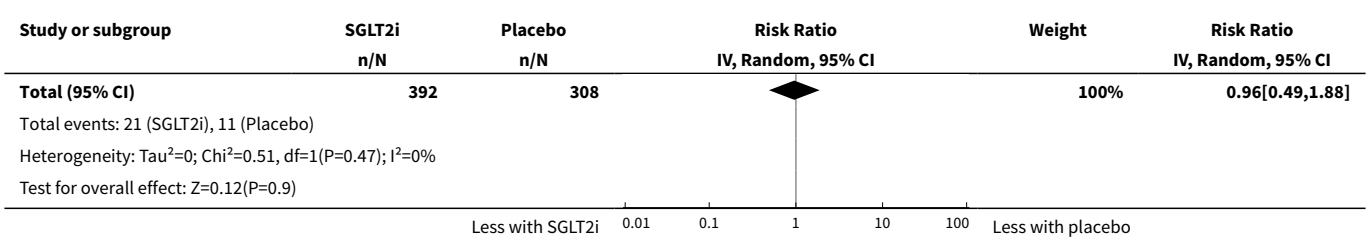


Analysis 1.31. Comparison 1 SGLT2 inhibitors versus placebo, Outcome 31 Acute kidney injury.



Analysis 1.32. Comparison 1 SGLT2 inhibitors versus placebo, Outcome 32 Doubling of serum creatinine.





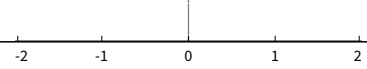
Comparison 2. DPP-4 inhibitors versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 HbA1c	7	867	Mean Difference (IV, Random, 95% CI)	-0.62 [-0.85, -0.39]
2 Fasting blood glucose	4	589	Mean Difference (IV, Random, 95% CI)	-0.47 [-1.08, 0.15]
3 Death (all causes)	6	4211	Risk Ratio (IV, Random, 95% CI)	0.89 [0.75, 1.07]
4 All cardiovascular death	2	5897	Risk Ratio (IV, Random, 95% CI)	0.93 [0.77, 1.11]
5 Myocardial infarction	4	6121	Risk Ratio (IV, Random, 95% CI)	1.08 [0.88, 1.33]
6 Stroke	3	6030	Risk Ratio (IV, Random, 95% CI)	0.92 [0.69, 1.24]
7 Heart failure	4	6115	Risk Ratio (IV, Random, 95% CI)	1.18 [0.98, 1.44]
8 Weight	2	210	Mean Difference (IV, Random, 95% CI)	0.16 [-0.58, 0.90]
9 eGFR [mL/min/1.73 m^2]	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
10 Serum creatinine	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
11 Urinary albumin/creatinine ratio	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
12 Total cholesterol	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
13 LDL cholesterol	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
14 Hypoglycaemia	11	1443	Risk Ratio (IV, Random, 95% CI)	1.07 [0.80, 1.42]
15 Discontinuation of medication due to adverse events	7	1257	Risk Ratio (IV, Random, 95% CI)	0.94 [0.61, 1.45]
16 Hyperkalaemia	2	502	Risk Ratio (IV, Random, 95% CI)	1.30 [0.81, 2.08]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17 Hypoglycaemia requiring third party assistance	6	3383	Risk Ratio (IV, Random, 95% CI)	0.72 [0.25, 2.03]
18 New or worsening retinopathy	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
19 Peripheral oedema	4	763	Risk Ratio (IV, Random, 95% CI)	0.84 [0.58, 1.22]
20 Diarrhoea	2	502	Risk Ratio (IV, Random, 95% CI)	1.39 [0.80, 2.41]
21 Constipation	2	224	Risk Ratio (IV, Random, 95% CI)	0.79 [0.09, 6.84]
22 Malignancy	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
23 Pancreatic cancer	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
24 Pancreatitis	2	3693	Risk Ratio (IV, Random, 95% CI)	0.99 [0.14, 7.05]
25 Liver impairment	2	451	Risk Ratio (IV, Random, 95% CI)	1.42 [0.26, 7.64]
26 Upper respiratory tract infection	3	593	Risk Ratio (IV, Random, 95% CI)	0.63 [0.38, 1.04]
27 Cellulitis	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
28 Urinary tract infection	4	763	Risk Ratio (IV, Random, 95% CI)	0.82 [0.50, 1.35]
29 Acute kidney injury	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 DPP-4 inhibitors versus placebo, Outcome 1 HbA1c.

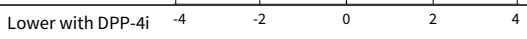
Study or subgroup	DPP-4i N	DPP-4i Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Nowicki 2011	78	-1.1 (2.3)	82	-0.4 (1.3)		9.54%	-0.72[-1.3,-0.14]
Yki-Järvinen 2013	32	-0.4 (0.9)	38	-0.1 (1.1)		12.38%	-0.29[-0.75,0.17]
McGill 2013	66	-0.7 (1.2)	62	0 (1.3)		13.19%	-0.72[-1.15,-0.29]
GUARD 2017	66	-0.8 (1.1)	66	0.4 (1.1)		14.53%	-1.21[-1.6,-0.82]
Barnett 2013	43	-0.7 (0.6)	21	-0 (0.6)		16.5%	-0.65[-0.98,-0.32]
Chan 2008a	55	-0.6 (0.8)	25	-0.2 (0.6)		16.63%	-0.4[-0.72,-0.08]
Laakso 2015	113	-0.5 (1.2)	120	-0.1 (1.2)		17.22%	-0.42[-0.72,-0.12]
Total ***	**453**		**414**			**100%**	**-0.62[-0.85,-0.39]**
Heterogeneity: Tau^2=0.05; Chi^2=14.75, df=6(P=0.02); I^2=59.32%							
Test for overall effect: Z=5.34(P<0.0001)							



Lower with DPP-4i — Lower with placebo

Analysis 2.2. Comparison 2 DPP-4 inhibitors versus placebo, Outcome 2 Fasting blood glucose.

Study or subgroup	DPP-4i N	DPP-4i Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Laakso 2015	112	0 (4.5)	119	0.5 (4.9)		22.04%	-0.52[-1.73,0.69]
McGill 2013	63	-0.3 (3.4)	57	-0.4 (3.3)		22.46%	0.08[-1.12,1.28]
Nowicki 2011	77	-0.4 (3.7)	81	-0.4 (3.5)		24.8%	0[-1.13,1.13]
Chan 2008a	55	-1.4 (2.7)	25	-0.2 (1.8)		30.7%	-1.2[-2.19,-0.21]
Total ***	**307**		**282**			**100%**	**-0.47[-1.08,0.15]**
Heterogeneity: Tau²=0.06; Chi²=3.57, df=3(P=0.31); I²=15.9%							
Test for overall effect: Z=1.49(P=0.14)							



Analysis 2.3. Comparison 2 DPP-4 inhibitors versus placebo, Outcome 3 Death (all causes).

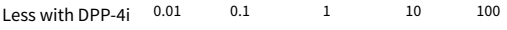
Study or subgroup	DPP-4i n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Yki-Järvinen 2013	1/59	2/68		0.58%	0.58[0.05,6.2]
Lukashevich 2011	4/216	1/153		0.68%	2.83[0.32,25.1]
Chan 2008a	5/65	1/26		0.74%	2[0.25,16.3]
McGill 2013	3/68	3/65		1.33%	0.96[0.2,4.57]
Nowicki 2011	3/85	4/85		1.51%	0.75[0.17,3.25]
TECOS 2013	187/1666	210/1655		95.15%	0.88[0.74,1.06]
Total (95% CI)	**2159**	**2052**		**100%**	**0.89[0.75,1.07]**
Total events: 203 (DPP-4i), 221 (Placebo)					
Heterogeneity: Tau²=0; Chi²=1.85, df=5(P=0.87); I²=0%					
Test for overall effect: Z=1.22(P=0.22)					

Analysis 2.4. Comparison 2 DPP-4 inhibitors versus placebo, Outcome 4 All cardiovascular death.

Study or subgroup	DPP-4i n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
SAVOR-TIMI 53 2011	85/1294	83/1282		38.33%	1.01[0.76,1.36]
TECOS 2013	125/1666	142/1655		61.67%	0.87[0.69,1.1]
Total (95% CI)	**2960**	**2937**		**100%**	**0.93[0.77,1.11]**
Total events: 210 (DPP-4i), 225 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.61, df=1(P=0.43); I²=0%					
Test for overall effect: Z=0.84(P=0.4)					

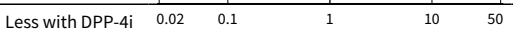
Analysis 2.5. Comparison 2 DPP-4 inhibitors versus placebo, Outcome 5 Myocardial infarction.

Study or subgroup	DPP-4i n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Chan 2008a	3/65	0/26		0.49%	2.86[0.15,53.58]
McGill 2013	4/68	2/65		1.52%	1.91[0.36,10.08]
SAVOR-TIMI 53 2011	74/1294	66/1282		40.38%	1.11[0.8,1.53]
TECOS 2013	101/1666	97/1655		57.61%	1.03[0.79,1.36]
Total (95% CI)	**3093**	**3028**		**100%**	**1.08[0.88,1.33]**
Total events: 182 (DPP-4i), 165 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.01, df=3(P=0.8); I^2=0%					
Test for overall effect: Z=0.74(P=0.46)					



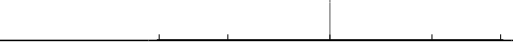
Analysis 2.6. Comparison 2 DPP-4 inhibitors versus placebo, Outcome 6 Stroke.

Study or subgroup	DPP-4i n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
McGill 2013	1/68	1/65		1.17%	0.96[0.06,14.97]
SAVOR-TIMI 53 2011	23/1294	24/1282		27.65%	0.95[0.54,1.67]
TECOS 2013	57/1666	62/1655		71.18%	0.91[0.64,1.3]
Total (95% CI)	**3028**	**3002**		**100%**	**0.92[0.69,1.24]**
Total events: 81 (DPP-4i), 87 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=2(P=0.99); I^2=0%					
Test for overall effect: Z=0.52(P=0.6)					



Analysis 2.7. Comparison 2 DPP-4 inhibitors versus placebo, Outcome 7 Heart failure.

Study or subgroup	DPP-4i n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Yki-Järvinen 2013	1/59	1/68		0.49%	1.15[0.07,18.02]
Chan 2008a	5/65	1/26		0.84%	2[0.25,16.3]
TECOS 2013	91/1666	84/1655		44.46%	1.08[0.81,1.44]
SAVOR-TIMI 53 2011	118/1294	92/1282		54.21%	1.27[0.98,1.65]
Total (95% CI)	**3084**	**3031**		**100%**	**1.18[0.98,1.44]**
Total events: 215 (DPP-4i), 178 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.94, df=3(P=0.82); I^2=0%					
Test for overall effect: Z=1.72(P=0.09)					



Analysis 2.8. Comparison 2 DPP-4 inhibitors versus placebo, Outcome 8 Weight.

Study or subgroup	DPP-4i N	DPP-4i Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Chan 2008a	55	0 (2.2)	25	-0.6 (2)		42.07%	0.6[-0.38,1.58]
GUARD 2017	64	-0.3 (2.6)	66	-0.1 (1.8)		57.93%	-0.16[-0.94,0.62]
Total ***	**119**		**91**			**100%**	**0.16[-0.58,0.9]**
Heterogeneity: Tau^2=0.09; Chi^2=1.42, df=1(P=0.23); I^2=29.43%							
Test for overall effect: Z=0.43(P=0.67)							

Analysis 2.9. Comparison 2 DPP-4 inhibitors versus placebo, Outcome 9 eGFR [mL/min/1.73 m^2].

Study or subgroup	DPP-4i N	DPP-4i Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
GUARD 2017	64	-2.1 (4.6)	66	-0.1 (4.1)		-1.99[-3.49,-0.49]

Analysis 2.10. Comparison 2 DPP-4 inhibitors versus placebo, Outcome 10 Serum creatinine.

Study or subgroup	DPP-4i N	DPP-4i Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Chan 2008a	55	10.6 (26.5)	25	6.2 (30.9)		4.42[-9.59,18.43]

Analysis 2.11. Comparison 2 DPP-4 inhibitors versus placebo, Outcome 11 Urinary albumin/creatinine ratio.

