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Glucose-lowering agents for treating pre-existing and new-onset diabetes in kidney transplant recipients (Review)

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Glucose-lowering agents for treating pre-existing and new-onset diabetes in kidney transplant recipients
(Review)

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[Intervention Review]

Glucose-lowering agents for treating pre-existing and new-onset diabetes in kidney transplant recipients

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ABSTRACT

Background

Kidney transplantation is the preferred management for patients with end-stage kidney disease (ESKD). However, it is often complicated by worsening or new-onset diabetes. The safety and efficacy of glucose-lowering agents after kidney transplantation is largely unknown. This is an update of a review first published in 2017.

Objectives

To evaluate the efficacy and safety of glucose-lowering agents for treating pre-existing and new onset diabetes in people who have undergone kidney transplantation.

Search methods

We searched the Cochrane Kidney and Transplant Register of Studies up to 16 January 2020 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), quasi-RCTs and cross-over studies examining head-to-head comparisons of active regimens of glucose-lowering therapy or active regimen compared with placebo/standard care in patients who have received a kidney transplant and have diabetes were eligible for inclusion.

Data collection and analysis

Four authors independently assessed study eligibility and quality and performed data extraction. Continuous outcomes were expressed as post-treatment mean differences (MD) or standardised mean difference (SMD). 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

Ten studies (21 records, 603 randomised participants) were included - three additional studies (five records) since our last review. Four studies compared more intensive versus less intensive insulin therapy; two studies compared dipeptidyl peptidase-4 (DPP-4) inhibitors to placebo; one study compared DPP-4 inhibitors to insulin glargine; one study compared sodium glucose co-transporter 2 (SGLT2) inhibitors to placebo; and two studies compared glitazones and insulin to insulin therapy alone. The majority of studies had an unclear to a high risk of bias. There were no studies examining the effects of biguanides, glinides, GLP-1 agonists, or sulphonylureas.

Compared to less intensive insulin therapy, it is unclear if more intensive insulin therapy has an effect on transplant or graft survival (4 studies, 301 participants: RR 1.12, 95% CI 0.32 to 3.94; $I^2 = 49\%$; very low certainty evidence), delayed graft function (2 studies, 153 participants: RR 0.63, 0.42 to 0.93; $I^2 = 0\%$; very low certainty evidence), HbA1c (1 study, 16 participants; very low certainty evidence), fasting blood glucose (1 study, 24 participants; very low certainty evidence), kidney function markers (1 study, 26 participants; very low certainty evidence), death (any cause) (3 studies, 208 participants" RR 0.68, 0.29 to 1.58; $I^2 = 0\%$; very low certainty evidence), hypoglycaemia (4 studies, 301 participants; very low certainty evidence) and medication discontinuation due to adverse effects (1 study, 60 participants; very low certainty evidence).

Compared to placebo, it is unclear whether DPP-4 inhibitors have an effect on hypoglycaemia and medication discontinuation (2 studies, 51 participants; very low certainty evidence). However, DPP-4 inhibitors may reduce HbA1c and fasting blood glucose but not kidney function markers (1 study, 32 participants; low certainty evidence).

Compared to insulin glargine, it is unclear if DPP-4 inhibitors have an effect on HbA1c, fasting blood glucose, hypoglycaemia or discontinuation due to adverse events (1 study, 45 participants; very low certainty evidence).

Compared to placebo, SGLT2 inhibitors probably do not affect kidney graft survival (1 study, 44 participants; moderate certainty evidence), but may reduce HbA1c without affecting fasting blood glucose and eGFR long-term (1 study, 44 participants, low certainty evidence). SGLT2 inhibitors probably do not increase hypoglycaemia, and probably have little or no effect on medication discontinuation due to adverse events. However, all participants discontinuing SGLT2 inhibitors had urinary tract infections (1 study, 44 participants, moderate certainty evidence).

Compared to insulin therapy alone, it is unclear if glitazones added to insulin have an effect on HbA1c or kidney function markers (1 study, 62 participants; very low certainty evidence). However, glitazones may make little or no difference to fasting blood glucose (2 studies, 120 participants; low certainty evidence), and medication discontinuation due to adverse events (1 study, 62 participants; low certainty evidence).

No studies of DPP-4 inhibitors, or glitazones reported effects on transplant or graft survival, delayed graft function or death (any cause).

Authors' conclusions

The efficacy and safety of glucose-lowering agents in the treatment of pre-existing and new-onset diabetes in kidney transplant recipients is questionable. Evidence from existing studies examining the effect of intensive insulin therapy, DPP-4 inhibitors, SGLT inhibitors and glitazones is mostly of low to very low certainty. Appropriately blinded, larger, and higher quality RCTs are needed to evaluate and compare the safety and efficacy of contemporary glucose-lowering agents in the kidney transplant population.

PLAIN LANGUAGE SUMMARY

Glucose-lowering agents for treating pre-existing and new-onset diabetes in kidney transplant recipients

What is the issue?

Kidney transplantation is often complicated by worsening or new-onset diabetes. The safety and effectiveness of drugs used to lower glucose in this setting is largely unknown.

What did we do?

We evaluated the effectiveness and safety of glucose-lowering drugs in people with diabetes who have received a kidney transplant by searching the Cochrane Kidney and Transplant Specialised Register. We updated our original review by including all randomised controlled and cross-over studies examining this question to 16 January 2020.

What did we find?

We included ten studies (including three additional studies) with a total of 603 randomised people receiving kidney transplants. Four studies compared more intensive to less intensive insulin therapy; two studies compared dipeptidyl peptidase-4 (DPP-4) inhibitors to placebo; one study compared DPP-4 inhibitors to insulin glargine; one study compared sodium glucose co-transporter 2 (SGLT2) inhibitors to placebo; and two studies compared glitazones plus insulin to insulin therapy alone. From these studies, the effects of more compared to less intensive insulin treatment on kidney transplant survival, blood glucose control, death, and treatment side-effects including

hypoglycaemia, are not well understood. Based on one study, DPP-4 inhibitors may improve blood glucose control without affecting kidney function markers. The rate of side-effects of DPP-4 inhibitors compared to placebo or insulin is also not well understood. Based on one study, SGLT2 inhibitors probably do not affect kidney transplant survival, but may improve long-term blood glucose control without affecting long-term kidney function. SGLT2 inhibitors probably do not cause low sugar levels and have little or no effect on people stopping the medication. However, in the study, people who stop SGLT2 inhibitors had urinary tract infections. Glitazones and insulin may not have an effect on blood glucose control or side-effects compared to insulin alone. The effects of using DPP-4 inhibitors compared to placebo or insulin, or glitazones and insulin compared to insulin alone, on survival of the kidney transplant and death is also unclear.

Conclusion

Contemporary evidence concerning glucose-lowering treatment for diabetes in people who have received kidney transplants is limited. Larger, higher quality studies are needed to evaluate the safety and effectiveness of current glucose lowering treatments.

SUMMARY OF FINDINGS

Summary of findings 1. More intensive versus less intensive insulin therapy for treating pre-existing and new-onset diabetes in kidney transplant recipients

More intensive versus less intensive insulin therapy for treating pre-existing and new-onset diabetes in kidney transplant recipients

Patient or population: pre-existing and new-onset diabetes in kidney transplant recipients

Setting: any

Intervention: more intensive insulin therapy

Comparison: less intensive insulin therapy

Outcomes	No. of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with less intensive insulin therapy	Risk difference with more intensive insulin therapy
Transplant or graft survival assessed with: graft loss/rejection Time frame: 13 months to 5 years	301 (4)	⊕⊕⊕⊕ VERY LOW 1, 2, 3, 4	RR 1.12 (0.32 to 3.94)	63 per 1,000	8 more per 1,000 (43 fewer to 186 more)
Delayed graft function Time frame: 1 to 3 years	153 (2)	⊕⊕⊕⊕ VERY LOW 3, 5, 6, 7	RR 0.63 (0.42 to 0.93)	430 per 1,000	159 fewer per 1,000 (250 fewer to 30 fewer)
HbA1c Time frame: 13 months	16 (1)	⊕⊕⊕⊕ VERY LOW 3, 8, 9	--	Barbosa 1983 reported HbA1c changed from 15 ± 2.3% (mean ± SEM: 140 ± 25 mmol/mol, month 7) to 13 ± 0.9% (119 ± 10 mmol/mol, month 13) in the less intensive group, and changed from 11 ± 0.4% (97 ± 4 mmol/mol, month 7) to 10 ± 0.8% (86 ± 9 mmol/mol, month 13) in the more intensive group	
FBG (mmol/L) Time frame: 13 months	24 (1)	⊕⊕⊕⊕ VERY LOW 3, 8, 9	--	Barbosa 1983 reported that intensive insulin therapy achieved a lower FBG (mean ± SEM: 7.22 ± 0.50 mmol/L) compared with less intensive insulin therapy (13.44 ± 1.22 mmol/L) at 13 months (the study lasted for 2 years)	
Kidney function markers: creatinine, eGFR	36 (1)	⊕⊕⊕⊕ VERY LOW 3, 4, 9, 10	--	HiRT 2016 reported eGFR increased by 4.6 (95% CI -9.75, 18.95) mL/min/1.73 m ² , and serum creatinine changed by -10.6 (95% CI -37.0, 15.7) µmol/L after 1 year follow-up of 36 participants	

Time frame: 1 year					
Death (any cause)	208 (3)	⊕⊕⊕⊕ VERY LOW 3, 4, 11	RR 0.68 (0.29 to 1.58)	118 per 1,000	38 fewer per 1,000 (84 fewer to 69 more)
Time frame: 1 to 5 years					
Hypoglycaemia	301 (4)	⊕⊕⊕⊕ VERY LOW 1, 3, 5	--	<p>Barbosa 1983 reported in the narrative that intensive insulin therapy resulted in more frequent and severe episodes of hypoglycaemia compared with standard insulin therapy. Barbosa 1994 reported only severe hypoglycaemic episodes, that is, those requiring third party assistance. More intensive insulin therapy resulted in a higher rate of severe hypoglycaemia compared with less intensive insulin therapy (1.7 episodes/patient/year versus < 0.1 episodes/patient/year, P < 0.001). Of the 29 episodes of severe hypoglycaemia resulting in hospital admission, 26 occurred in the intensive insulin group. A patient in the intensive insulin group remained comatose for 6 days and required a 2-week hospital admission. In Hermayer 2012, intensive insulin therapy may have increased the risk of severe hypoglycaemia (< 2.2 mmol/L), however the 95% CI indicated there may be no difference (RR 3.90, 95% CI 0.85 to 17.78) compared to less intensive insulin therapy. HiRT 2016 reported no episodes of hypoglycaemia in either arm</p>	
Time frame: 13 months to 5 years					
Discontinuation of medication due to adverse events	60 (1)	⊕⊕⊕⊕ VERY LOW 3, 10	No events	HiRT 2016 reported the outcome, but no events were observed (n = 60)	
Time frame: 1 year					