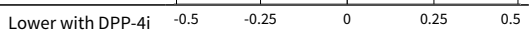
Study or subgroup	DPP-4i N	DPP-4i Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Chan 2008a	55	25.4 (159.2)	25	56.2 (247.5)		-30.8[-136.55,74.95]

Analysis 2.12. Comparison 2 DPP-4 inhibitors versus placebo, Outcome 12 Total cholesterol.

Study or subgroup	DPP-4i N	DPP-4i Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
GUARD 2017	64	-0.2 (0.6)	66	0.1 (0.6)		-0.33[-0.54,-0.12]

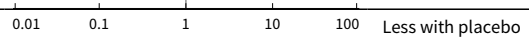
Analysis 2.13. Comparison 2 DPP-4 inhibitors versus placebo, Outcome 13 LDL cholesterol.

Study or subgroup	DPP-4i N	DPP-4i Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
GUARD 2017	64	-0.2 (0.6)	66	0.1 (0.5)		-0.23[-0.42,-0.04]



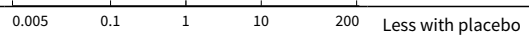
Analysis 2.14. Comparison 2 DPP-4 inhibitors versus placebo, Outcome 14 Hypoglycaemia.

Study or subgroup	DPP-4i n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Ito 2011a	0/30	0/21			Not estimable
Abe 2016	0/41	0/41			Not estimable
Lewin 2012	1/9	3/8		1.83%	0.3[0.04,2.31]
Barnett 2013	10/26	1/10		2.07%	3.85[0.56,26.28]
Chan 2008a	3/65	6/26		4.14%	0.2[0.05,0.74]
Nowicki 2011	8/85	4/85		5.08%	2[0.63,6.39]
GUARD 2017	7/66	5/66		5.6%	1.4[0.47,4.19]
Yki-Järvinen 2013	21/59	27/68		17.62%	0.9[0.57,1.41]
Lukashevich 2011	49/216	26/153		18.42%	1.33[0.87,2.05]
Laakso 2015	41/113	48/122		22.17%	0.92[0.66,1.28]
McGill 2013	43/68	32/65		23.07%	1.28[0.95,1.74]
Total (95% CI)	**778**	**665**		**100%**	**1.07[0.8,1.42]**
Total events: 183 (DPP-4i), 152 (Placebo)					
Heterogeneity: Tau^2=0.07; Chi^2=14.57, df=8(P=0.07); I^2=45.1%					
Test for overall effect: Z=0.46(P=0.65)					



Analysis 2.15. Comparison 2 DPP-4 inhibitors versus placebo, Outcome 15 Discontinuation of medication due to adverse events.

Study or subgroup	DPP-4i n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
GUARD 2017	0/66	2/66		2.03%	0.2[0.01,4.09]
Yki-Järvinen 2013	3/59	2/68		6.01%	1.73[0.3,10]
Chan 2008a	5/65	2/26		7.45%	1[0.21,4.83]
Laakso 2015	4/113	6/122		12.05%	0.72[0.21,2.48]
Nowicki 2011	6/85	6/85		15.54%	1[0.34,2.98]
McGill 2013	9/68	11/65		28.01%	0.78[0.35,1.76]
Lukashevich 2011	15/216	9/153		28.9%	1.18[0.53,2.63]
Total (95% CI)	**672**	**585**		**100%**	**0.94[0.61,1.45]**
Total events: 42 (DPP-4i), 38 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.18, df=6(P=0.9); I^2=0%					
Test for overall effect: Z=0.27(P=0.78)					



Analysis 2.16. Comparison 2 DPP-4 inhibitors versus placebo, Outcome 16 Hyperkalaemia.

Study or subgroup	DPP-4i n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Lukashevich 2011	14/216	7/153		28.26%	1.42[0.59,3.43]
McGill 2013	21/68	16/65		71.74%	1.25[0.72,2.18]
Total (95% CI)	**284**	**218**		**100%**	**1.3[0.81,2.08]**
Total events: 35 (DPP-4i), 23 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.05, df=1(P=0.82); I^2=0%					
Test for overall effect: Z=1.09(P=0.28)					

Favours DPP-Less with — Less with placebo

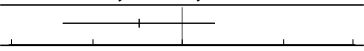
Analysis 2.17. Comparison 2 DPP-4 inhibitors versus placebo, Outcome 17 Hypoglycaemia requiring third party assistance.

Study or subgroup	DPP-4i n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Abe 2016	0/41	0/41			Not estimable
GUARD 2017	0/66	0/66			Not estimable
Chan 2008a	0/65	2/26		9.44%	0.08[0,1.65]
McGill 2013	3/68	3/65		22.32%	0.96[0.2,4.57]
Lukashevich 2011	3/216	6/153		25.29%	0.35[0.09,1.39]
SAVOR-TIMI 53 2011	72/1294	47/1282		42.95%	1.52[1.06,2.17]
Total (95% CI)	**1750**	**1633**		**100%**	**0.72[0.25,2.03]**
Total events: 78 (DPP-4i), 58 (Placebo)					
Heterogeneity: Tau^2=0.62; Chi^2=7.58, df=3(P=0.06); I^2=60.4%					
Test for overall effect: Z=0.62(P=0.53)					

Less with DPP-4i — Less with placebo

Analysis 2.18. Comparison 2 DPP-4 inhibitors versus placebo, Outcome 18 New or worsening retinopathy.

Study or subgroup	DPP-4i n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
TECOS 2013	72/1667	85/1657		0.84[0.62,1.14]

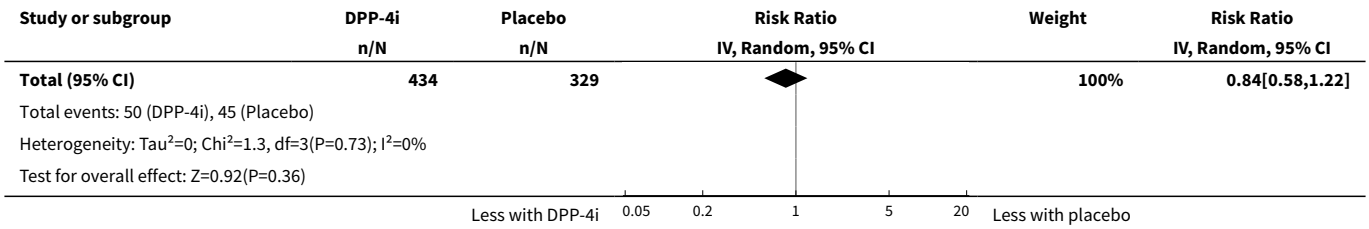


Less with DPP-4i — Less with placebo

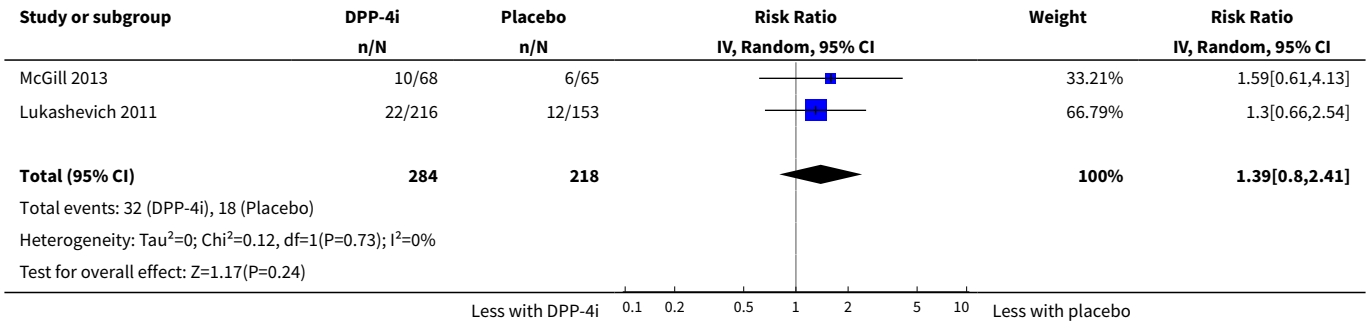
Analysis 2.19. Comparison 2 DPP-4 inhibitors versus placebo, Outcome 19 Peripheral oedema.

Study or subgroup	DPP-4i n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Chan 2008a	2/65	2/26		3.82%	0.4[0.06,2.69]
Nowicki 2011	3/85	6/85		7.58%	0.5[0.13,1.93]
McGill 2013	7/68	7/65		14.13%	0.96[0.35,2.57]
Lukashevich 2011	38/216	30/153		74.48%	0.9[0.58,1.38]

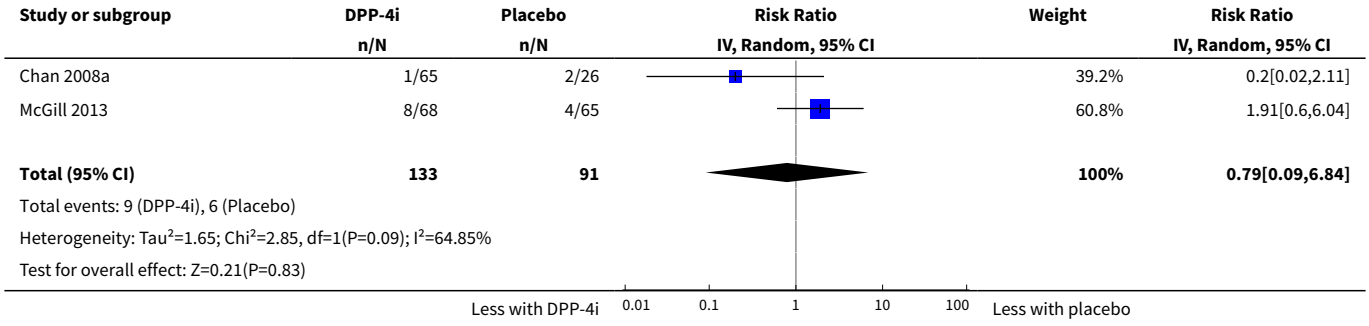
Less with DPP-4i — Less with placebo



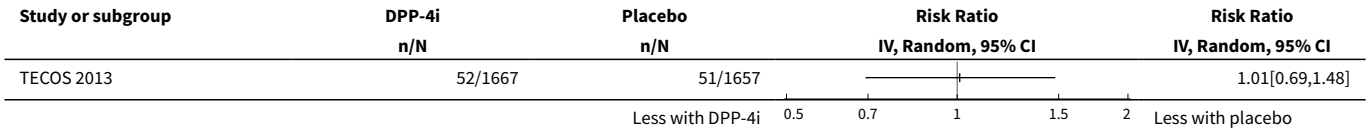
Analysis 2.20. Comparison 2 DPP-4 inhibitors versus placebo, Outcome 20 Diarrhoea.



Analysis 2.21. Comparison 2 DPP-4 inhibitors versus placebo, Outcome 21 Constipation.

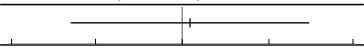


Analysis 2.22. Comparison 2 DPP-4 inhibitors versus placebo, Outcome 22 Malignancy.



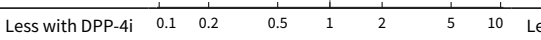
Analysis 2.23. Comparison 2 DPP-4 inhibitors versus placebo, Outcome 23 Pancreatic cancer.

Study or subgroup	DPP-4i n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Chan 2008a	1/65	0/26		1.23[0.05,29.19]



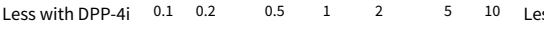
Analysis 2.24. Comparison 2 DPP-4 inhibitors versus placebo, Outcome 24 Pancreatitis.

Study or subgroup	DPP-4i n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Lukashevich 2011	0/216	0/153			Not estimable
TECOS 2013	2/1667	2/1657		100%	0.99[0.14,7.05]
Total (95% CI)	**1883**	**1810**		**100%**	**0.99[0.14,7.05]**
Total events: 2 (DPP-4i), 2 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.01(P=1)					



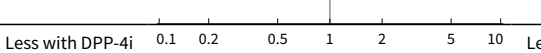
Analysis 2.25. Comparison 2 DPP-4 inhibitors versus placebo, Outcome 25 Liver impairment.