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

CI: confidence interval; **eGFR:** estimates glomerular filtration rate; **FBG:** fasting blood glucose; **HbA1c:** glycated haemoglobin A1c; **RR:** risk ratio; **SEM:** standard error of the mean

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

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

¹ Downgraded 2 levels because all studies had high risk of performance bias, high or unknown risk of detection bias, majority had high risk of attrition bias, and majority had an unknown risk of selection bias

² Wide variance of point estimates across studies

³ Small sample size

⁴ The CI includes both appreciable benefit and harm

⁵ [HiRT 2016](#) was an open-label study

- ⁶ The primary outcome reported in the manuscript ([HiRT 2016](#)) was different from the registered one (reporting bias)
⁷ Wide variance of point estimates across studies
⁸ High risk of performance, attrition, and outcome reporting bias. Unclear risk of selection and detection bias
⁹ Surrogate outcome
¹⁰ Downgraded 2 levels due to a high risk of performance, detection, and outcome reporting bias
¹¹ A study with the highest weight ([Barbosa 1994](#)) was unblinded (performance bias), and a large number of patients did not complete the study (attrition bias)

Summary of findings 2. DPP-4 inhibitors versus placebo for treating pre-existing and new-onset diabetes in kidney transplant recipients

DPP-4 inhibitors versus placebo for treating pre-existing and new-onset diabetes in kidney transplant recipients

Patient or population: pre-existing and new-onset diabetes in kidney transplant recipients

Setting: any

Intervention: DPP-4 inhibitors

Comparison: placebo

Outcomes	No. of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo	Risk difference with DPP-4 inhibitors
Transplant or graft survival	Not reported	--	--	--	--
Delayed graft function	Not reported	--	--	--	--
HbA1c Time frame: 3 months	32 (1)	⊕⊕⊕⊕ LOW 1, 2	-	The mean HbA1c in the placebo group was -0.1% (-1 mmol/mol)	The mean HbA1c was 0.5% lower in the DPP-4 inhibitors group (0.85% lower to 0.15% lower); 5 mmol/mol lower (9 lower to 2 lower)
FBG Time frame: 3 months	32 (1)	⊕⊕⊕⊕ LOW 1, 2	--	The mean FBG in the placebo group was -0.18 mmol/L	The mean FBG was 0.75 mmol/L lower in the DPP-4 inhibitors group (1.48 lower to 0.02 lower)
Kidney function markers assessed with: eGFR Time frame: 3 months	32 (1)	⊕⊕⊕⊕ LOW 1, 2	--	The mean eGFR in the placebo group was 2.1 mL/min/1.73 m ²	The mean eGFR in the DPP-4 inhibitor group was 0.2 mL/min/1.73 m ² lower (6.07 lower to 5.67 higher)
Death (any cause)	Not reported	-	--	-	-
Hypoglycaemia	51 (2)	⊕⊕⊕⊕ VERY LOW 1, 3	--	Haidinger 2010 did not report any hypoglycaemia in the vildagliptin group (n = 16)	

Time frame: 8 to 16 weeks				Strom Halden 2014 reported 2 patients had asymptomatic moderate hypoglycaemia in the sitagliptin group (n = 19) although these patients were also receiving glipizide
Discontinuation of medication due to adverse events	51 (2)	VERY LOW 1, 3	--	Haidinger 2010 reported no discontinuation of medication due to adverse events (n = 32) Strom Halden 2014 reported one event in the sitagliptin group (n 19)
Time frame: 8 to 16 weeks				

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

CI: confidence interval; **eGFR:** estimates glomerular filtration rate; **FBG:** fasting blood glucose; **HbA1c:** glycated haemoglobin A1c; **RR:** risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

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

¹ Small sample size

² Surrogate outcome

³ Downgraded 2 levels because one out of two studies had a high risk of selection, performance and detection bias.

Summary of findings 3. DPP-4 inhibitors versus insulin glargine for treating pre-existing and new onset diabetes in kidney transplant recipients

DPP-4 inhibitors versus insulin glargine for treating pre-existing and new onset diabetes in kidney transplant recipients

Patient or population: pre-existing and new onset diabetes in kidney transplant recipients

Setting: any

Intervention: DPP-4 inhibitors

Comparison: insulin glargine

Outcomes	No. of participants (studies)	Certainty of the evidence (GRADE)	Impact
Transplant or graft survival	Not reported	--	--
Delayed graft function	Not reported	--	--

HbA1c Time frame: 12 weeks	45 (1)	⊕⊕⊕⊕ VERY LOW 1, 2, 3	In Soliman 2013 , sitagliptin therapy had an equivalent effect on lowering HbA1c from baseline compared with insulin glargine therapy ($-0.6 \pm 0.5\%$ vs $-0.6 \pm 0.6\%$ (-7 ± 5 mmol/mol vs -7 ± 7 mmol/mol), $P = \text{NS}$)
FBG Time frame: 12 weeks	45 (1)	⊕⊕⊕⊕ VERY LOW 1, 2, 3	In Soliman 2013 , the fasting sugar for patients on treatment with sitagliptin was similar to that with insulin glargine (4.92 ± 1.42 mmol/L vs 4.76 ± 1.09 mmol/L, $P = \text{NS}$)
Kidney function markers assessed with: creatinine, eGFR, albuminuria	Not reported	--	--
Death (any cause)	Not reported	--	--
Hypoglycaemia Time frame: 12 weeks	45 (1)	⊕⊕⊕⊕ VERY LOW 1, 3	In Soliman 2013 , patients receiving sitagliptin had a similar number of hypoglycaemic events (5/28 patients; 17.8%) compared with patients receiving insulin glargine (3/17; 17.6%), however hypoglycaemia was not defined, and no severe episodes were reported
Discontinuation due to adverse events Time frame: 12 weeks	45 (1)	⊕⊕⊕⊕ VERY LOW 1, 3	In Soliman 2013 , neither patients receiving sitagliptin nor patients receiving insulin glargine discontinued treatment due to serious adverse events

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

CI: confidence interval; **eGFR:** estimates glomerular filtration rate; **FBG:** fasting blood glucose; **HbA1c:** glycated haemoglobin A1c; **NS:** not significant; **RR:** risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

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

¹ Downgraded 2 levels because of an unclear risk of selection and detection bias, and a high risk of performance and attrition bias

² Surrogate outcome

³ Small sample size

Summary of findings 4. SGLT2 inhibitors versus placebo for treating pre-existing and new-onset diabetes in kidney transplant recipients

SGLT2 inhibitors versus placebo for treating pre-existing and new-onset diabetes in kidney transplant recipients

Patient or population: pre-existing and new-onset diabetes in kidney transplant recipients
Setting: any
Intervention: SGLT2 inhibitors
Comparison: placebo

Outcomes	No. of participants (studies)	Certainty of the evidence (GRADE)	Impact
Transplant or graft survival assessed with: graft loss/rejection Time frame: 24 weeks	44 (1)	⊕⊕⊕⊖ MODERATE ¹	EMPA-Renal Tx 2019 reported that no patients in either the group receiving empagliflozin or placebo were suspected of having a kidney graft rejection. Follow-up, however was only over 24 weeks
Delayed graft function	Not reported	--	--
HbA1c Time frame: 24 weeks	44 (1)	⊕⊕⊕⊖ LOW ^{1, 2}	EMPA-Renal Tx 2019 reported that in patients with pre-existing or new onset diabetes receiving a kidney graft, empagliflozin significantly reduced the median HbA1c compared to placebo (-0.2%, (-0.6, -0.1) vs 0.1%, (-0.1, 0.4), P = 0.025 (-2.0 mmol/mol (-6.5, -1.0) vs 1.0 mmol/mol (-0.75, 3.8), P = 0.018))
FBG (mmol/L) Time frame: 24 weeks	44 (1)	⊕⊕⊕⊖ LOW ^{1, 2}	EMPA-Renal Tx 2019 reported that in patients with pre-existing or new onset diabetes receiving a kidney graft, empagliflozin did not reduce the median FBG compared to placebo (-0.65 mmol/L, (-1.2, -0.13) vs 0.30 mmol/L (-0.45, 0.55) P = 0.272)
Kidney function markers assessed with: creatinine, eGFR Time frame: 24 weeks	44 (1)	⊕⊕⊕⊖ LOW ^{1, 2}	EMPA-Renal Tx 2019 reported that in patients with pre-existing or new onset diabetes receiving a kidney graft, empagliflozin had a similar effect on change in eGFR compared to placebo at 24 weeks. (-3.0 mL/min/1.73 m ² , (-7.0, 0) vs -1.0 mL/min/1.73 m ² (-2.8, 0.75) P = 1). However, at 8 weeks, there was a temporary decline in eGFR compared to placebo (-4.0 mL/min/1.73 m ² (-7.0, -1.0) vs -1 mL/min/1.73 m ² (-2.0, 2.0), P < 0.05)
Death (any cause)	Not reported	--	--
Hypoglycaemia Time frame: 24 weeks	44 (1)	⊕⊕⊕⊖ MODERATE ¹	EMPA-Renal Tx 2019 reported no episodes of hypoglycaemia in either the treatment or placebo group
Discontinuation of medication due to adverse events Time frame: 24 weeks	49 (1)	⊕⊕⊕⊖ MODERATE ¹	EMPA-Renal Tx 2019 reported that two patients receiving empagliflozin (2/24) withdrew from the study, one patient due to urosepsis, and one patient due to repeated urinary tract infections. One patient was withdrawn from the placebo arm due to colon cancer (1/25)

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

CI: confidence interval; **eGFR:** estimates glomerular filtration rate; **FBG:** fasting blood glucose; **HbA1c:** glycated haemoglobin A1c **RR:** risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

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

¹ Downgraded by one due to small sample size

² Surrogate outcome

Summary of findings 5. Glitazones and insulin versus placebo and insulin for treating pre-existing and new onset diabetes in kidney transplant recipients

Glitazones and insulin versus placebo and insulin for treating pre-existing and new onset diabetes in kidney transplant recipients

Patient or population: pre-existing and new onset diabetes in kidney transplant recipients

Setting: any

Intervention: glitazones plus insulin

Comparison: placebo plus insulin

Outcomes	No. of participants (studies) Follow up	Certainty of the evidence (GRADE)	Impact
Transplant or graft survival	Not reported	--	--
Delayed graft function	Not reported	--	--
HbA1c Time frame: 16 weeks	62 (1)	⊕⊕⊕⊕ VERY LOW ^{1, 2, 3}	Kharazmkia 2014 reported that pioglitazone and insulin therapy significantly lowered HbA1c from baseline compared with insulin therapy alone (-1.21 ± 1.2 vs $0.39 \pm 1.0\%$ (-13 ± 13 vs 4 ± 11 mmol/mol) $P < 0.001$)
FBG (mmol/L) Time frame: 16 weeks	120 (2)	⊕⊕⊕⊕ LOW ^{2, 4}	In Arashnia 2015 , pioglitazone and insulin therapy decreased the FBG to a similar extent as insulin therapy alone (-0.6 mmol/L, -1.47 to 0.27 mmol/L). Similarly in Kharazmkia 2014 , pioglitazone and insulin therapy had equivalent effects on post intervention FBG compared with insulin therapy alone (mean $\pm$ SD: 6.58 ± 2.71 vs 7.28 ± 2.78 mmol/L $P = 0.14$)
Kidney function markers assessed with: creatinine, eGFR, albuminuria	62 (1)	⊕⊕⊕⊕ VERY LOW ^{1, 2, 3}	Kharazmkia 2014 reported that pioglitazone and insulin therapy had similar effects to insulin therapy on change in creatinine levels from baseline (3.54 ± 15.03 vs 10.61 ± 18.57 μ mol/L, $P = 0.53$)

Time frame: 16 weeks			
Death (any cause)	Not reported	--	--
Hypoglycaemia	Not reported	--	--
Discontinuation of medication due to adverse events	71 (1)	⊕⊕⊕⊕ LOW 1, 3	Kharazmkia 2014 reported that four participants dropped out due to adverse effects of pioglitazone (three had mild to moderate lower extremity oedema and one had insomnia) compared to none in the insulin only arm (P = 0.113)
Time frame: 16 weeks			

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

CI: confidence interval; **eGFR:** estimates glomerular filtration rate; **FBG:** fasting blood glucose; **HbA1c:** glycated haemoglobin A1c **RR:** risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

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

¹ Outcome reporting bias

² Surrogate outcome

³ Small sample size

⁴ 1 study had an unclear risk of selection bias, and the other had a high risk of outcome reporting bias

BACKGROUND

Description of the condition

Diabetes is global health problem, affecting 8.4% of adults or 451 million people globally (Cho 2018). By 2045, it is estimated that 9.9% of adults or 693 million people will have diabetes (Cho 2018). Chronic kidney disease (CKD) is also a global health problem, affecting up to 6.7% of adults in developed countries (Jager 2017). Diabetes commonly co-exists with chronic kidney disease (CKD), either co-incidentally, or as a cause of CKD (Tuttle 2014). Diabetes is the commonest cause of end-stage kidney disease (ESKD) with 40% of patients with CKD and ESKD having co-morbid diabetes (USR 2016). People with diabetes and chronic kidney disease (CKD) have increased morbidity and death mainly due to cardiovascular disease, with this risk increasing as the severity of CKD progresses (Radbill 2008).

Kidney transplantation is an important management option for patients with ESKD. Kidney transplantation is associated with 25% to 65% better patient survival compared to continuing on dialysis (Meier-Kriesche 2001; Rabbat 2000; Schnuelle 1998; Wolfe 1999). This survival benefit is mainly attributable to decreased cardiovascular disease risk (Lentine 2005; Meier-Kriesche 2004).

However, kidney transplantation is also associated with worsening glycaemic control in those recipients with pre-transplant diabetes. This is because the immunosuppressive agents required after transplantation, such as calcineurin inhibitors, mammalian target of rapamycin inhibitors and/or prednisolone decrease insulin sensitivity and impair insulin secretion (Duijnhoven 2001; Dumler 2007; Guerra 2012; Shivaswamy 2016). Furthermore, in those recipients without pre-transplant diabetes, kidney transplantation increases the risk of developing new-onset diabetes after transplantation (NODAT) (ADA 2019; Davidson 2003). The incidence of NODAT one year after kidney transplantation ranges from 2% to 52% (Kesiraju 2014). Post-transplant diabetes is the "umbrella term" that has been used to describe patients with diabetes post-transplant irrespective of whether they have pre-transplant diabetes (detected or undetected) or NODAT (ADA 2019; Sharif 2014). In the absence of pre-existing diabetes, the diagnosis should be made in the absence of infection once transplant recipients have had their maintenance immunosuppression and kidney function stabilised. This is to exclude transient post-transplantation hyperglycaemia which can occur in up to 90% of kidney transplant recipients in the first few weeks of transplantation (ADA 2019; Sharif 2014).

Description of the intervention

Glucose-lowering agents include oral agents, insulin, and non-insulin injectables. While the mainstay of treating type 1 diabetes is insulin, possible pharmacological interventions for people with type 2 diabetes and NODAT range from oral agents, to insulin and non-insulin injectables and may be used in a stepwise and additive fashion. The exception is the immediate post-transplant period, especially in hospital, where insulin may be more effective (Hecking 2013; Sharif 2014). Commonly available classes of glucose-lowering medications are biguanides, thiazolidinediones or glitazones, second generation sulphonylureas, glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 analogues, sodium glucose co-transporter 2 (SGLT2) inhibitors and insulins (ADA 2019; Davies 2018). Experimental

and emerging classes of glucose-lowering medications are dual peroxisome proliferator-activated receptor agonists, amylin analogues, bromocriptine and GPR40 or free fatty acid receptor 1 agonists.

How the intervention might work

In people with diabetes, epidemiological studies show that poor glycaemic control is associated with increased incidence of both macrovascular and microvascular complications, including kidney function decline (Bash 2008; Khaw 2004; Klein 1994; Meigs 1997; Selvin 2004). In transplant recipients, pre-existing diabetes is associated with an increased risk of post-transplant and wound infections, delayed graft function, early onset of acute rejection, increased cardiovascular disease and decreased survival (Cosio 2008; Klein 1994; Kyriakides 1975; Lansang 2006; Parekh 2010; Thomas 2001; Wiesbauer 2010). Similarly, NODAT is associated with an increased risk of diabetes-related complications, cardiovascular disease, graft failure, and death (Burroughs 2007; Cole 2008; Hjelmseath 2006; Kasiske 2003).

Consequently, good glycaemic control may decrease these risks. Large scale studies of people with diabetes and preserved kidney function have shown that intensive glucose control reduces the incidence and progression of microvascular outcomes and particularly kidney complications (ADVANCE 2008; CONTROL Group 2009; DCCT Group 1993; DCCT Group 1995; DCCT Group 2005; Duckworth 2009; Holman 2008; Ismail-Beigi 2010; UKPDS 1998a; UKPDS 1998b). Extrapolating this to recipients of kidney transplants, good glycaemic control may preserve kidney function and prevent development and progression of other microvascular complications. In addition, certain glucose-lowering agents such as liraglutide, semaglutide and dulaglutide (Gerstein 2019a; Gerstein 2019b; Mann 2017; Marso 2016a; Marso 2016b) and glucose-lowering classes such as SGLT2 inhibitors (Neuen 2019; Perkovic 2018; Perkovic 2019; Wiviott 2019; Zelniker 2019; Zinman 2015) have beneficial effects on cardiovascular and kidney outcomes independent of their glucose-lowering properties. This may also extend to people receiving kidney transplants. Finally, there is some evidence that good glycaemic control as evidenced by a lower fasting blood glucose (FBG), may improve survival of the kidney transplant (Schiel 2005).

Why it is important to do this review

Optimal management of elevated glucose level in kidney transplant recipients with post-transplant diabetes can be challenging. Glucose-lowering agent choice and dose must be tailored to prevent potential interactions with immunosuppressive medications (Wallia 2016). Additionally, altered drug metabolism and clearance due to kidney insufficiency, increases the risk of hypoglycaemia (Moen 2009). Despite this, significant knowledge gaps surround the efficacy and safety of glucose-lowering interventions in patients with kidney transplantation. In the absence of large randomised controlled trials (RCTs), glucose-lowering agent choice is often individualised according to side-effect profile, renal function and potential for interaction with immunosuppressive medications, with recommendations often based on expert opinion (ADA 2019; Davidson 2003; KDIGO 2009; Sharif 2014), and extrapolated from RCTs of non-transplant type 2 diabetes patients (Davies 2018; KDIGO 2009).

Given the uncertainty surrounding the efficacy and safety of contemporary pharmacological interventions for improving glucose control in the kidney transplant population, we updated our previous systematic review to inform clinical practice and highlight areas requiring further research.

This is an update of our review published in 2017 ([Lo 2017](#)). The original purpose of the 2017 review was to investigate the efficacy and safety of contemporary glucose-lowering agents for diabetes in both people with CKD (including people with ESKD) and kidney transplant recipients ([Lo 2015](#)). However, due to the different challenges of managing blood glucose levels in kidney transplant recipients compared with other patients with CKD, the efficacy and safety of contemporary glucose-lowering in these different populations were examined in two separate reviews:

1. Glucose-lowering agents for treating pre-existing and new-onset diabetes in kidney transplant recipients ([Lo 2017](#)).
2. Insulin and glucose-lowering agents for treating people with diabetes and chronic kidney disease ([Lo 2018](#)).

OBJECTIVES

To evaluate the efficacy and safety of pharmacological interventions for lowering glucose levels in patients who have undergone kidney transplantation and have diabetes.

METHODS

Criteria for considering studies for this review

Types of studies

1. All 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) looking at glucose-lowering therapy
3. Cross-over studies (only first phase data considered).

Types of participants

Inclusion criteria

Adults (aged 18 years or over) and children (aged up to 18 years) who are kidney transplant recipients with type 1 or type 2 diabetes, or NODAT.

Exclusion criteria

1. Treatment with first generation sulphonylureas
2. Pancreas transplantation
3. Islet cell transplantation.

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/standard care were eligible for inclusion.

- a. Metformin
- b. Insulin
- c. Sulphonylurea (excluding first generation)

- d. Glucagon-like peptide-1 agonists
- e. Glinides
- f. Glitazones
- g. alpha-glucosidase inhibitors
- h. DPP-4 inhibitors
- i. SGLT2 inhibitors
- j. Dual peroxisome proliferator-activated receptor agonists
- k. Amylin analogues
- l. Bromocriptine
- m. GPR40 or free fatty acid receptor 1 agonists.