Study or subgroup	DPP-4i n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Abe 2016	0/41	0/41			Not estimable
Lukashevich 2011	4/216	2/153		100%	1.42[0.26,7.64]
Total (95% CI)	**257**	**194**		**100%**	**1.42[0.26,7.64]**
Total events: 4 (DPP-4i), 2 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.41(P=0.69)					



Analysis 2.26. Comparison 2 DPP-4 inhibitors versus placebo, Outcome 26 Upper respiratory tract infection.

Study or subgroup	DPP-4i n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Chan 2008a	5/65	5/26		18.67%	0.4[0.13,1.27]
McGill 2013	5/68	7/65		20.66%	0.68[0.23,2.04]
Lukashevich 2011	17/216	17/153		60.68%	0.71[0.37,1.34]
Total (95% CI)	**349**	**244**		**100%**	**0.63[0.38,1.04]**
Total events: 27 (DPP-4i), 29 (Placebo)					
Heterogeneity: $Tau^2=0$; $Chi^2=0.75$, df=2(P=0.69); $I^2=0\%$					
Test for overall effect: Z=1.81(P=0.07)					



Analysis 2.27. Comparison 2 DPP-4 inhibitors versus placebo, Outcome 27 Cellulitis.

Study or subgroup	DPP-4i n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Ito 2011a	0/30	0/21		Not estimable

Less with DPP-4i 0.01 0.1 1 10 100 Less with placebo

Analysis 2.28. Comparison 2 DPP-4 inhibitors versus placebo, Outcome 28 Urinary tract infection.

Study or subgroup	DPP-4i n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Nowicki 2011	6/85	3/85		13.47%	2[0.52,7.74]
Chan 2008a	7/65	3/26		15.2%	0.93[0.26,3.34]
McGill 2013	6/68	8/65		24.54%	0.72[0.26,1.95]
Lukashevich 2011	13/216	14/153		46.79%	0.66[0.32,1.36]
Total (95% CI)	**434**	**329**		**100%**	**0.82[0.5,1.35]**
Total events: 32 (DPP-4i), 28 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.13, df=3(P=0.55); I^2=0%					
Test for overall effect: Z=0.77(P=0.44)					

Less with DPP-4i 0.1 0.2 0.5 1 2 5 10 Less with placebo

Analysis 2.29. Comparison 2 DPP-4 inhibitors versus placebo, Outcome 29 Acute kidney injury.

Study or subgroup	DPP-4i n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
McGill 2013	5/68	4/65		1.19[0.34,4.25]

Less with DPP-4i 0.1 0.2 0.5 1 2 5 10 Less with placebo

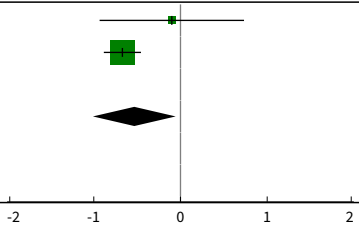
Comparison 3. GLP-1 agonists versus placebo

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 HbA1c	2	283	Mean Difference (IV, Random, 95% CI)	-0.53 [-1.01, -0.06]
2 Fasting blood glucose	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Death (all causes)	2	301	Risk Ratio (IV, Random, 95% CI)	3.91 [0.44, 34.58]
4 Myocardial infarction	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
5 Heart failure	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
6 Weight	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7 Systolic blood pressure	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
8 Diastolic blood pressure	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
9 Serum creatinine	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
10 Total cholesterol	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
11 HDL cholesterol	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
12 LDL cholesterol	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
13 Triglyceride	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
14 Hypoglycaemia	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
15 Discontinuation of medication due to adverse events	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
16 Gastrointestinal disorders	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
17 Vomiting	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
18 Pancreatitis	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
19 Nausea	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

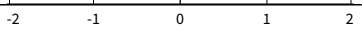
Analysis 3.1. Comparison 3 GLP-1 agonists versus placebo, Outcome 1 HbA1c.

Study or subgroup	GLP-1 agonists N	GLP-1 agonists Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Idorn 2013	10	-0.5 (1)	10	-0.4 (1)		24.06%	-0.1[-0.93,0.73]
LIRA-RENAL 2016	127	-1 (0.9)	136	-0.4 (0.9)		75.94%	-0.67[-0.88,-0.46]
Total * **	**137**		**146**			**100%**	**-0.53[-1.01,-0.06]**
Heterogeneity: Tau²=0.07; Chi²=1.69, df=1(P=0.19); I²=40.77%							
Test for overall effect: Z=2.19(P=0.03)							



Analysis 3.2. Comparison 3 GLP-1 agonists versus placebo, Outcome 2 Fasting blood glucose.

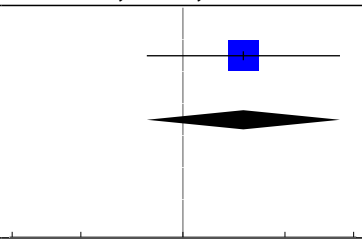
Study or subgroup	GLP-1 agonists N	GLP-1 agonists Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
LIRA-RENAL 2016	109	-1.6 (2.5)	122	-0.5 (2.4)		-1.08[-1.71,-0.45]



Lower with GLP-1 — Lower with placebo

Analysis 3.3. Comparison 3 GLP-1 agonists versus placebo, Outcome 3 Death (all causes).

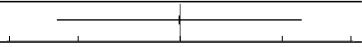
Study or subgroup	GLP-1 agonists n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Idorn 2013	0/14	0/10			Not estimable
LIRA-RENAL 2016	4/140	1/137		100%	3.91[0.44,34.58]
Total (95% CI)	**154**	**147**		**100%**	**3.91[0.44,34.58]**
Total events: 4 (GLP-1 agonists), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.23(P=0.22)					



Less with GLP-1 — Less with placebo

Analysis 3.4. Comparison 3 GLP-1 agonists versus placebo, Outcome 4 Myocardial infarction.

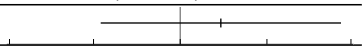
Study or subgroup	GLP-1 agonists n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
LIRA-RENAL 2016	1/140	1/137		0.98[0.06,15.49]



Less with GLP-1 — Less with placebo

Analysis 3.5. Comparison 3 GLP-1 agonists versus placebo, Outcome 5 Heart failure.

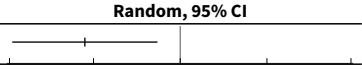
Study or subgroup	GLP-1 agonists n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
LIRA-RENAL 2016	1/140	0/137		2.94[0.12,71.46]



Less with GLP-1 — Less with placebo

Analysis 3.6. Comparison 3 GLP-1 agonists versus placebo, Outcome 6 Weight.

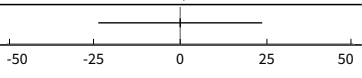
Study or subgroup	GLP-1 agonists N	GLP-1 agonists Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Idorn 2013	10	-2.4 (2.5)	10	-0.2 (1)		-2.2[-3.87,-0.53]



Lower with GLP-1 — Lower with placebo

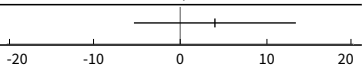
Analysis 3.7. Comparison 3 GLP-1 agonists versus placebo, Outcome 7 Systolic blood pressure.

Study or subgroup	GLP-1 agonists N	GLP-1 agonists Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Idorn 2013	10	-3.6 (32.9)	10	-3.6 (19.3)		0[-23.63,23.63]



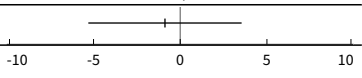
Analysis 3.8. Comparison 3 GLP-1 agonists versus placebo, Outcome 8 Diastolic blood pressure.

Study or subgroup	GLP-1 agonists N	GLP-1 agonists Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Idorn 2013	10	4.8 (9.5)	10	0.8 (11.7)		4[-5.34,13.34]



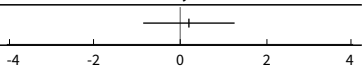
Analysis 3.9. Comparison 3 GLP-1 agonists versus placebo, Outcome 9 Serum creatinine.

Study or subgroup	GLP-1 agonists N	GLP-1 agonists Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Idorn 2013	10	-0.9 (6.2)	10	0 (3.5)		-0.88[-5.3,3.54]



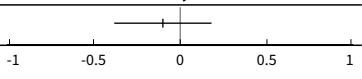
Analysis 3.10. Comparison 3 GLP-1 agonists versus placebo, Outcome 10 Total cholesterol.

Study or subgroup	GLP-1 agonists N	GLP-1 agonists Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Idorn 2013	10	-0.3 (0.6)	10	-0.5 (1.6)		0.2[-0.85,1.25]



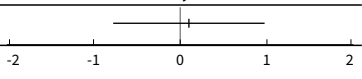
Analysis 3.11. Comparison 3 GLP-1 agonists versus placebo, Outcome 11 HDL cholesterol.

Study or subgroup	GLP-1 agonists N	GLP-1 agonists Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Idorn 2013	10	-0.2 (0.3)	10	-0.1 (0.3)		-0.1[-0.38,0.18]



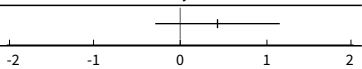
Analysis 3.12. Comparison 3 GLP-1 agonists versus placebo, Outcome 12 LDL cholesterol.

Study or subgroup	GLP-1 agonists N	GLP-1 agonists Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Idorn 2013	10	-0.3 (0.6)	10	-0.4 (1.3)		0.1[-0.77,0.97]



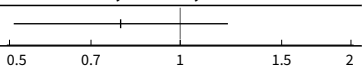
Analysis 3.13. Comparison 3 GLP-1 agonists versus placebo, Outcome 13 Triglyceride.

Study or subgroup	GLP-1 agonists N	GLP-1 agonists Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Idorn 2013	10	0.3 (0.5)	10	-0.1 (1)		0.43[-0.29,1.15]



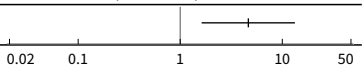
Analysis 3.14. Comparison 3 GLP-1 agonists versus placebo, Outcome 14 Hypoglycaemia.

Study or subgroup	GLP-1 agonists n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
LIRA-RENAL 2016	29/140	36/137		0.79[0.51,1.21]



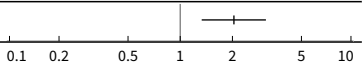
Analysis 3.15. Comparison 3 GLP-1 agonists versus placebo, Outcome 15 Discontinuation of medication due to adverse events.

Study or subgroup	GLP-1 agonists n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
LIRA-RENAL 2016	19/140	4/137		4.65[1.62,13.31]



Analysis 3.16. Comparison 3 GLP-1 agonists versus placebo, Outcome 16 Gastrointestinal disorders.

Study or subgroup	GLP-1 agonists n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
LIRA-RENAL 2016	50/140	24/137		2.04[1.33,3.12]



Analysis 3.17. Comparison 3 GLP-1 agonists versus placebo, Outcome 17 Vomiting.

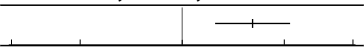
Study or subgroup	GLP-1 agonists n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
LIRA-RENAL 2016	10/140	4/137		2.45[0.79,7.61]

Analysis 3.18. Comparison 3 GLP-1 agonists versus placebo, Outcome 18 Pancreatitis.

Study or subgroup	GLP-1 agonists n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
LIRA-RENAL 2016	1/140	0/137		2.94[0.12,71.46]

Analysis 3.19. Comparison 3 GLP-1 agonists versus placebo, Outcome 19 Nausea.

Study or subgroup	GLP-1 agonists n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
LIRA-RENAL 2016	30/140	6/137		4.89[2.1,11.38]



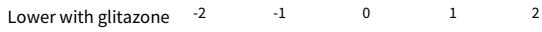
Comparison 4. Glitazone versus placebo/control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 HbA1c	2	88	Mean Difference (IV, Random, 95% CI)	-0.41 [-1.15, 0.32]
2 Fasting blood glucose	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Death (all causes)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4 Heart failure	2	123	Risk Ratio (IV, Random, 95% CI)	0.34 [0.01, 8.13]
5 Systolic blood pressure	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6 Diastolic blood pressure	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7 Total cholesterol	2	72	Mean Difference (IV, Random, 95% CI)	0.60 [-0.02, 1.23]
8 HDL cholesterol	2	72	Mean Difference (IV, Random, 95% CI)	0.07 [-0.25, 0.40]
9 LDL cholesterol	2	72	Mean Difference (IV, Random, 95% CI)	0.39 [-0.60, 1.39]
10 Triglyceride	2	72	Mean Difference (IV, Random, 95% CI)	-0.34 [-2.99, 2.30]
11 Hypoglycaemia	2		Risk Ratio (IV, Random, 95% CI)	Totals not selected
12 Hypoglycaemia requiring third party assistance	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
13 Peripheral oedema	3	134	Risk Ratio (IV, Random, 95% CI)	3.05 [0.33, 28.32]
14 Fluid overload	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
15 Fracture	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
16 Gastrointestinal disorders	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
17 Liver impairment	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

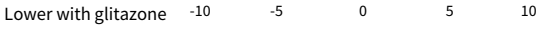
Analysis 4.1. Comparison 4 Glitazone versus placebo/control, Outcome 1 HbA1c.