Types of outcome measures

1. Efficacy
2. Safety

Primary outcomes

1. Transplant or graft survival
2. Delayed graft function/dialysis within 7 days
3. Glycated haemoglobin A1c (HbA1c)
4. FBG
5. Kidney function markers including creatinine, estimated glomerular filtration rate (eGFR), albuminuria

Secondary outcomes

1. Death (any cause)
2. Macrovascular events (cardiovascular death, non-fatal myocardial infarction (MI), non-fatal stroke, heart failure)
3. Microvascular events (new or worsening kidney disease, doubling of serum creatinine (SCr), retinopathy)
4. Systolic and diastolic blood pressure (BP)
5. Lipids (high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride)
6. Body weight
7. Safety
 - a. Hypoglycaemia, including severe hypoglycaemia (i.e. hypoglycaemia requiring third party assistance)
 - b. Discontinuation of medication due to adverse events
 - c. Gastrointestinal side effects
 - d. Oedema
 - e. Lactic acidosis
 - f. Liver abnormalities/failure
 - g. Cancer events
 - h. Other adverse events as described by authors
8. Quality of life.

Search methods for identification of studies

Electronic searches

We searched the [Cochrane Kidney and Transplant Register of Studies](#) to 16 January 2020 through contact with the Information Specialist using search terms relevant to this review. The 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. Searches of kidney and transplant journals, and the proceedings and abstracts from major kidney and transplant 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 Register are identified through searches of CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of search strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available on the [Cochrane Kidney and Transplant website](#).

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. Contacting relevant individuals/organisations seeking information about unpublished or incomplete studies.
3. Grey literature sources (e.g. abstracts, dissertations, and theses), in addition to those already included in the Cochrane Kidney and Transplant Register of Studies, were not searched.

Data collection and analysis

Selection of studies

The search strategy described was used to obtain titles and abstracts of studies potentially relevant to the review. Titles and abstracts were screened independently by two authors, who discarded studies that were not applicable. However, studies and reviews thought to include relevant data or information on studies were retained initially. Two authors (CL and TT) independently assessed retrieved abstracts, and if necessary, the full text to determine which studies satisfied inclusion criteria.

Data extraction and management

Data extraction was carried out independently by two authors using standardised data extraction forms: CL and TT extracted data for newly included studies while MO and MJ extracted data for previously included studies. Where more than one publication of one study was found, reports were grouped together and the publication with the most complete data was included. When relevant outcomes were only published in earlier versions these data were used. Any discrepancy between published versions was to be highlighted. Disagreements were resolved by consultation with another author (SZ).

Assessment of risk of bias in included studies

The following items were assessed using the risk of bias assessment tool ([Higgins 2003](#)) (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?

Measures of treatment effect

For dichotomous outcomes (death (any cause), macrovascular events, microvascular events) results were expressed as risk ratios (RR) or hazard ratios (HR) 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.

Adverse effects were to be tabulated and assessed with descriptive techniques. Where possible, the risk difference (RD) with 95% CI was calculated for each adverse effect, either compared to no treatment or to another agent. Due to a lack of uniformity between studies in the adverse effects reported, only the key adverse effects of a) hypoglycaemia and b) discontinuation of medication due to adverse events were tabulated where possible. The other adverse effects were reported only in the main text.

Unit of analysis issues

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

Dealing with missing data

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

Assessment of heterogeneity

We first assessed the heterogeneity by visual inspection of the forest plot. We then analysed the data using a Chi² test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance, and with the I² test ([Higgins 2003](#)). The I² statistic, describes the percentage of total variation across studies that is due to heterogeneity rather than sampling error ([Higgins 2003](#)). The interpretation of I² 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 I² depends on the magnitude and direction of treatment effects and the strength of

evidence for heterogeneity (e.g. P-value from the Chi² test) ([Higgins 2011](#)).

Assessment of reporting biases

If possible, funnel plots were to be used to assess for the potential existence of small study bias ([Higgins 2011](#)). However, reporting bias could not be assessed as only two studies could be pooled for one outcome.

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 RD with 95% CI was calculated.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was used to explore possible sources of heterogeneity according to the following characteristics if an adequate number of studies were available.

- 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).

Due to the small number of included studies, subgroup analyses were not performed.

Sensitivity analysis

We planned to perform sensitivity analyses to explore the influence of the following factors on effect size.

- Repeating the analysis excluding unpublished studies
- Repeating the analysis taking account of risk of bias, 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

We presented the main results of the review in [Summary of findings 1](#); [Summary of findings 2](#); [Summary of findings 3](#); [Summary of findings 4](#); [Summary of findings 5](#). 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 ([Schunemann 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](#); [GRADE 2011](#)). The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias ([Schunemann 2011b](#)). We have presented the following outcomes in the 'Summary of findings' tables.

- Transplant or graft survival
- Delayed graft function
- HbA1c
- FBG
- Kidney function markers including creatinine, eGFR, albuminuria
- Death (any cause)
- Hypoglycaemia
- Discontinuation of medication due to adverse events

RESULTS

Description of studies

See [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Results of the search

We identified 55 records (28 studies). Following assessment of the titles, abstracts, and full-text, we included ten studies (21 records), and excluded 14 studies (30 records). Two studies (two records) ([Lakhani 2016](#); [NCT00507494](#)) are awaiting classification, and two ongoing studies (two records) ([NCT03642184](#); [VAT 2013](#)) will be assessed in a future update of this review ([Figure 1](#)).

Figure 1. Study flow diagram

Included studies

We included ten studies (Arashnia 2015; Barbosa 1983; Barbosa 1994; EMPA-Renal Tx 2019; Haidinger 2010; Hermayer 2012; HiRT 2016; Kharazmkia 2014; Soliman 2013; Strom Halden 2014) that randomised 603 participants. Study sample size ranged from 19 (Strom Halden 2014) to 104 (Hermayer 2012) and most were conducted in single centre hospital clinics associated with kidney transplant units. Study follow-up ranged from two months (Strom Halden 2014) to five years (Barbosa 1994).

Nine studies were parallel RCTs (Arashnia 2015; Barbosa 1983; Barbosa 1994; EMPA-Renal Tx 2019; Haidinger 2010; Hermayer 2012; HiRT 2016; Kharazmkia 2014; Soliman 2013) and one was a cross-over RCT (Strom Halden 2014). Only Arashnia 2015; EMPA-

Renal Tx 2019; Haidinger 2010 and Kharazmkia 2014 were double blinded.

Four studies compared more versus less intensive regimens of insulin from the immediate post-transplant period onwards in patients with pre-existing type 1 diabetes (Barbosa 1983; Barbosa 1994), both type 1 and type 2 diabetes (Hermayer 2012), or diabetes with the type undefined (HiRT 2016).

Three studies compared DPP-4 inhibitors either with placebo or glargine insulin in patients with NODAT. Haidinger 2010 compared vildagliptin with placebo; Strom Halden 2014 compared sitagliptin and placebo in a cross-over RCT; and Soliman 2013 compared sitagliptin to glargine.

EMPA-Renal Tx 2019, compared empagliflozin (an SGLT2 inhibitor) to placebo in patients with NODAT.

Arashnia 2015 and Kharazmkia 2014 compared pioglitazone and insulin therapy with insulin therapy alone in patients with diabetic kidney disease who had received kidney transplants.

See [Characteristics of included studies](#).

Excluded studies

Reasons for exclusion were as follows (see [Characteristics of excluded studies](#)).

- Wrong population (Clodi 1997; Han 2010; Hecking 2012; Re 2010; SAPT-NODAT 2012; TransDiab 2017; Werzowa 2013; Yates 2014)
- Wrong intervention or control group (Kim 1997a; LANDMARK 2 2009; Orazio 2011; Sharif 2009; TRIMECO 2018)
- Mechanistic rather than an interventional study (Halden 2016).

Risk of bias in included studies

Overall, one study was judged to have a low risk of bias (EMPA-Renal Tx 2019), two studies were judged to have an unclear risk of bias (Arashnia 2015; Haidinger 2010), and all other included studies were found to be at high risk of bias (Barbosa 1983; Barbosa 1994; Hermayer 2012; HiRT 2016; Kharazmkia 2014; Soliman 2013; Strom Halden 2014) (Figure 2; 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.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): All outcomes	Blinding of outcome assessment (detection bias): All outcomes	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)	Other bias
Arashnia 2015	?	?	+	+	+	+	+
Barbosa 1983	?	?	-	?	-	-	-
Barbosa 1994	?	?	-	?	-	+	-
EMPA-Renal Tx 2019	+	+	+	+	+	+	+
Haidinger 2010	+	+	+	?	+	+	+
Hermayer 2012	?	?	-	-	-	+	+
HiRT 2016	+	+	-	-	+	-	+
Kharazmkia 2014	+	+	+	+	+	-	+
Soliman 2013	?	?	-	?	-	+	+
Strom Halden 2014	+	-	-	-	?	?	?

Allocation

Random sequence generation

Five studies were judged to be at low risk of bias (EMPA-Renal Tx 2019; Haidinger 2010; HiRT 2016; Kharazmkia 2014; Strom Halden 2014) and five studies were judged unclear (Arashnia 2015; Barbosa 1983; Barbosa 1994; Hermayer 2012; Soliman 2013).

Allocation concealment

Four studies were judged to be at low risk of bias (EMPA-Renal Tx 2019; Haidinger 2010; HiRT 2016; Kharazmkia 2014), one was judged to be at high risk of bias (Strom Halden 2014), and five studies were judged unclear (Arashnia 2015; Barbosa 1983; Barbosa 1994; Hermayer 2012; Soliman 2013).

Blinding

Performance bias

Six studies were judged to be at high risk of bias (Barbosa 1983; Barbosa 1994; Hermayer 2012; HiRT 2016; Soliman 2013; Strom Halden 2014) and four studies were at low risk of bias (Arashnia 2015; EMPA-Renal Tx 2019; Haidinger 2010; Kharazmkia 2014).

Detection bias

Three studies were judged to be a low risk of bias (Arashnia 2015; EMPA-Renal Tx 2019; Kharazmkia 2014), three were at high risk of bias (Hermayer 2012; HiRT 2016; Strom Halden 2014), and four studies were judged unclear (Barbosa 1983; Barbosa 1994; Haidinger 2010; Soliman 2013).

Incomplete outcome data

Five studies were judged to be at low risk of bias (Arashnia 2015; EMPA-Renal Tx 2019; Haidinger 2010; HiRT 2016; Kharazmkia 2014), four were at high risk of bias (Barbosa 1983; Barbosa 1994; Hermayer 2012; Soliman 2013), and one study was judged unclear (Strom Halden 2014).

Selective reporting

Six studies were judged to be at low risk of bias (Arashnia 2015; Barbosa 1994; EMPA-Renal Tx 2019; Haidinger 2010; Hermayer 2012; Soliman 2013). Three studies were at high risk of reporting bias (Barbosa 1983; HiRT 2016; Kharazmkia 2014). One study was judged unclear (Strom Halden 2014).

Other potential sources of bias

Seven studies were judged to be at low risk of bias (Arashnia 2015; EMPA-Renal Tx 2019; Haidinger 2010; Hermayer 2012; HiRT 2016; Kharazmkia 2014; Soliman 2013), two studies were at high risk of bias (Barbosa 1983; Barbosa 1994), and one study was judged unclear (Strom Halden 2014). Strom Halden 2014 was a cross-over RCT and there was no washout period between the four weeks of sitagliptin and non-sitagliptin treatment. For patients randomised to sitagliptin treatment first and then crossed over to the non-sitagliptin treatment, the perceived effectiveness of sitagliptin might have been attenuated by the lack of a wash-out period. However as per the protocol, only first phase data was considered in this systematic review.

Effects of interventions

See: **Summary of findings 1** More intensive versus less intensive insulin therapy for treating pre-existing and new-onset diabetes in kidney transplant recipients; **Summary of findings 2** DPP-4 inhibitors versus placebo for treating pre-existing and new-onset diabetes in kidney transplant recipients; **Summary of findings 3** DPP-4 inhibitors versus insulin glargine for treating pre-existing and new onset diabetes in kidney transplant recipients; **Summary of findings 4** SGLT2 inhibitors versus placebo for treating pre-existing and new-onset diabetes in kidney transplant recipients; **Summary of findings 5** Glitazones and insulin versus placebo and insulin for treating pre-existing and new onset diabetes in kidney transplant recipients

Primary outcomes

Transplant or graft survival

More intensive versus less intensive insulin therapy

In people with pre-existing diabetes receiving a kidney graft, it is unclear if more intensive therapy improves transplant or graft survival by decreasing graft loss and/or rejection compared to less intensive insulin therapy (**Analysis 1.1** (4 studies, 301 participants): RR 1.12, 95% CI 0.32 to 3.94; $I^2 = 49\%$; very low certainty evidence) (Barbosa 1983; Barbosa 1994; Hermayer 2012; HiRT 2016).

DPP-4 inhibitors versus placebo

Haidinger 2010 and Strom Halden 2014 did not report this outcome. However, in response to our enquiry, Strom Halden 2014 reported 100% transplant and graft survival during the eight week cross-over study.

DPP-4 inhibitors versus insulin glargine

Soliman 2013 did not report this outcome.

SGLT2 inhibitors versus placebo

EMPA-Renal Tx 2019 reported that no patients in either treatment group were suspected of having a kidney graft rejection.

Glitazones and insulin versus insulin alone

Arashnia 2015 and Kharazmkia 2014 did not report this outcome.

Delayed graft function or dialysis within 7 days

More intensive versus less intensive insulin therapy

In people with pre-existing diabetes receiving a kidney graft, it is unclear if more intensive therapy reduces delayed graft function compared to less intensive insulin therapy (**Analysis 1.2** (2 studies, 153 participants): RR 0.63, 95% CI 0.42 to 0.93; $I^2 = 0\%$; very low certainty evidence) (Hermayer 2012; HiRT 2016). Delayed graft function was defined as either as a day-10 SCr > 221 $\mu\text{mol/L}$ or the need for dialysis within first seven days in Hermayer 2012, and as the need for dialysis within the first seven days in HiRT 2016.

DPP-4 inhibitors versus placebo

Haidinger 2010 and Strom Halden 2014 did not report this outcome. However, in response to our enquiry, Haidinger 2010 confirmed in correspondence that there was no difference in graft and kidney transplant function between vildagliptin and placebo group participants.

DPP-4 inhibitors versus insulin glargine

[Soliman 2013](#) did not report this outcome.

SGLT2 inhibitors versus placebo

[EMPA-Renal Tx 2019](#) did not report this outcome.

Glitazones and insulin versus insulin alone

[Arashnia 2015](#) and [Kharazmkia 2014](#) did not report this outcome.

Glycated haemoglobin A1c (HbA1c)

More intensive versus less intensive insulin therapy

In people with pre-existing diabetes receiving a kidney graft it is unclear if more intensive lowers the HbA1c (1 study, 16 participants; very low certainty evidence) compared to less intensive insulin therapy. [Barbosa 1983](#) reported that HbA1c changed from $15 \pm 2.3\%$ (mean $\pm$ SEM: 140 ± 25 mmol/mol, month 7) to $13 \pm 0.9\%$ (119 ± 10 mmol/mol, month 13) in the less intensive group, and changed from $11 \pm 0.4\%$ (97 ± 4 mmol/mol, month 7) to $10 \pm 0.8\%$ (86 ± 9 mmol/mol, month 13) in the more intensive group.

DPP-4 inhibitors versus placebo

In people with NODAT, [Haidinger 2010](#) reported vildagliptin may lower HbA1c compared to placebo ([Analysis 2.1](#) (32 participants): MD -0.5%, 95% CI -0.85% to -0.15% (MD -5 mmol/mol, 95% CI -9 to -2); low certainty evidence).

DPP-4 inhibitors versus insulin glargine

In people with NODAT, it is unclear if sitagliptin has an equivalent effect to insulin glargine therapy on lowering HbA1c (1 study, 45 participants; very low certainty evidence). [Soliman 2013](#) reported that sitagliptin therapy had an equivalent effect on lowering HbA1c from baseline compared with insulin glargine therapy ($-0.6 \pm 0.5\%$ versus $-0.6 \pm 0.6\%$ (-7 ± 5 versus -7 ± 7 mmol/mol).

SGLT2 inhibitors versus placebo

[EMPA-Renal Tx 2019](#) reported that in patients with NODAT, empagliflozin significantly reduced the median HbA1c compared to placebo (-0.2% , -0.6 , -0.1) versus 0.1% , -0.1 , 0.4), $P = 0.025$ (-2.0 mmol/mol -6.5 , -1.0) versus 1.0 mmol/mol (-0.75 , 3.8), $P = 0.018$)).

Glitazones and insulin versus insulin alone

In people with pre-existing diabetes receiving a kidney graft, it is unclear if glitazones and insulin therapy have an effect on HbA1c compared to insulin therapy alone (1 study, 62 participants, very low certainty evidence). [Kharazmkia 2014](#) reported that pioglitazone and insulin therapy significantly lowered HbA1c from baseline compared with insulin therapy alone (-1.21 ± 1.2 versus $0.39 \pm 1.0\%$ (-13 ± 13 versus 4 ± 11 mmol/mol) $P < 0.001$).

Fasting blood glucose

More intensive versus less intensive insulin therapy

In people with pre-existing diabetes receiving a kidney graft, it is unclear if more versus less intensive insulin therapy lowers FDG (1 study, 24 participants; very low certainty evidence). [Barbosa 1983](#) reported that intensive insulin therapy achieved a lower FBG (mean $\pm$ SEM: 7.22 ± 0.50 mmol/L) compared with less intensive insulin therapy (13.44 ± 1.22 mmol/L) at 13 months (the study lasted for two years).

[Hermayer 2012](#) reported mean BGL rather than FBG. Intensive insulin therapy achieved a significantly lower mean BGL (mean $\pm$ SEM: 6.81 ± 0.19 mmol/L) compared with less intensive insulin therapy (9.85 mmol/L ± 0.19 , $P < 0.001$). However, these results were heavily influenced by the intensive group having more frequent BGL assessments in the first 72 hours post-transplant. When only BGL values after 72 hours were considered, there were no significant differences in BGL between the intensive and standard groups (8.71 ± 0.51 mmol/L versus 8.61 ± 0.49 mmol/L; $P = 0.90$).

DPP-4 inhibitors versus placebo

[Haidinger 2010](#) reported in people with NODAT, vildagliptin may lower FBG compared to placebo ([Analysis 2.2](#) (32 participants): MD -0.75 mmol/L, 95% CI -1.48 to -0.02 mmol/L; low certainty evidence). First phase data from the cross-over study by [Strom Halden 2014](#) were unavailable.

DPP-4 inhibitors versus insulin glargine

In people with NODAT, it is unclear if sitagliptin has an equivalent effect to insulin glargine on lowering FBG (1 study, 45 participants; very low certainty evidence). [Soliman 2013](#) reported that the FBG for patients on treatment with sitagliptin was similar to that with insulin glargine (4.92 ± 1.42 versus 4.76 ± 1.09 mmol/L).

SGLT2 inhibitors versus placebo

[EMPA-Renal Tx 2019](#) reported that in patients with NODAT, empagliflozin did not reduce the median FBG compared to placebo (-0.65 mmol/L, -1.2 to -0.13) versus 0.30 mmol/L (-0.45 to 0.55); $P = 0.272$).

Glitazones and insulin versus insulin alone

In people with pre-existing diabetes receiving a kidney graft, glitazones plus insulin probably makes little or no difference to FBG compared to insulin alone (2 studies, 120 participants, low certainty evidence). In [Arashnia 2015](#), pioglitazone and insulin therapy decreased the FBG to a similar extent as insulin therapy alone (-0.6 mmol/L, -1.47 to 0.27 mmol/L). Similarly in [Kharazmkia 2014](#), pioglitazone and insulin therapy had equivalent effects on post intervention FBG compared with insulin therapy alone (mean $\pm$ SD: 6.58 ± 2.71 versus 7.28 ± 2.78 mmol/L; $P = 0.14$).

Kidney function markers (including creatinine, eGFR, albuminuria)

More intensive versus less intensive insulin therapy

In people with pre-existing diabetes receiving a kidney graft, it is unclear if more versus less intensive insulin therapy affects kidney function markers (1 study, 36 participants, very low certainty evidence). [HiRT 2016](#) reported that eGFR increased by 4.6 mL/min/ 1.73 m² (95% CI -9.75 to 18.95), and SCr changed by -10.6 μ mol/L (95% CI -37.0 to 15.7) after 1 year follow-up of 36 participants.

DPP-4 inhibitors versus placebo

[Haidinger 2010](#) reported in people with NODAT, vildagliptin may make little or no difference to eGFR ([Analysis 2.3](#) (32 participants): MD -0.2 mmol/L, 95% CI -6.07 to 5.67 mmol/L; low certainty evidence) compared to placebo. In correspondence, [Strom Halden 2014](#), reported no development of proteinuria or albuminuria during the study using sitagliptin; [Haidinger 2010](#) reported no significant change in albuminuria and proteinuria in both vildagliptin and placebo groups during follow-up.