Study or subgroup	Glitazone N	Glitazone Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Pfutzner 2011	19	-0.6 (0.9)	17	0.2 (1.1)		47.05%	-0.81[-1.46,-0.16]
Wong 2005	26	-0.4 (1.2)	26	-0.3 (0.8)		52.95%	-0.06[-0.61,0.49]
Total ***	**45**		**43**			**100%**	**-0.41[-1.15,0.32]**
Heterogeneity: Tau^2=0.19; Chi^2=2.98, df=1(P=0.08); I^2=66.42%							
Test for overall effect: Z=1.1(P=0.27)							



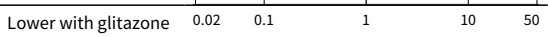
Analysis 4.2. Comparison 4 Glitazone versus placebo/control, Outcome 2 Fasting blood glucose.

Study or subgroup	Glitazone N	Glitazone Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Pfutzner 2011	19	-2 (3.9)	17	0.9 (3.8)		-2.91[-5.44,-0.38]



Analysis 4.3. Comparison 4 Glitazone versus placebo/control, Outcome 3 Death (all causes).

Study or subgroup	Glitazone n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Wong 2005	1/26	2/26		0.5[0.05,5.18]

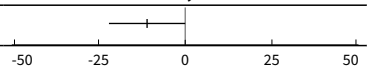


Analysis 4.4. Comparison 4 Glitazone versus placebo/control, Outcome 4 Heart failure.

Study or subgroup	Glitazone n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Jin 2007	0/30	0/30			Not estimable
Abe 2010a	0/31	1/32		100%	0.34[0.01,8.13]
Total (95% CI)	**61**	**62**		**100%**	**0.34[0.01,8.13]**
Total events: 0 (Glitazone), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.66(P=0.51)					

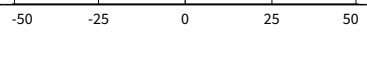
Analysis 4.5. Comparison 4 Glitazone versus placebo/control, Outcome 5 Systolic blood pressure.

Study or subgroup	Glitazone N	Glitazone Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Wong 2005	26	-8 (23)	26	3 (17)		-11[-21.99,-0.01]



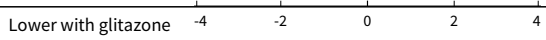
Analysis 4.6. Comparison 4 Glitazone versus placebo/control, Outcome 6 Diastolic blood pressure.

Study or subgroup	Glitazone N	Glitazone Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Wong 2005	26	-9.8 (20)	26	4 (18)		-13.79[-24.13,-3.45]



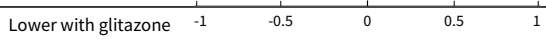
Analysis 4.7. Comparison 4 Glitazone versus placebo/control, Outcome 7 Total cholesterol.

Study or subgroup	Glitazone N	Glitazone Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Pfutzner 2011	13	-0.4 (1.2)	7	-1 (1.9)		16.62%	0.67[-0.87,2.21]
Wong 2005	26	0.4 (1.3)	26	-0.2 (1.2)		83.38%	0.59[-0.1,1.28]
Total ***	**39**		**33**			**100%**	**0.6[-0.02,1.23]**
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.93); I^2=0%							
Test for overall effect: Z=1.88(P=0.06)							

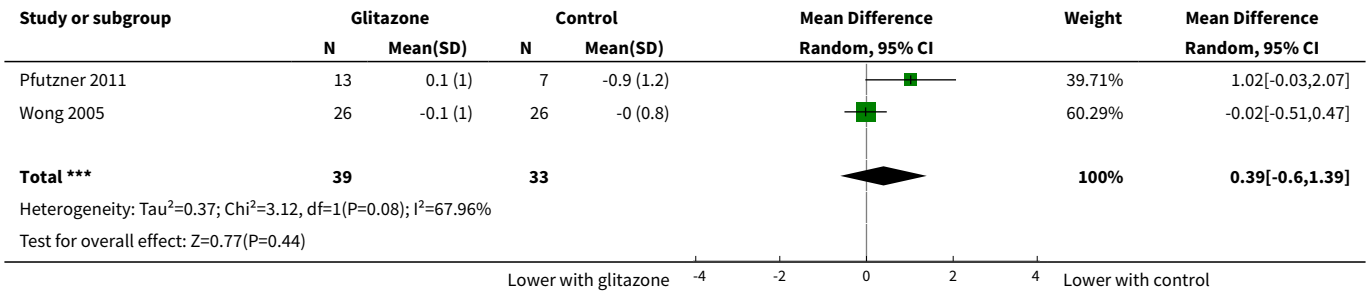


Analysis 4.8. Comparison 4 Glitazone versus placebo/control, Outcome 8 HDL cholesterol.

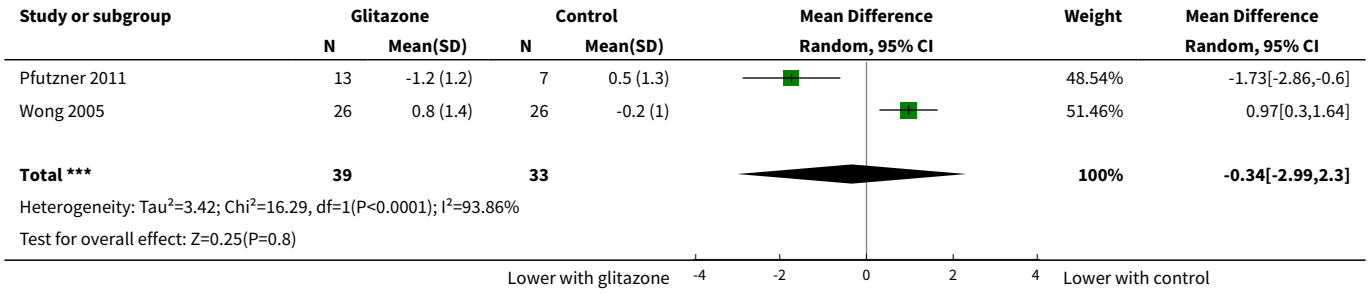
Study or subgroup	Glitazone N	Glitazone Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Pfutzner 2011	13	0 (0.2)	7	-0.2 (0.2)		49.16%	0.24[0.06,0.42]
Wong 2005	26	-0.1 (0.3)	26	0 (0.3)		50.84%	-0.09[-0.25,0.07]
Total ***	**39**		**33**			**100%**	**0.07[-0.25,0.4]**
Heterogeneity: Tau^2=0.05; Chi^2=6.84, df=1(P=0.01); I^2=85.37%							
Test for overall effect: Z=0.44(P=0.66)							



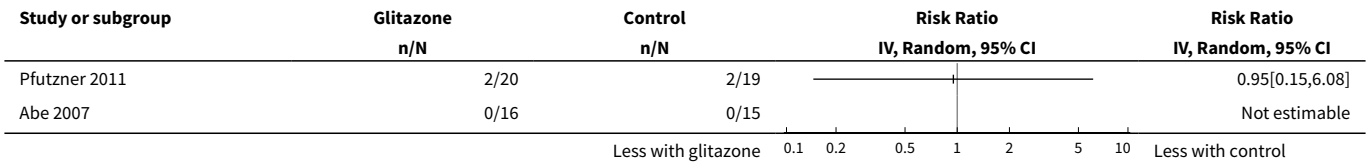
Analysis 4.9. Comparison 4 Glitazone versus placebo/control, Outcome 9 LDL cholesterol.



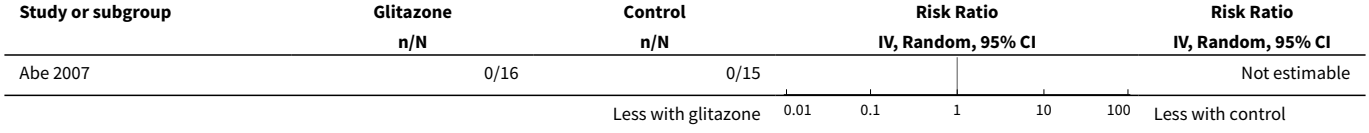
Analysis 4.10. Comparison 4 Glitazone versus placebo/control, Outcome 10 Triglyceride.



Analysis 4.11. Comparison 4 Glitazone versus placebo/control, Outcome 11 Hypoglycaemia.

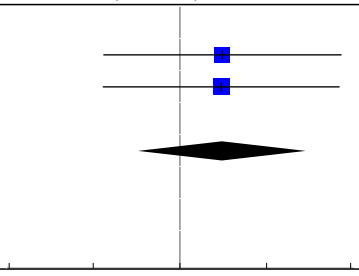


Analysis 4.12. Comparison 4 Glitazone versus placebo/control, Outcome 12 Hypoglycaemia requiring third party assistance.



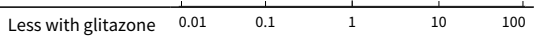
Analysis 4.13. Comparison 4 Glitazone versus placebo/control, Outcome 13 Peripheral oedema.

Study or subgroup	Glitazone n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Abe 2007	0/16	0/15			Not estimable
Abe 2010a	1/31	0/32		49.67%	3.09[0.13,73.17]
Abe 2008a	1/20	0/20		50.33%	3[0.13,69.52]
Total (95% CI)	**67**	**67**		**100%**	**3.05[0.33,28.32]**
Total events: 2 (Glitazone), 0 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.99); I^2=0%					
Test for overall effect: Z=0.98(P=0.33)					



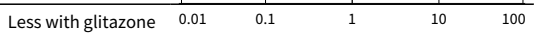
Analysis 4.14. Comparison 4 Glitazone versus placebo/control, Outcome 14 Fluid overload.

Study or subgroup	Glitazone n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Abe 2007	0/16	0/15		Not estimable



Analysis 4.15. Comparison 4 Glitazone versus placebo/control, Outcome 15 Fracture.

Study or subgroup	Glitazone n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Abe 2008a	0/20	0/20		Not estimable

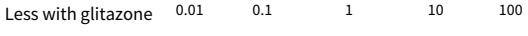


Analysis 4.16. Comparison 4 Glitazone versus placebo/control, Outcome 16 Gastrointestinal disorders.

Study or subgroup	Glitazone n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Pfutzner 2011	7/20	13/19		0.51[0.26,1]

Analysis 4.17. Comparison 4 Glitazone versus placebo/control, Outcome 17 Liver impairment.

Study or subgroup	Glitazone n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Abe 2007	0/16	0/15		Not estimable



Comparison 5. Glinides versus placebo/control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hypoglycaemia	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2 Hypoglycaemia requiring third party assistance	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3 Peripheral oedema	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4 Liver impairment	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

Analysis 5.1. Comparison 5 Glinides versus placebo/control, Outcome 1 Hypoglycaemia.

Study or subgroup	Glinides n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Abe 2010	0/18	0/18		Not estimable

Less with glinides 0.01 0.1 1 10 100 Less with control

Analysis 5.2. Comparison 5 Glinides versus placebo/control, Outcome 2 Hypoglycaemia requiring third party assistance.

Study or subgroup	Glinides n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Abe 2010	0/18	0/18		Not estimable

Less with glinides 0.01 0.1 1 10 100 Less with control

Analysis 5.3. Comparison 5 Glinides versus placebo/control, Outcome 3 Peripheral oedema.

Study or subgroup	Glinides n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Abe 2010	0/18	0/18		Not estimable

Less with glinides 0.01 0.1 1 10 100 Less with control

Analysis 5.4. Comparison 5 Glinides versus placebo/control, Outcome 4 Liver impairment.

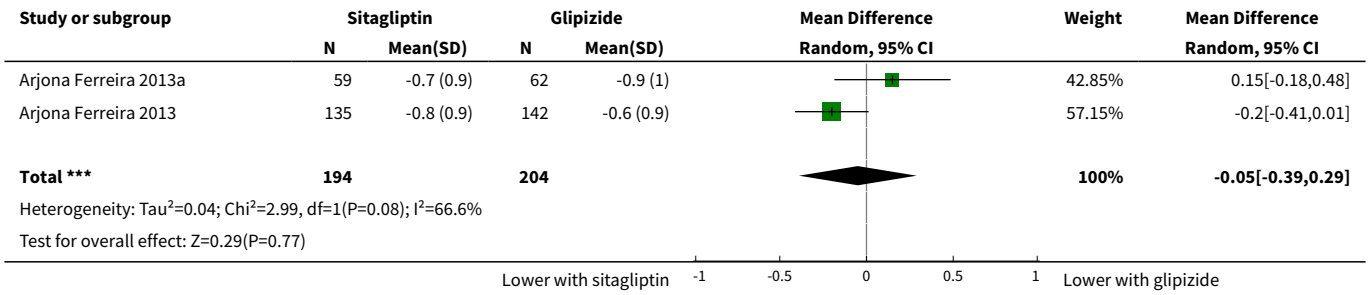
Study or subgroup	Glinides n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Abe 2010	0/18	0/18		Not estimable

Less with glinides 0.01 0.1 1 10 100 Less with control

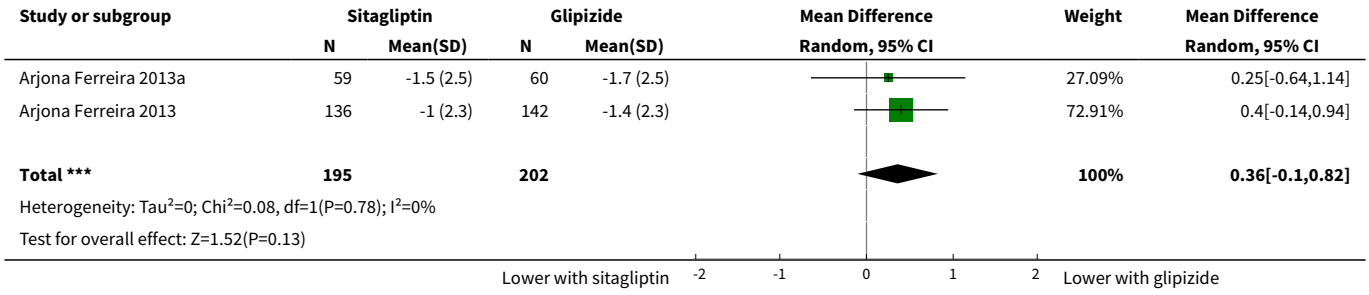
Comparison 6. Sitagliptin versus glipizide

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 HbA1c	2	398	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.39, 0.29]
2 Fasting blood glucose	2	397	Mean Difference (IV, Random, 95% CI)	0.36 [-0.10, 0.82]
3 Death (all causes)	2	551	Risk Ratio (IV, Random, 95% CI)	0.55 [0.22, 1.36]
4 Myocardial infarction	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
5 Stroke	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
6 Total cholesterol	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7 HDL cholesterol	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
8 LDL cholesterol	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
9 Triglyceride	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
10 Hypoglycaemia	2	551	Risk Ratio (IV, Random, 95% CI)	0.40 [0.23, 0.69]
11 Discontinuation of medication due to adverse events	2	551	Risk Ratio (IV, Random, 95% CI)	0.93 [0.54, 1.60]
12 Hypoglycaemia requiring third party assistance	2	551	Risk Ratio (IV, Random, 95% CI)	0.35 [0.09, 1.37]
13 Peripheral oedema	2	551	Risk Ratio (IV, Random, 95% CI)	0.71 [0.11, 4.80]
14 Fracture	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
15 Vomiting	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
16 Diarrhoea	2	551	Risk Ratio (IV, Random, 95% CI)	0.79 [0.39, 1.60]
17 Malignancy	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
18 Pancreatic cancer	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
19 Upper respiratory tract infection	2	551	Risk Ratio (IV, Random, 95% CI)	0.60 [0.31, 1.17]
20 Urinary tract infection	2	551	Risk Ratio (IV, Random, 95% CI)	1.29 [0.24, 6.94]
21 Cellulitis	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

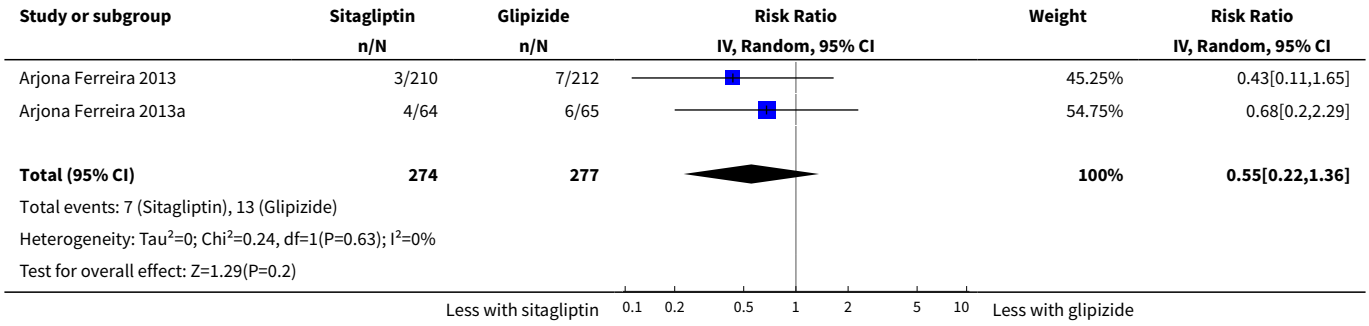
Analysis 6.1. Comparison 6 Sitagliptin versus glipizide, Outcome 1 HbA1c.



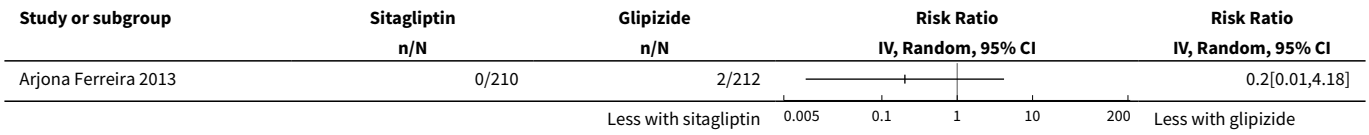
Analysis 6.2. Comparison 6 Sitagliptin versus glipizide, Outcome 2 Fasting blood glucose.



Analysis 6.3. Comparison 6 Sitagliptin versus glipizide, Outcome 3 Death (all causes).

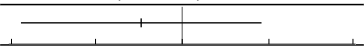


Analysis 6.4. Comparison 6 Sitagliptin versus glipizide, Outcome 4 Myocardial infarction.



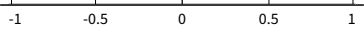
Analysis 6.5. Comparison 6 Sitagliptin versus glipizide, Outcome 5 Stroke.

Study or subgroup	Sitagliptin n/N	Glipizide n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Arjona Ferreira 2013	0/210	1/212		0.34[0.01,8.21]



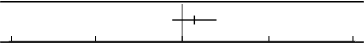
Analysis 6.6. Comparison 6 Sitagliptin versus glipizide, Outcome 6 Total cholesterol.

Study or subgroup	Sitagliptin N	Sitagliptin Mean(SD)	Glipizide N	Glipizide Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Arjona Ferreira 2013	137	-0 (0.6)	139	0.1 (0.6)		-0.18[-0.33,-0.03]



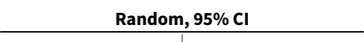
Analysis 6.7. Comparison 6 Sitagliptin versus glipizide, Outcome 7 HDL cholesterol.

Study or subgroup	Sitagliptin N	Sitagliptin Mean(SD)	Glipizide N	Glipizide Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Arjona Ferreira 2013	136	0.1 (0.5)	139	0.1 (0.5)		0.07[-0.06,0.2]



Analysis 6.8. Comparison 6 Sitagliptin versus glipizide, Outcome 8 LDL cholesterol.

Study or subgroup	Sitagliptin N	Sitagliptin Mean(SD)	Glipizide N	Glipizide Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Arjona Ferreira 2013	136	-0 (1)	139	0.3 (1)		-0.3[-0.54,-0.06]

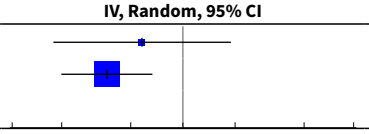


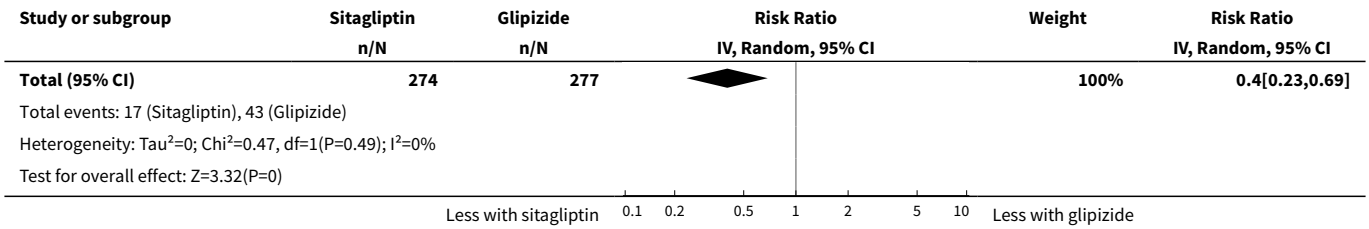
Analysis 6.9. Comparison 6 Sitagliptin versus glipizide, Outcome 9 Triglyceride.

Study or subgroup	Sitagliptin N	Sitagliptin Mean(SD)	Glipizide N	Glipizide Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Arjona Ferreira 2013	137	-0.1 (0.4)	139	-0 (0.6)		-0.06[-0.18,0.06]

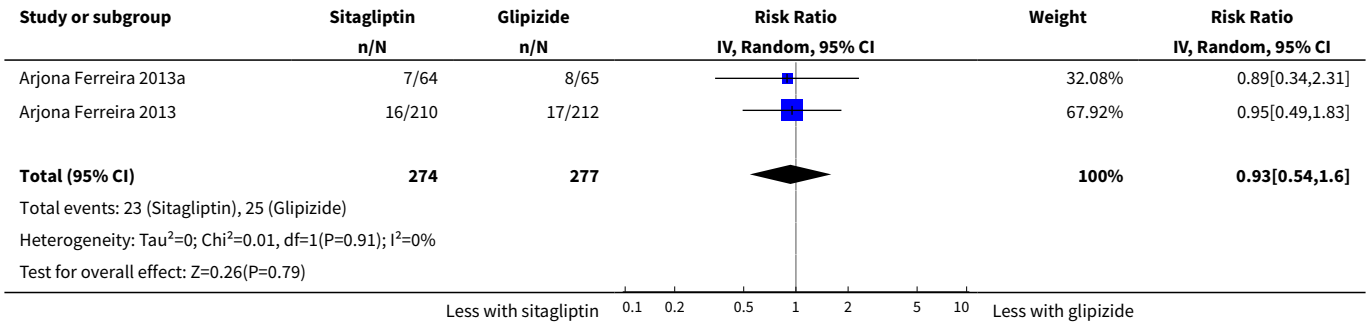
Analysis 6.10. Comparison 6 Sitagliptin versus glipizide, Outcome 10 Hypoglycaemia.