DPP-4 inhibitors versus insulin glargine

[Soliman 2013](#) did not report kidney function markers.

SGLT2 inhibitors versus placebo

[EMPA-Renal Tx 2019](#) reported that in patients with NODAT, empagliflozin had a similar effect on change in eGFR compared to placebo at 24 weeks ($-3 \text{ mL/min/1.73 m}^2$, (95% CI -7.0 to 0) versus $-1.0 \text{ mL/min/1.73 m}^2$ (-2.8 to 0.75) $P = 1$). However, at 8 weeks, there was a temporary decline in eGFR compared to placebo ($-4 \text{ mL/min/1.73 m}^2$ (95% CI -7 to -1) versus $-1 \text{ mL/min/1.73 m}^2$ (-2 to 2); $P < 0.05$).

Glitazones and insulin versus insulin alone

In people with pre-existing diabetes receiving a kidney graft, it is unclear if glitazones plus insulin therapy have an effect on kidney function markers compared to insulin therapy alone (1 study, 62 participants, very low certainty evidence). [Kharazmkia 2014](#) reported that pioglitazone and insulin therapy had similar effects to insulin therapy on change in creatinine levels from baseline (3.54 ± 15.03 versus $10.61 \pm 18.57 \text{ } \mu\text{mol/L}$; $P = 0.53$).

Secondary outcomes

Death (any cause)

More intensive versus less intensive insulin therapy

In people with pre-existing diabetes receiving a kidney graft, it is unclear if more intensive therapy reduces the number of deaths (any cause) compared to less intensive insulin therapy ([Analysis 1.6](#) (3 studies, 208 participants): RR 0.68, 95% CI 0.29 to 1.58; $I^2 = 0\%$; very low certainty evidence) ([Barbosa 1983](#); [Barbosa 1994](#); [HiRT 2016](#)).

DPP-4 inhibitors versus placebo

[Haidinger 2010](#) and [Strom Halden 2014](#) did not report this outcome. However, in response to our enquiry, [Haidinger 2010](#), confirmed that there were no deaths in the vildagliptin or placebo groups and [Strom Halden 2014](#) reported no deaths over eight weeks of follow-up.

DPP-4 inhibitors versus insulin glargine

[Soliman 2013](#) did not report this outcome.

SGLT2 inhibitors versus placebo

[EMPA-Renal Tx 2019](#) did not report this outcome.

Glitazones and insulin versus insulin alone

[Arashnia 2015](#) and [Kharazmkia 2014](#) did not report this outcome.

Macrovascular and microvascular events

More intensive versus less intensive insulin therapy

[Barbosa 1983](#); [Barbosa 1994](#) and [Hermayer 2012](#) did not report these outcomes.

[HiRT 2016](#) reported no episodes of stroke in either group over one year of follow-up.

DPP-4 inhibitors versus placebo

[Haidinger 2010](#) and [Strom Halden 2014](#) did not report these outcomes. However, in response to our enquiry, [Haidinger 2010](#), reported no macrovascular events in either the vildagliptin or placebo groups.

DPP-4 inhibitors versus insulin glargine

[Soliman 2013](#) did not report this outcome.

SGLT2 inhibitors versus placebo

[EMPA-Renal Tx 2019](#) did not report this outcome.

Glitazones and insulin versus insulin alone

[Arashnia 2015](#) and [Kharazmkia 2014](#) did not report these outcomes

Systolic and diastolic blood pressure

More intensive versus less intensive insulin therapy

[Barbosa 1994](#) reported the effect of more intensive compared with less intensive insulin therapy on systolic and diastolic BP. At baseline, mean ($\pm$ SD) baseline systolic BP was higher in the more intensive insulin therapy group ($132 \pm 9 \text{ mm Hg}$) compared with the less intensive insulin therapy group ($126 \pm 10 \text{ mm Hg}$, $P = 0.03$). However, there was no significant difference between mean ($\pm$ SD) baseline diastolic BP in the more intensive ($78 \pm 4.9 \text{ mm Hg}$) compared with the less intensive group ($78 \pm 5.2 \text{ mm Hg}$, $P = 0.99$). During the study there was no significant difference in mean ($\pm$ SD) systolic (131 ± 7 versus $129 \pm 9 \text{ mm Hg}$, $P = 0.39$) or diastolic (77 ± 6 versus $75 \pm 8 \text{ mm Hg}$, $P = 0.88$) BP between the intensive and standard groups.

DPP-4 inhibitors versus placebo

[Haidinger 2010](#) and [Strom Halden 2014](#) reported the effects of DPP-4 inhibitors versus placebo on BP. Results could not be pooled, because first phase data from [Strom Halden 2014](#) were unavailable. [Haidinger 2010](#) reported no significant difference between vildagliptin and placebo groups at baseline in mean ($\pm$ SD) systolic (131.9 ± 6 versus $127.9 \pm 10.2 \text{ mm Hg}$, $P = 0.19$) or diastolic BP (72.6 ± 7.6 versus $77.3 \pm 9.7 \text{ mm Hg}$, $P = 0.14$). At three months, there was no significant change from baseline in mean ($\pm$ SD) systolic/diastolic BP in the vildagliptin ($-0.4/1.1 \pm 6.6/6.4 \text{ mm Hg}$ both $P > 0.1$) or placebo group ($2.5/1.9 \pm 11.3/10.1 \text{ mm Hg}$ both $P > 0.1$).

DPP-4 inhibitors versus insulin glargine

[Soliman 2013](#) did not report this outcome.

SGLT2 inhibitors versus placebo

[EMPA-Renal Tx 2019](#) reported that in patients with NODAT, empagliflozin had a similar effect on median change in both systolic and diastolic BP compared to placebo at 24 weeks (-5 mm Hg (95% CI -12 to 1) versus 2 mm Hg (95% CI -6 to 8), $P = 0.06$ for systolic BP, and -4 mm Hg (95% CI -9 to 1) versus 1 mm Hg (95% CI -5 to 6), $P = 0.105$ for diastolic BP, respectively).

Glitazones and insulin versus insulin alone

[Arashnia 2015](#) and [Kharazmkia 2014](#) did not report this outcome.

Lipids (total cholesterol, HDL, LDL, triglycerides)

More intensive versus less intensive insulin therapy

Barbosa 1983; Barbosa 1994; Hermayer 2012; and HiRT 2016 did not report this outcome.

DPP-4 inhibitors versus placebo

Haidinger 2010 reported that at baseline there was no significant difference between the vildagliptin and placebo groups in terms of mean ($\pm$ SD) total cholesterol (5.61 ± 1.27 versus 5.06 ± 0.85 mmol/L, $P = 0.16$), LDL (3.28 ± 1.17 versus 2.82 ± 0.73 mmol/L, $P = 0.35$), HDL (1.45 ± 0.6 versus 1.47 ± 0.6 mmol/L, $P = 0.61$), and triglycerides (2.03 ± 0.89 versus 1.95 ± 0.97 mmol/L, $P = 0.80$). At three months there was no significant change in any lipid parameter in both the vildagliptin and the placebo groups. Strom Halden 2014 did not report this outcome.

DPP-4 inhibitors versus insulin glargine

Soliman 2013 reported that 100 mg of sitagliptin led to statistically significant but clinically small decreases in levels of total cholesterol (3.65 ± 0.50 versus 4.35 ± 0.56 mmol/L, $P < 0.05$), and triglycerides (1.49 ± 0.20 versus 1.17 ± 0.23); and higher levels of HDL (1.15 ± 0.21 versus 1.05 ± 0.14 mmol/L) compared to insulin glargine outcome.

SGLT2 inhibitors versus placebo

EMPA-Renal Tx 2019 did not report this outcome.

Glitazones and insulin versus insulin alone

In people with pre-existing diabetes receiving a kidney graft, glitazones and insulin may lower total cholesterol compared to insulin alone (Analysis 4.1 (2 studies, 120 participants): MD -0.49 mmol/L 95% -0.75 to -0.23; $I^2 = 0\%$; low certainty evidence) (Arashnia 2015; Kharazmkia 2014).

In people with pre-existing diabetes receiving a kidney graft, glitazones and insulin may raise HDL cholesterol compared to insulin alone (Analysis 4.2 (2 studies, 120 participants): MD 0.12 mmol/L 95% 0.01 to 0.24; $I^2 = 0\%$; low certainty evidence) (Arashnia 2015; Kharazmkia 2014).

In people with pre-existing diabetes receiving a kidney graft, glitazones and insulin may lower LDL cholesterol compared to insulin alone (Analysis 4.3 (2 studies, 120 participants): MD -0.27 mmol/L 95% CI -0.47 to -0.06, $I^2 = 1\%$; low certainty evidence) (Arashnia 2015; Kharazmkia 2014).

In people with pre-existing diabetes receiving a kidney graft, it is unclear if glitazones and insulin lowers triglycerides compared to insulin alone (Analysis 4.4 (2 studies, 120 participants): MD -0.3 mmol/L 95% CI -0.49 to -0.12, $I^2 = 64\%$; very low certainty evidence) (Arashnia 2015; Kharazmkia 2014).

Body weight

More intensive versus less intensive insulin therapy

Barbosa 1983; Barbosa 1994; Hermayer 2012; and HiRT 2016 did not report this outcome.

DPP-4 inhibitors versus placebo

Strom Halden 2014 did not report this outcome.

In correspondence, Haidinger 2010 confirmed no difference in body weight between the vildagliptin and placebo groups.

DPP-4 inhibitors versus insulin glargine

Soliman 2013 reported that 100 mg of sitagliptin resulted in a minimal but statistically more weight loss (0.4 kg) compared to insulin glargine which resulted in 0.8 kg weight gain ($P < 0.05$).

SGLT2 inhibitors versus placebo

EMPA-Renal Tx 2019 reported that in patients with NODAT, empagliflozin significantly decreased body weight compared to placebo (-2.5 kg (95% CI -4 to -0.05) versus 1.0 kg (95% CI 0.0 to 2.08), $P = 0.014$).

Glitazones and insulin versus insulin alone

In people with pre-existing diabetes receiving a kidney graft, it is unclear if glitazones and insulin cause weight gain compared to insulin alone (Analysis 4.5 (2 studies, 120 participants): MD 1.56 kg 95% -1.87 to 4.99; $I^2 = 82\%$; very low certainty evidence) (Arashnia 2015; Kharazmkia 2014).