Study or subgroup	Sitagliptin n/N	Glipizide n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Arjona Ferreira 2013a	4/64	7/65		20.83%	0.58[0.18,1.89]
Arjona Ferreira 2013	13/210	36/212		79.17%	0.36[0.2,0.67]

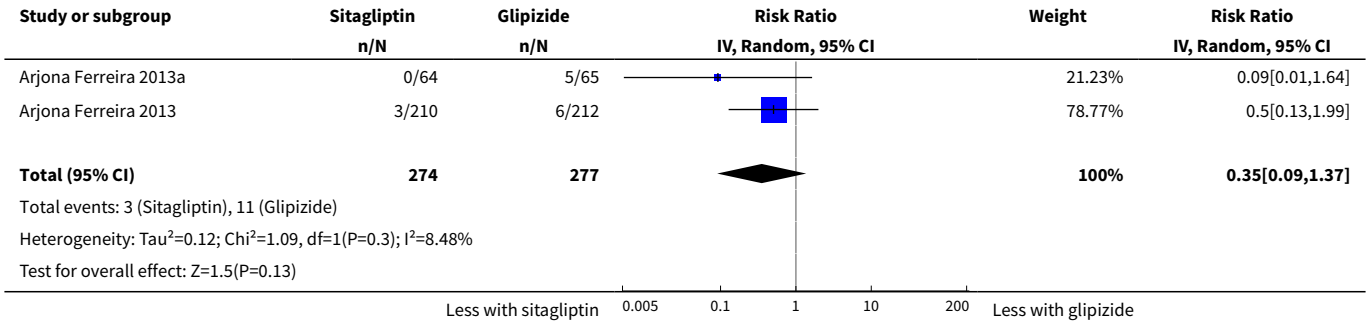




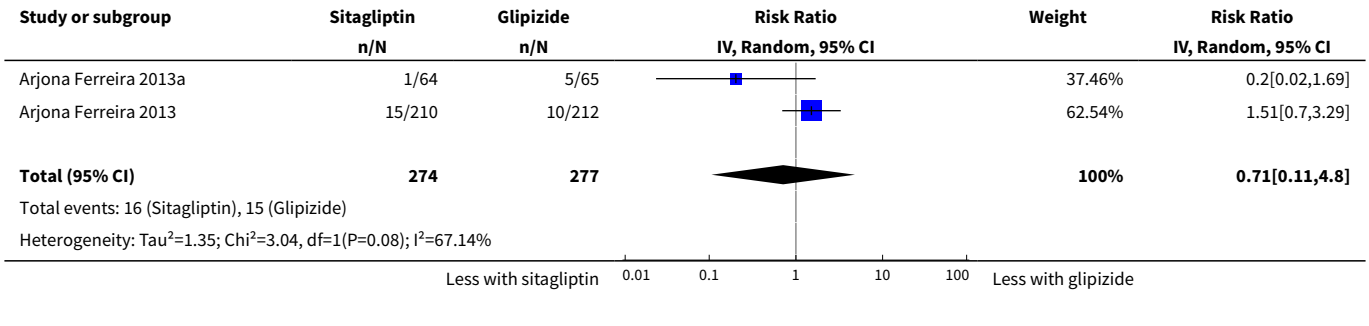
Analysis 6.11. Comparison 6 Sitagliptin versus glipizide, Outcome 11 Discontinuation of medication due to adverse events.

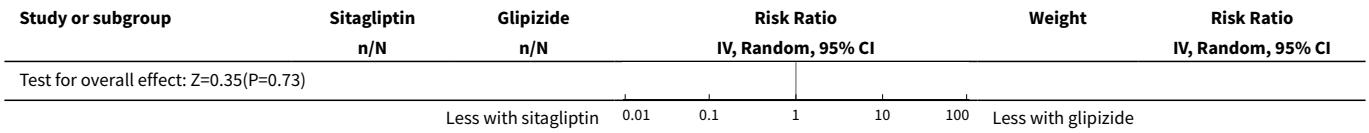


Analysis 6.12. Comparison 6 Sitagliptin versus glipizide, Outcome 12 Hypoglycaemia requiring third party assistance.

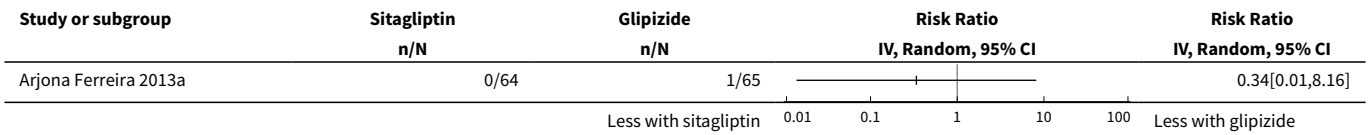


Analysis 6.13. Comparison 6 Sitagliptin versus glipizide, Outcome 13 Peripheral oedema.

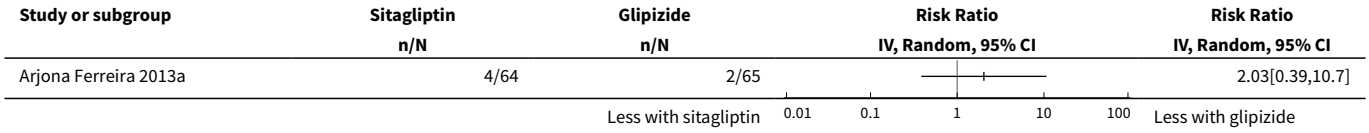




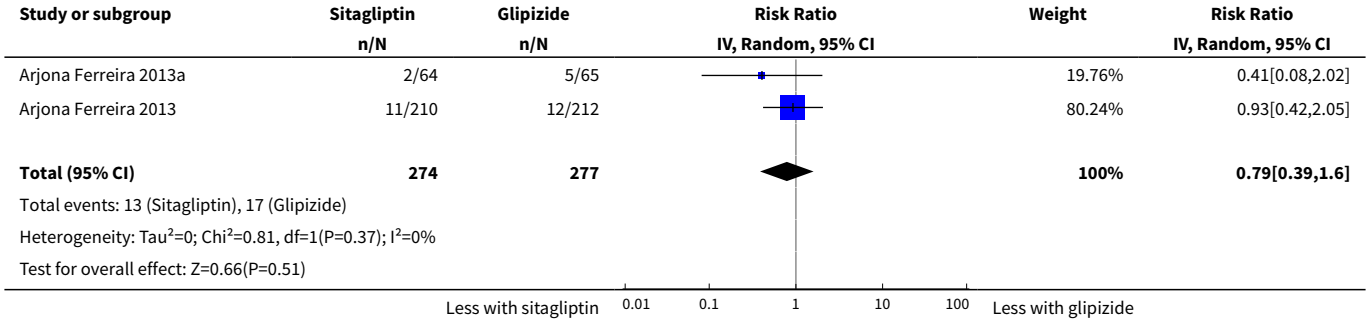
Analysis 6.14. Comparison 6 Sitagliptin versus glipizide, Outcome 14 Fracture.



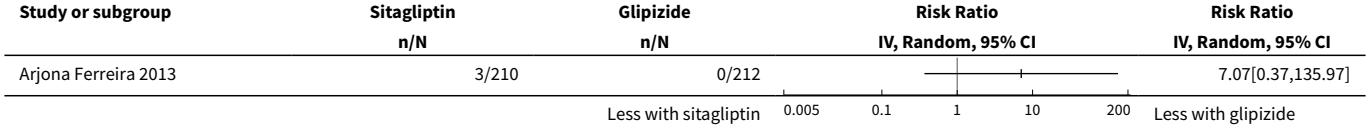
Analysis 6.15. Comparison 6 Sitagliptin versus glipizide, Outcome 15 Vomiting.



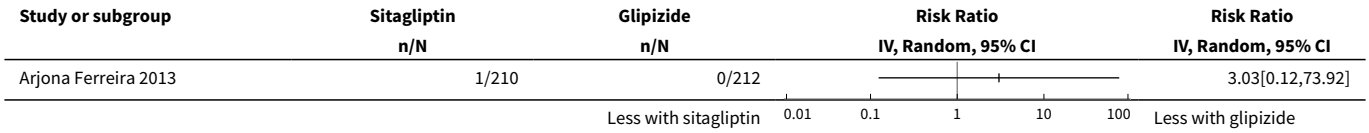
Analysis 6.16. Comparison 6 Sitagliptin versus glipizide, Outcome 16 Diarrhoea.



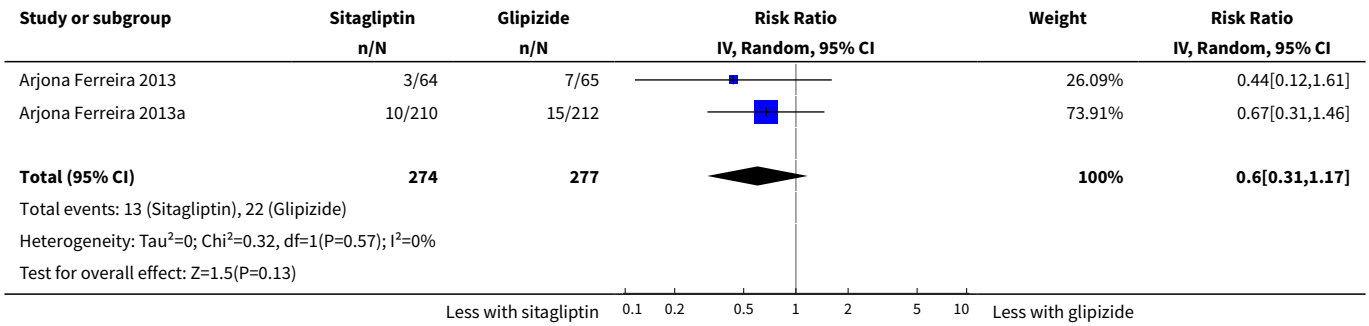
Analysis 6.17. Comparison 6 Sitagliptin versus glipizide, Outcome 17 Malignancy.



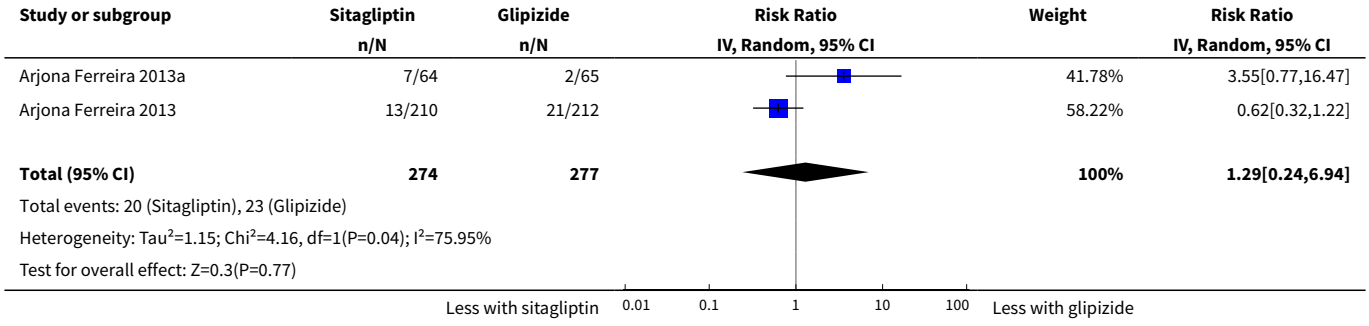
Analysis 6.18. Comparison 6 Sitagliptin versus glipizide, Outcome 18 Pancreatic cancer.



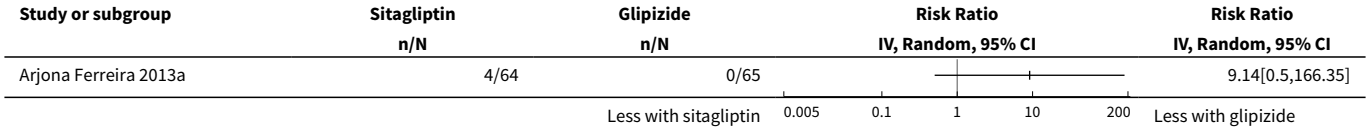
Analysis 6.19. Comparison 6 Sitagliptin versus glipizide, Outcome 19 Upper respiratory tract infection.



Analysis 6.20. Comparison 6 Sitagliptin versus glipizide, Outcome 20 Urinary tract infection.



Analysis 6.21. Comparison 6 Sitagliptin versus glipizide, Outcome 21 Cellulitis.

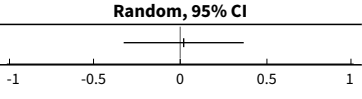


Comparison 7. Vildagliptin versus sitagliptin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 HbA1c	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Fasting blood glucose	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Death (all causes)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4 Hypoglycaemia	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
5 Discontinuation of medication due to adverse events	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
6 Peripheral oedema	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
7 Pancreatitis	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
8 Liver impairment	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

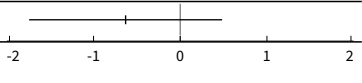
Analysis 7.1. Comparison 7 Vildagliptin versus sitagliptin, Outcome 1 HbA1c.

Study or subgroup	Vildagliptin N	Vildagliptin Mean(SD)	Sitagliptin N	Sitagliptin Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Kothny 2015	78	-0.5 (1.1)	62	-0.6 (1)		0.02[-0.33,0.37]



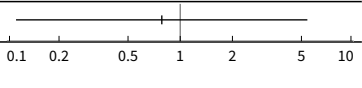
Analysis 7.2. Comparison 7 Vildagliptin versus sitagliptin, Outcome 2 Fasting blood glucose.

Study or subgroup	Vildagliptin N	Vildagliptin Mean(SD)	Sitagliptin N	Sitagliptin Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Kothny 2015	79	-0.5 (3.3)	62	0.2 (3.4)		-0.63[-1.74,0.48]



Analysis 7.3. Comparison 7 Vildagliptin versus sitagliptin, Outcome 3 Death (all causes).

Study or subgroup	Vildagliptin n/N	Sitagliptin n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Kothny 2015	2/83	2/65		0.78[0.11,5.41]



Analysis 7.4. Comparison 7 Vildagliptin versus sitagliptin, Outcome 4 Hypoglycaemia.

Study or subgroup	Vildagliptin n/N	Sitagliptin n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Kothny 2015	13/83	10/65		1.02[0.48,2.17]

Less with vildagliptin 0.1 0.2 0.5 1 2 5 10 Less with sitagliptin

Analysis 7.5. Comparison 7 Vildagliptin versus sitagliptin, Outcome 5 Discontinuation of medication due to adverse events.

Study or subgroup	Vildagliptin n/N	Sitagliptin n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Kothny 2015	6/83	6/65		0.78[0.26,2.32]

Less with vildagliptin 0.01 0.1 1 10 100 Less with sitagliptin

Analysis 7.6. Comparison 7 Vildagliptin versus sitagliptin, Outcome 6 Peripheral oedema.

Study or subgroup	Vildagliptin n/N	Sitagliptin n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Kothny 2015	19/83	16/65		0.93[0.52,1.66]

Less with vildagliptin 0.1 0.2 0.5 1 2 5 10 Less with sitagliptin

Analysis 7.7. Comparison 7 Vildagliptin versus sitagliptin, Outcome 7 Pancreatitis.

Study or subgroup	Vildagliptin n/N	Sitagliptin n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Kothny 2015	0/83	0/65		Not estimable

Less with vildagliptin 0.01 0.1 1 10 100 Less with sitagliptin

Analysis 7.8. Comparison 7 Vildagliptin versus sitagliptin, Outcome 8 Liver impairment.

Study or subgroup	Vildagliptin n/N	Sitagliptin n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Kothny 2015	0/83	2/65		0.16[0.01,3.22]

Less with vildagliptin 0.005 0.1 1 10 200 Less with sitagliptin

Comparison 8. Albiglutide versus sitagliptin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 HbA1c	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

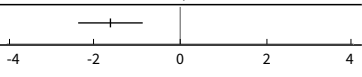
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Fasting blood glucose	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 8.1. Comparison 8 Albiglutide versus sitagliptin, Outcome 1 HbA1c.

Study or subgroup	Albiglutide N	Albiglutide Mean(SD)	Sitagliptin N	Sitagliptin Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Leiter 2014	117	-0.9 (1)	114	-0.3 (1)		-0.52[-0.77,-0.27]

Analysis 8.2. Comparison 8 Albiglutide versus sitagliptin, Outcome 2 Fasting blood glucose.

Study or subgroup	Albiglutide N	Albiglutide Mean(SD)	Sitagliptin N	Sitagliptin Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Leiter 2014	118	-1.4 (2.9)	116	0.2 (2.9)		-1.61[-2.35,-0.87]



Comparison 9. Aleglitazar versus pioglitazone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 HbA1c	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Fasting blood glucose	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Heart failure	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4 Death (all causes)	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
5 All cardiovascular death	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
6 Myocardial infarction	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
7 Stroke	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
8 Weight	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
9 eGFR	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

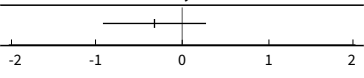
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10 Systolic blood pressure	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
11 Diastolic blood pressure	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
12 Serum creatinine	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
13 Hypoglycaemia	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
14 Hypoglycaemia requiring third party assistance	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
15 Peripheral oedema	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
16 Fracture	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
17 Malignancy	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

Analysis 9.1. Comparison 9 Aleglitazar versus pioglitazone, Outcome 1 HbA1c.

Study or subgroup	Aleglitazar N	Aleglitazar Mean(SD)	Pioglitazone N	Pioglitazone Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
AleNephro 2014	148	-0.7 (1.2)	147	-0.8 (1.2)		0.09[-0.19,0.37]

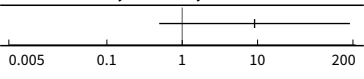
Analysis 9.2. Comparison 9 Aleglitazar versus pioglitazone, Outcome 2 Fasting blood glucose.

Study or subgroup	Aleglitazar N	Aleglitazar Mean(SD)	Pioglitazone N	Pioglitazone Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
AleNephro 2014	148	-2 (2.6)	147	-1.6 (2.6)		-0.32[-0.91,0.27]



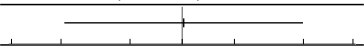
Analysis 9.3. Comparison 9 Aleglitazar versus pioglitazone, Outcome 3 Heart failure.

Study or subgroup	Aleglitazar n/N	Pioglitazone n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
AleNephro 2014	4/149	0/151		9.12[0.5,167.92]



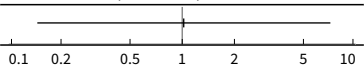
Analysis 9.4. Comparison 9 Aleglitazar versus pioglitazone, Outcome 4 Death (all causes).

Study or subgroup	Aleglitazar n/N	Pioglitazone n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
AleNephro 2014	3/149	3/152		1.02[0.21,4.97]



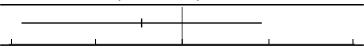
Analysis 9.5. Comparison 9 Aleglitazar versus pioglitazone, Outcome 5 All cardiovascular death.

Study or subgroup	Aleglitazar n/N	Pioglitazone n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
AleNephro 2014	2/149	2/152		1.02[0.15,7.15]



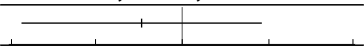
Analysis 9.6. Comparison 9 Aleglitazar versus pioglitazone, Outcome 6 Myocardial infarction.

Study or subgroup	Aleglitazar n/N	Pioglitazone n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
AleNephro 2014	0/149	1/152		0.34[0.01,8.28]



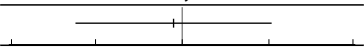
Analysis 9.7. Comparison 9 Aleglitazar versus pioglitazone, Outcome 7 Stroke.

Study or subgroup	Aleglitazar n/N	Pioglitazone n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
AleNephro 2014	0/149	1/152		0.34[0.01,8.28]



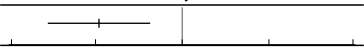
Analysis 9.8. Comparison 9 Aleglitazar versus pioglitazone, Outcome 8 Weight.

Study or subgroup	Aleglitazar N	Aleglitazar Mean(SD)	Pioglitazone N	Pioglitazone Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
AleNephro 2014	149	2.4 (5)	147	2.5 (5)		-0.1[-1.23,1.03]



Analysis 9.9. Comparison 9 Aleglitazar versus pioglitazone, Outcome 9 eGFR.

Study or subgroup	Aleglitazar N	Aleglitazar Mean(SD)	Pioglitazone N	Pioglitazone Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
AleNephro 2014	148	-15 (25.8)	147	-5.4 (26)		-9.6[-15.5,-3.7]



Analysis 9.10. Comparison 9 Aleglitazar versus pioglitazone, Outcome 10 Systolic blood pressure.

Study or subgroup	Aleglitazar		Pioglitazone		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
AleNephro 2014	149	1.7 (17.1)	147	2.3 (17)		-0.6[-4.49,3.29]

Lower with aleglitazar -10 -5 0 5 10 Lower with pioglitazone

Analysis 9.11. Comparison 9 Aleglitazar versus pioglitazone, Outcome 11 Diastolic blood pressure.

Study or subgroup	Aleglitazar		Pioglitazone		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
AleNephro 2014	149	-2.2 (10.6)	147	-0.5 (10.8)		-1.7[-4.14,0.74]

Lower with aleglitazar -10 -5 0 5 10 Lower with pioglitazone

Analysis 9.12. Comparison 9 Aleglitazar versus pioglitazone, Outcome 12 Serum creatinine.

Study or subgroup	Aleglitazar		Pioglitazone		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
AleNephro 2014	148	0.2 (0.3)	147	0.1 (0.3)		0.12[0.05,0.19]

Lower with aleglitazar -1 -0.5 0 0.5 1 Lower with pioglitazone

Analysis 9.13. Comparison 9 Aleglitazar versus pioglitazone, Outcome 13 Hypoglycaemia.

Study or subgroup	Aleglitazar	Pioglitazone	Risk Ratio	Risk Ratio
	n/N	n/N	IV, Random, 95% CI	IV, Random, 95% CI
AleNephro 2014	29/149	22/152		1.34[0.81,2.23]

Less with aleglitazar 0.1 0.2 0.5 1 2 5 10 Less with pioglitazone

Analysis 9.14. Comparison 9 Aleglitazar versus pioglitazone, Outcome 14 Hypoglycaemia requiring third party assistance.

Study or subgroup	Aleglitazar	Pioglitazone	Risk Ratio	Risk Ratio
	n/N	n/N	IV, Random, 95% CI	IV, Random, 95% CI
AleNephro 2014	2/149	0/152		5.1[0.25,105.34]

Less with aleglitazar 0.005 0.1 1 10 200 Less with pioglitazone

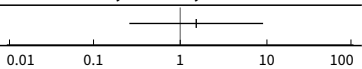
Analysis 9.15. Comparison 9 Aleglitazar versus pioglitazone, Outcome 15 Peripheral oedema.

Study or subgroup	Aleglitazar	Pioglitazone	Risk Ratio	Risk Ratio
	n/N	n/N	IV, Random, 95% CI	IV, Random, 95% CI
AleNephro 2014	18/149	30/152		0.61[0.36,1.05]

Less with aleglitazar 0.1 0.2 0.5 1 2 5 10 Less with pioglitazone

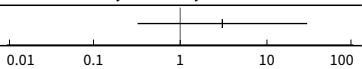
Analysis 9.16. Comparison 9 Aleglitazar versus pioglitazone, Outcome 16 Fracture.

Study or subgroup	Aleglitazar n/N	Pioglitazone n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
AleNephro 2014	3/149	2/152		1.53[0.26,9.03]



Analysis 9.17. Comparison 9 Aleglitazar versus pioglitazone, Outcome 17 Malignancy.

Study or subgroup	Aleglitazar n/N	Pioglitazone n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
AleNephro 2014	3/149	1/152		3.06[0.32,29.09]

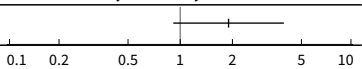


Comparison 10. Insulin glulisine and glargine 0.5 versus 0.25 U/kg/d

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hypoglycaemia < 3.89 mmol/L	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2 Hypoglycaemia < 2.78 mmol/L	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

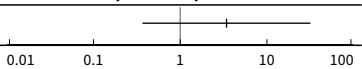
Analysis 10.1. Comparison 10 Insulin glulisine and glargine 0.5 versus 0.25 U/kg/d, Outcome 1 Hypoglycaemia < 3.89 mmol/L.

Study or subgroup	Glulisine 0.5 U/kg/d n/N	Glulisine 0.25 U/kg/d n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Baldwin 2012	15/50	9/57		1.9[0.91,3.96]



Analysis 10.2. Comparison 10 Insulin glulisine and glargine 0.5 versus 0.25 U/kg/d, Outcome 2 Hypoglycaemia < 2.78 mmol/L.