Safety

Hypoglycaemia

More intensive versus less intensive insulin therapy

In people with pre-existing diabetes receiving a kidney graft, it is unclear if more intensive insulin therapy increases the risk of hypoglycaemia (4 studies, 301 participants; very low certainty evidence) compared to less intensive insulin therapy. Barbosa 1983 reported in the narrative that intensive insulin therapy resulted in more frequent and severe episodes of hypoglycaemia compared with standard insulin therapy. Barbosa 1994 reported only severe hypoglycaemic episodes, that is, those requiring third-party assistance. More intensive insulin therapy resulted in a higher rate of severe hypoglycaemia compared with less intensive insulin therapy (1.7 episodes/patient/year versus < 0.1 /patient/year, $P < 0.001$). Of the 29 episodes of severe hypoglycaemia resulting in hospital admission, 26 occurred in the intensive insulin group. A patient in the intensive insulin group remained comatose for six days and required a two-week hospital admission. In Hermayer 2012, intensive insulin therapy may have increased the risk of severe hypoglycaemia (< 2.2 mmol/L), however the 95% CI indicated there may be no difference (RR 3.90, 95% CI 0.85 to 17.78) compared to less intensive insulin therapy. HiRT 2016 reported no episodes of hypoglycaemia in either arm (Table 1).

DPP-4 inhibitors versus placebo

In people with NODAT, it is unclear if DPP-4 inhibitors increase the risk of hypoglycaemia (2 studies, 51 participants; very low certainty evidence). Haidinger 2010 did not report any hypoglycaemia in the vildagliptin group ($n = 16$). Strom Halden 2014 reported that 2 patients had asymptomatic moderate hypoglycaemia in the sitagliptin group ($n = 19$), although these patients were also receiving glipizide (Table 2).

DPP-4 inhibitors versus insulin glargine

In people with NODAT it is unclear if sitagliptin has an equivalent effect to insulin glargine on hypoglycaemia (1 study, 45 participants; very low certainty evidence). In Soliman 2013, patients receiving sitagliptin had a similar number of hypoglycaemic events

(5/28 patients; 17.8%) compared with patients receiving insulin glargine (3/17; 17.6%), however hypoglycaemia was not defined, and no severe episodes were reported (Table 3).

SGLT2 inhibitors versus placebo

EMPA-Renal Tx 2019 reported no episodes of hypoglycaemia in either the treatment or placebo group (Table 4).

Glitazones and insulin versus insulin alone

Arashnia 2015 and Kharazmkia 2014 did not report hypoglycaemia as an outcome (Table 5).

Discontinuation of medication due to adverse events

More intensive versus less intensive insulin therapy

It is unclear if more versus less intensive insulin therapy affects the rate of discontinuation of medication due to adverse events (1 study, 60 participants; very low certainty evidence). HiRT 2016 reported this outcome, but no events were observed (Table 1).

DPP-4 inhibitors versus placebo

It is unclear if DPP-4 inhibitors have an effect on the risk of medication discontinuation due to adverse events (2 studies, 51 participants; very low certainty evidence). Haidinger 2010 reported no discontinuation of medication due to adverse events ($n = 32$) and Strom Halden 2014 reported one event in the sitagliptin group ($n = 19$) (Table 2).

DPP-4 inhibitors versus insulin glargine

It is unclear if sitagliptin has an equivalent rate as insulin glargine for discontinuation due to adverse events (1 study, 45 participants; very low certainty evidence). In Soliman 2013, neither patients receiving sitagliptin nor patients receiving insulin glargine discontinued treatment due to serious adverse events (Table 3).

SGLT2 inhibitors versus placebo

EMPA-Renal Tx 2019 reported that two patients receiving empagliflozin withdrew from the study, one patient due to urosepsis, and one patient due to repeated urinary tract infections (2/24). In comparison, one patient was withdrawn from the placebo arm due to colon cancer (1/25). In addition, one patient withdrew consent and one patient was discontinued from the placebo arm because he/she no longer fulfilled the criteria for post-transplant diabetes (Table 4).

Glitazones and insulin versus insulin alone

In people with pre-existing diabetes receiving a kidney graft glitazones and insulin may result in discontinuation of medications due to adverse events compared to insulin alone (1 study, 62 participants low certainty evidence). Kharazmkia 2014 reported that four participants dropped out due to adverse effects of pioglitazone (three had mild to moderate lower extremity oedema and one had insomnia), compared to none in those receiving insulin only ($P = 0.11$) (Table 5).

Other adverse events

More intensive versus less intensive insulin therapy

HiRT 2016 also reported that there were no seizures in the intensive or less intensive insulin therapy group over one year of follow-up.

DPP-4 inhibitors versus placebo

Haidinger 2010 reported similar rates of adverse events (5/16; 31.3%) in the vildagliptin group compared with the placebo group (6/16; 37.5%), with small but similar numbers of episodes of angina (1 versus 0), elevated liver enzymes (2 versus 1), elevated pancreatic enzymes (0 versus 1), elevated triglycerides (0 versus 1), cough (0 versus 1), conjunctivitis (1 versus 0), urinary tract infections (1 versus 1) and leukopenia (0 versus 1). There were no reported drug interactions with any immunosuppressive agents being taken.

Strom Halden 2014 reported an association between sitagliptin use and an increase in uric acid level (median, IQR: 25, -2 to 45 $\mu\text{mol/L}$) but no episodes of gout were reported. Sitagliptin did not interact with any immunosuppressive agents - there were no significant changes in trough concentrations of cyclosporin A ($P = 0.45$), tacrolimus ($P = 0.07$), everolimus ($P = 1.00$) and mycophenolate mofetil ($P = 0.65$) following sitagliptin treatment.

DPP-4 inhibitors versus insulin glargine

Soliman 2013 reported an overall low incidence of adverse events which were mild in both the sitagliptin and insulin glargine groups.

SGLT2 inhibitors versus placebo

EMPA-Renal Tx 2019 reported similar number of patients reporting adverse events in the empagliflozin and placebo group (7/24 versus 6/25, $P = 0.68$). There was one serious adverse event reported in the empagliflozin group who withdrew from the study due to urosepsis (also mentioned in the paragraph above), however this person had previous episodes of urinary tract infections prior to being enrolled in the study. Of note there was one episode each of genital itching and genital yeast infection reported in the empagliflozin group compared to none in the placebo group. Additionally, the number of reported urinary tract infections was similar in both groups (3 versus 3). There were no reported episodes of diabetic ketoacidosis in the study, although this outcome was not specifically mentioned.

EMPA-Renal Tx 2019 reported that there was no difference in the trough levels of immunosuppressive drugs between patients receiving empagliflozin compared to those receiving placebo. However, in the placebo group, one patient switched from tacrolimus to cyclosporin. In addition, one patient receiving empagliflozin and three patients receiving placebo, had their calcineurin inhibitor doses adjusted.

Glitazones and insulin versus insulin alone

Kharazmkia 2014 reported that no study participants had transient elevation of liver enzyme levels two or more times the upper limits or episodes of liver toxicity, severe cardiac failure, or change in creatinine levels. Pioglitazone did not affect cyclosporin levels or dose.

Quality of life

None of the included studies reported quality of life as an outcome.

Sensitivity analysis and publication bias

Sensitivity analyses and assessment for publication bias via a funnel plot were not possible due to the limited number of included studies.

DISCUSSION

Summary of main results

This review provides an updated overview of the efficacy and safety of glucose-lowering agents for treating diabetes in patients with kidney transplantation. We found that robust evidence for the use of glucose-lowering agents is still lacking.

Ten studies (21 records, 603 randomised participants) were included - three additional studies (five records) since our last review. Four studies compared more intensive versus less intensive insulin therapy; two studies compared DPP-4 inhibitors to placebo; one study compared DPP-4 inhibitors to insulin glargine; one study compared SGLT2 inhibitors to placebo; and two studies compared glitazones and insulin to insulin therapy alone. The majority of studies had an unclear to a high risk of bias. There were no studies examining the effects of biguanides, glinides, GLP-1 agonists, or sulphonylureas.

Compared to less intensive insulin therapy, it is unclear if more intensive insulin therapy has an effect on improving transplant or graft survival (4 studies, 301 participants: RR 1.12, 95% CI 0.32 to 3.94; $I^2 = 49\%$; very low certainty evidence), delayed graft function (2 studies, 153 participants: RR 0.63, 0.42 to 0.93; $I^2 = 0\%$; very low certainty evidence), HbA1c (1 study, 16 participants; very low certainty evidence), FBG (1 study, 24 participants; very low certainty evidence), kidney function markers (1 study, 26 participants; very low certainty evidence), death (any cause) (3 studies, 208 participants: RR 0.68, 0.29 to 1.58; $I^2 = 0\%$; very low certainty evidence), hypoglycaemia (4 studies, 301 participants; very low certainty evidence) and medication discontinuation due to adverse effects (1 study, 60 participants; very low certainty evidence).

Compared to placebo, it is unclear whether DPP-4 inhibitors have an effect on hypoglycaemia and medication discontinuation (2 studies, 51 participants; very low certainty evidence). However, DPP-4 inhibitors may reduce HbA1c and FBG but not kidney function markers (1 study, 32 participants; low certainty evidence).

Compared to insulin glargine, it is unclear if DPP-4 inhibitors have an effect on HbA1c, FBG, hypoglycaemia, or discontinuation due to adverse events (1 study, 45 participants; very low certainty evidence).

Compared to placebo, SGLT2 inhibitors probably do not affect kidney graft survival (1 study, 44 participants; moderate certainty evidence), but may reduce HbA1c, and may not affect FBG and eGFR long-term (1 study, 44 participants; low certainty evidence). SGLT2 inhibitors probably do not increase hypoglycaemia, and probably have little or no effect on medication discontinuation due to adverse events. However, all participants discontinuing SGLT2 inhibitors had urinary tract infections (1 study, 44 participants, moderate certainty evidence).

Compared to insulin therapy alone, it is unclear if glitazones added to insulin have an effect on HbA1c or kidney function markers (1 study, 62 participants; very low certainty evidence). However, glitazones may make little or no difference to FBG (2 studies, 120 participants; low certainty evidence), and medication discontinuation due to adverse events (1 study, 62 participants; low certainty evidence).

No studies of DPP-4 inhibitors, or glitazones reported effects on transplant or graft survival, delayed graft function or death (any cause).

Overall completeness and applicability of evidence

We planned to perform meta-analyses for all outcomes. However, despite our attempts to contact the relevant authors, for several studies, outcomes were unavailable or were not available in a suitable format to be used in meta-analyses. Two studies are still awaiting classification ([Characteristics of studies awaiting classification](#)) pending publication and availability of results. Two studies are currently ongoing ([Characteristics of ongoing studies](#)). Our review will be updated once further data are made available.