Study or subgroup	Glulisine 0.5 U/kg/d n/N	Glulisine 0.25 U/kg/d n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Baldwin 2012	3/50	1/57		3.42[0.37,31.84]



APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor: [Renal Replacement Therapy] this term only 2. MeSH descriptor: [Renal Dialysis] explode all trees 3. MeSH descriptor: [Hemofiltration] explode all trees 4. MeSH descriptor: [Renal Insufficiency] this term only 5. MeSH descriptor: [Renal Insufficiency, Chronic] explode all trees 6. MeSH descriptor: [Kidney Diseases] this term only 7. MeSH descriptor: [Uremia] this term only 8. haemodialysis or haemodialysis:ti,ab,kw (Word variations have been searched) 9. hemofiltration or haemofiltration:ti,ab,kw (Word variations have been searched) 10. hemodiafiltration or haemodiafiltration:ti,ab,kw (Word variations have been searched) 11. dialysis:ti,ab,kw (Word variations have been searched) 12. CAPD or CCPD or APD:ti,ab,kw (Word variations have been searched) 13. end-stage renal or end-stage kidney or endstage renal or endstage kidney:ti,ab,kw (Word variations have been searched) 14. ESRF or ESKF or ESRD or ESKD:ti,ab,kw (Word variations have been searched) 15. chronic kidney or chronic renal:ti,ab,kw (Word variations have been searched) 16. CKF or CKD or CRF or CRD:ti,ab,kw (Word variations have been searched) 17. predialysis or pre-dialysis:ti,ab,kw (Word variations have been searched) 18. uremi* or uraemia*:ti,ab,kw (Word variations have been searched) 19. {or #1-#18} 20. MeSH descriptor: [Diabetic Nephropathies] this term only 21. diabetic nephropath*:ti,ab,kw (Word variations have been searched) 22. diabetic kidney or diabetic renal:ti,ab,kw (Word variations have been searched) 23. proteinuria* or albuminuria* or microalbuminuria* or macroalbuminuria*:ti,ab,kw (Word variations have been searched) 24. MeSH descriptor: [Diabetes Mellitus] explode all trees 25. MeSH descriptor: [Diabetes Mellitus, Type 1] explode all trees 26. MeSH descriptor: [Diabetes Mellitus, Type 2] this term only 27. {or #24-#26} 28. {and #23, #27} 29. {or #20-#22, #28} 30. {and #19, #29} 31. MeSH descriptor: [Hypoglycemic Agents] explode all trees 32. MeSH descriptor: [Sulfonylurea Compounds] explode all trees 33. MeSH descriptor: [Sodium-Glucose Transporter 2] this term only 34. MeSH descriptor: [Glucagon-Like Peptide 1] explode all trees 35. MeSH descriptor: [Thiazolidinediones] this term only 36. MeSH descriptor: [Amylin Receptor Agonists] explode all trees 37. metformin:ti,ab,kw (Word variations have been searched) 38. insulin:ti,ab,kw (Word variations have been searched) 39. glipizide or glimepride or gliclazide or glibenclamide or glyburide:ti,ab,kw (Word variations have been searched) 40. "sodium glucose co-transporter 2" or "Sodium glucose transporter 2":ti,ab,kw (Word variations have been searched) 41. canagliflozin or ipragliflozin or dapagliflozin or empagliflozin:ti,ab,kw (Word variations have been searched)

(Continued)

42.remogliflozin or sergliflozin or tofogliflozin:ti,ab,kw (Word variations have been searched)
43.ipragliflozin or ertugliflozin or luseogliflozin or sotagliflozin:ti,ab,kw (Word variations have been searched)
44.miglitol or voglibose or alogliptin or gemigliptin:ti,ab,kw (Word variations have been searched)
45.linagliptin or saxagliptin or sitagliptin or vildagliptin:ti,ab,kw (Word variations have been searched)
46.anagliptin or teneligliptin or gemigliptin or dutogliptin:ti,ab,kw (Word variations have been searched)
47.pramlintide or exenatide or liraglutide or taspoglutide:ti,ab,kw (Word variations have been searched)
48.albiglutide or lixisenatide or albiglutide or dulaglutide:ti,ab,kw (Word variations have been searched)
49.Glitazone or pioglitazone or rivoglitazone or rosiglitazone or troglitazone:ti,ab,kw (Word variations have been searched)
50.nateglinide or repaglinide or mitiglinide or bromocriptine or pramlintide:ti,ab,kw (Word variations have been searched)
51.amylin analog*:ti,ab,kw (Word variations have been searched)
52.{or #31-#51}
53.{and #30, #52}

MEDLINE	1. Renal Replacement Therapy/ 2. exp Renal Dialysis/ 3. exp Hemofiltration/ 4. (haemodialysis or haemodialysis).tw. 5. (hemofiltration or haemofiltration).tw. 6. (hemodiafiltration or haemodiafiltration).tw. 7. dialysis.tw. 8. (CAPD or CCPD or APD).tw. 9. Renal Insufficiency/ 10.exp Renal Insufficiency, Chronic/ 11.Kidney Diseases/ 12.Uremia/ 13.(end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw. 14.(ESRF or ESKF or ESRD or ESKD).tw. 15.(chronic kidney or chronic renal).tw. 16.(CKF or CKD or CRF or CRD).tw. 17.(predialysis or pre-dialysis).tw. 18.ur?emi$.tw. 19.or/1-18 20.Diabetic Nephropathies/ 21.diabetic nephropath$.tw. 22.(diabetic kidney or diabetic renal).tw. 23.(proteinuria$ or albuminuria$ or microalbuminuria$ or macroalbuminuria$).tw. 24.diabetes mellitus/ or exp diabetes mellitus, type 1/ or exp diabetes mellitus, type 2/ 25.and/23-24 26.or/20-22,25 27.or/19,26 28.exp Hypoglycemic Agents/ 29.metformin.tw. 30.exp Sulfonylurea Compounds/ 31.(glipizide or glimepride or gliclazide or glibenclamide or glyburide).tw. 32.insulin.tw. 33.Sodium-Glucose Transporter 2/

(Continued)

	34.(Sodium glucose co-transporter 2 or Sodium glucose transporter 2).tw. 35.canagliflozin.tw. 36.ipragliflozin.tw. 37.dapagliflozin.tw. 38.empagliflozin.tw. 39.remogliflozin.tw. 40.sergliflozin.tw. 41.tofogliflozin.tw. 42.(ipragliflozin or ertugliflozin or luseogliflozin or sotagliflozin).tw. 43.miglitol.tw. 44.voglibose.tw. 45.alogliptin.tw. 46.gemigliptin.tw. 47.linagliptin.tw. 48.saxagliptin.tw. 49.sitagliptin.tw. 50.vildagliptin.tw. 51.(anagliptin or teneligliptin or gemigliptin or dutogliptin).tw. 52.Glucagon-Like Peptide 1/ 53.pramlintide.tw. 54.exenatide.tw. 55.liraglutide.tw. 56.taspoglutide.tw. 57.albiglutide.tw. 58.lixisenatide.tw. 59.(albiglutide or dulaglutide).tw. 60.Thiazolidinediones/ 61.glitazone$.tw. 62.pioglitazone.tw. 63.rivoglitazone.tw. 64.rosiglitazone.tw. 65.troglitazone.tw. 66.nateglinide.tw. 67.repaglinide.tw. 68.mitiglinide.tw. 69.Bromocriptine/ 70.bromocriptine.tw. 71.pramlintide.tw. 72.exp Amylin Receptor Agonists/ 73.amylin analog*.tw. 74.or/28-73 75.and/27,74
EMBASE	1. exp renal replacement therapy/ 2. kidney disease/ 3. chronic kidney disease/ 4. kidney failure/ 5. chronic kidney failure/ 6. mild renal impairment/ 7. moderate renal impairment/ 8. severe renal impairment/ 9. end stage renal disease/

(Continued)

10.renal replacement therapy-dependent renal disease/
11.(haemodialysis or haemodialysis).tw.
12.(hemofiltration or haemofiltration).tw.
13.(hemodiafiltration or haemodiafiltration).tw.
14.dialysis.tw.
15.(CAPD or CCPD or APD).tw.
16.(chronic kidney or chronic renal).tw.
17.(CKF or CKD or CRF or CRD).tw.
18.(end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw.
19.(ESRF or ESKF or ESRD or ESKD).tw.
20.(predialysis or pre-dialysis).tw.
21.or/1-20
22.diabetic nephropathy/
23.(diabetic kidney or diabetic renal).tw.
24.diabetic nephropath$.tw.
25.diabetes mellitus/
26.non insulin dependent diabetes mellitus/
27.insulin dependent diabetes mellitus/
28.or/25-27
29.(proteinuria$ or albuminuria$ or microalbuminuria$ or macroalbuminuria$).tw.
30.and/28-29
31.or/22-24,30
32.or/21,31
33.exp antidiabetic agent/
34.exp alpha glucosidase inhibitor/
35.exp glucagon like peptide 1 receptor agonist/
36.exp dipeptidyl peptidase IV inhibitor/
37.exp amylin derivative/
38.Bromocriptine/
39.or/33-38
40.and/32,39

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.
	Unclear: Insufficient information about the sequence generation process to permit judgement.
Allocation concealment Selection bias (biased allocation to interventions) due to	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequential-

(Continued)

inadequate concealment of allocations prior to assignment	ly numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear: Randomisation stated but no information on method used is available.
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse

(Continued)

	effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

HISTORY

Protocol first published: Issue 8, 2015
Review first published: Issue 9, 2018

Date	Event	Description
6 August 2015	Amended	Search strategies for MEDLINE, EMBASE & CENTRAL revised.

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: CL, MJ, SZ
2. Study selection: CL, TT, YW, JL
3. Extract data from studies: CL, TT, YW, JL
4. Enter data into RevMan: CL,TT
5. Carry out the analysis: CL,TT
6. Interpret the analysis: CL, TT, YH, MJ, AC, CH, HP, SB, VP, SZ
7. Draft the final review: CL, TT, VP, SZ
8. Disagreement resolution: SZ, MJ
9. Update the review: CL, TT, YH, MJ, AC, CH, HP, SB, VP, SZ

DECLARATIONS OF INTEREST

- Clement Lo: none known
- Tadashi Toyoma: none known
- Ying Wang: none known
- Jin Lin: none known
- Yoichiro Hirakawa: none known
- Min Jun: none known
- Sunil Badve: none known
- Helen Pilmore: none known
- Carmel Hawley has received fees from Amgen, Shire, Roche, Abbott, Bayer, Fresenius, Baxter, Gambro, Janssen-Cilag and Genzyme in relation to consultancy, speakers' fees, education, and grants for activities unrelated to this review
- Alan Cass: The Menzies School of Health Research has received unconditional research funding from AMGEN, Merck and Novartis for research in chronic kidney disease in Indigenous populations.

- Vlado Perkovic: has received support from Boehringer Ingelheim for Advisory Boards, and his employer has received payments from Boehringer Ingelheim and Merck for Advisory activities, and has a contract for the conduct of a clinical study of glucose-lowering with Janssen
- Sophia Zoungas has received fees from Abbvie, Amgen Australia Pty Ltd, AstraZeneca Pty Ltd, Bristol Myers Squibb Australia Pty Ltd, Boehringer Ingleheim, Janssen-Cilag Pty Ltd, Merck Sharp & Dohme (Australia) Pty Ltd, Novo Nordisk, Novartis Pharmaceuticals Australia, Ogilvy Healthworld, Sanofi, Servier Laboratories, and Takeda Pharmaceuticals Australia Pty Ltd in relation to consultancy, speakers' fees, education, and grants for activities unrelated to this review

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Due to a lack of uniform reporting in included studies of fatal and non-fatal myocardial infarcts and strokes, we reported myocardial infarction and strokes as secondary outcomes rather than non-fatal myocardial infarcts and strokes.

INDEX TERMS

Medical Subject Headings (MeSH)

Cause of Death; Diabetes Mellitus [blood] [*drug therapy] [mortality]; Diabetic Nephropathies [blood] [*drug therapy] [mortality]; Dipeptidyl-Peptidase IV Inhibitors [therapeutic use]; Glipizide [adverse effects] [therapeutic use]; Glucagon-Like Peptide 1 [agonists]; Glycated Hemoglobin A [drug effects]; Hypoglycemic Agents [adverse effects] [*therapeutic use]; Insulin [adverse effects] [*therapeutic use]; Randomized Controlled Trials as Topic; Renal Insufficiency, Chronic [blood] [*drug therapy] [mortality]; Sitagliptin Phosphate [adverse effects] [therapeutic use]; Sodium-Glucose Transporter 2; Sodium-Glucose Transporter 2 Inhibitors; Thiazolidinediones [therapeutic use]

MeSH check words

Humans