Another limiting factor was that most studies were conducted in Caucasian or African American patients with diabetes, affecting the generalisability of findings to other populations. This is especially relevant given that DPP-4 inhibitors have been reported to lower FBG to a greater extent in Asian compared with non-Asian patients ([Kim 2013](#)).

Despite the four studies comparing more intensive versus less intensive insulin therapy; two studies comparing DPP-4 inhibitors to placebo; one study comparing DPP-4 inhibitors to insulin glargine; one study comparing SGLT2 inhibitors to placebo, and two studies comparing glitazones plus insulin to insulin therapy alone, the majority of evidence for the use of these glucose-lowering drug classes for treating diabetes in kidney transplant recipients is still of low to very low certainty. No data concerning the efficacy and safety of biguanides, GLP-1 agonists, and sulphonylureas were identified.

Consequently, evidence to guide choice of glucose-lowering agents to treat diabetes in kidney transplant recipients is still lacking. More studies are urgently required to close this evidence gap.

Quality of the evidence

The quality of evidence for all examined outcomes was moderate to very low according to GRADE ([GRADE 2011](#)). Contributing factors to the low quality of evidence were that most studies had an unclear to high risk of bias, had small study sample sizes, and assessed surrogate rather than clinical outcomes.

Potential biases in the review process

The strengths of the review process were 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 reviewers assessed each study and any differences in interpretation were discussed with disagreements resolved by another reviewer. None of the authors assessing the studies or performing data extraction had any conflicts of interest to declare. A potential weakness is that due to the limited number of studies for each outcome, publication bias could not be assessed. Despite a comprehensive search, we were unable to exclude the possibility that studies with negative findings remained unpublished.

Agreements and disagreements with other studies or reviews

Although there have been several contemporary literature reviews on this topic ([Conte 2018](#); [Ghisal 2012](#); [Hecking 2013](#); [Sarno 2012](#); [Shivaswamy 2016](#); [Therasse 2013](#); [Wallia 2016](#); [Wissing 2014](#); [Yates](#)

2012), to our knowledge, our original and now updated reviews is the only systematic review comprehensively examining the safety and efficacy of all glucose-lowering agents in pre-existing and new-onset diabetes in kidney transplant recipients.

We found four studies (Barbosa 1983; Barbosa 1994; Hermayer 2012; HiRT 2016) examining the safety and efficacy of more versus less intensive insulin therapy in pre-existing and new-onset diabetes in kidney transplant recipients. The safety and efficacy of more intensive insulin therapy is still unclear. This is despite the addition of another RCT to the body of knowledge (HiRT 2016; Lo 2017). Based on pathophysiology and extrapolation from the non-transplant population, most reviews, guidelines and experts recommend use of insulin in the peri- and post- kidney transplant period for the management of uncontrolled hyperglycaemia in the setting of the physiological stress of surgery and high-dose corticosteroid requirements (ADA 2019; Shivaswamy 2016; Wallia 2016; Yates 2012). Inpatient glycaemic targets, extrapolated from the American Association of Clinical Endocrinologists/American Diabetes Association (ACCE/ADA) guidelines for inpatient management of hyperglycaemia (Conte 2018; KDIGO 2009; Moghissi 2009), recommend glucose levels < 10 mmol/L. Insulin is also recommended as a step-up therapy from oral agents in the scenario of treatment failure in the subacute and chronic outpatient setting (ADA 2019; Wissing 2014). Additionally, a general glycaemic target of 7% to 7.5% is recommended to prevent onset and progression of microvascular complications, with individualisation of glycaemic targets depending on co-morbidities (ADA 2019; Conte 2018; Shivaswamy 2016; Wallia 2016).

Our systematic review found two studies examining the safety and efficacy of DPP-4 inhibitors versus placebo and one study examining the safety and efficacy of DPP-4 inhibitor and insulin glargine versus insulin glargine alone, in pre-existing and new-onset diabetes in kidney transplant recipients. Compared to placebo, DPP-4 inhibitors may improve HbA1c and FBG but make no difference to kidney function markers (eGFR) based on one study. In contrast, non-randomised, uncontrolled studies (Boerner 2014; Lane 2011) have previously reported an HbA1c improvement, and no episodes of hypoglycaemia, reduction in eGFR or evidence of interaction with immunosuppressant therapy (tacrolimus and sirolimus). Similarly, in a retrospective "real world" study, Sanyal 2013 reported that 24 weeks of linagliptin significantly decreased HbA1c, fasting and postprandial glucose levels, with no alteration in tacrolimus levels or eGFR and minimal weight gain and hypoglycaemia.

Only EMPA-Renal Tx 2019 examined the safety and efficacy of SGLT2 inhibitors versus placebo. Compared to placebo, SGLT2 inhibitors probably do not affect kidney graft survival, and may reduce HbA1c modestly without increasing hypoglycaemia, affecting FBG, and eGFR long-term. However, eGFR transiently decreased at eight weeks. In addition, SGLT2 inhibitors probably have little or no effect on medication discontinuation due to adverse events. However, all participants discontinuing SGLT2 inhibitors had urinary tract infections. This is especially a concern, given kidney transplant recipients are already prone to urinary tract infections due to immunosuppression and they only have a single functioning kidney (Mahling 2019). However, there was a similar number of urinary tract infections between groups, the rate of genital fungal infections was low, and diabetic ketoacidosis was not mentioned as an outcome in the study. Other studies of SGLT2 inhibitors are either

non-randomised (Schwaiger 2019) or case series (AlKindi 2020; Mahling 2019). In Schwaiger 2019, 14 participants with diabetes and kidney transplants were matched with controls and switched from insulin to SGLT2 inhibitors for one month, before insulin was re-introduced if required. Empagliflozin provided worse glycaemic control compared to insulin but did not increase the rate of urinary tract infections compared to controls. There were no episodes of euglycaemic diabetic ketoacidosis. However, at one month, there was a transient deterioration in eGFR. In contrast, when SGLT2 inhibitors were added to other glucose lowering agents in two case series (n = 18) and followed over one year, SGLT2 inhibitors reduced HbA1c (albeit modestly in one case series), without a deterioration in kidney function, high rate of urinary tract infections, or episodes of ketoacidosis (AlKindi 2020; Mahling 2019). All these studies are probably too small to detect euglycaemic diabetic ketoacidosis given event rates are low in patients with diabetes (< one per 1000 patient-years; Zelniker 2019). Of note, EMPA-Renal Tx 2019, did not report macrovascular or microvascular complications as outcomes. This is of interest given the cardiovascular and renal benefits of SGLT2 inhibitors in patients with diabetes without kidney transplants (Neuen 2019; Perkovic 2018; Perkovic 2019; Wiviott 2019; Zelniker 2019; Zinman 2015). However, due to EMPA-Renal Tx 2019's small sample size and short duration of follow-up (24 weeks), even if these outcomes were included, they would be unlikely to be detected.

We report that compared to insulin therapy alone, the combination of glitazones and insulin may make little or no difference to FBG and medication discontinuation due to adverse events. However, it is unclear if glitazones and insulin have an effect on HbA1c or kidney function markers compared to insulin alone. Of note, the effects of glitazones on glycaemia may have been hidden by the effect of concurrent insulin therapy. This is because the insulin therapy seems to have been adjusted according to study protocols, to better control glucose levels (Arashnia 2015; Kharazmkia 2014). In addition, previous studies suggest a variable effect of glitazones on HbA1c with some demonstrating a decrease (Baldwin 2004; Luther 2004), and others no difference (Kurian 2008). Regarding effects on kidney functions markers, previous studies suggest no effect kidney function markers or immunosuppressant agent therapy levels (Baldwin 2004; Luther 2004; Pietruck 2005). However, the majority of these studies are small and include a mixture of patients with solid organ transplants - the majority having kidney transplants but some having both kidney and pancreas transplants (Baldwin 2004; Kurian 2008; Luther 2004; Pietruck 2005). Guidelines for diabetes and CKD (which may include the kidney transplant population), suggest that glitazones should be used cautiously (ERBP 2015; Tuttle 2014). The American Diabetes Association recommends that in general, glitazones should not be used in diabetes and CKD due to adverse effects "such as refractory fluid retention, hypertension, and increased fracture risk" (Tuttle 2014).

AUTHORS' CONCLUSIONS

Implications for practice

Currently, high certainty evidence concerning the efficacy and safety of glucose-lowering agents for treating pre-existing and new-onset diabetes in kidney transplant recipients is lacking.

The highest certainty evidence for glucose lowering efficacy lies with SGLT inhibitors and DPP-4 inhibitors but is of moderate to low certainty. Based on one study, SGLT2 inhibitors may

reduce HbA1c without affecting FBG and eGFR long-term. SGLT2 inhibitors probably do not affect kidney graft survival or increase hypoglycaemia. SGLT2 inhibitors probably make little or no difference to the rate of discontinuation due to adverse effects, although in the single study, patients who discontinued SGLT2 inhibitors had urinary tract infections. It is unknown if the cardio-renal benefits seen in patients with diabetes are also seen in kidney transplant recipients with diabetes. Based on one study, DPP-4 inhibitors may improve HbA1c and FBG without affecting kidney function markers. However, it is unclear if DPP-4 inhibitors have an effect on the rate of hypoglycaemia and medication discontinuation compared to placebo. In addition, the effect of DPP-4 inhibitors on graft survival and delayed graft function is unknown due to a lack of RCTs studying these outcomes. Moreover, the safety and efficacy of DPP-4 inhibitors compared to insulin glargine is unclear.

The safety and efficacy of more compared to less intensive insulin is unclear.

Glitazone therapy combined with insulin therapy compared to insulin therapy alone may not affect FBG or medication discontinuation due to adverse effects and the HbA1c lowering potential is unclear. Extrapolating from guidelines for diabetes and CKD in general, glitazones should be used cautiously due to risks of fluid retention, hypertension, and increased fracture risk.

The safety and efficacy of other common glucose lowering agents based on RCT data such as acarbose, GLP-1 agonists, and sulphonylureas are still unknown due to a lack of RCTs studying these agents.

In the absence of further evidence, glucose-lowering therapy should be individualised. It is reasonable to tailor medication choice according to the severity of hyperglycaemia, risk of interaction with immunosuppressives, kidney function, the limited existing data, and to data extrapolated from patients with diabetes but without a kidney transplant. As per previous recommendations from guidelines and other reviews, this may mean using insulin in the perioperative period ([ADA 2019](#); [KDIGO 2009](#); [Shivaswamy 2016](#); [Wallia 2016](#); [Yates 2012](#)). Longer-term therapy may include the use of other glucose lowering agents, particularly DPP-4 inhibitors, with or without insulin depending on the clinical situation, whilst carefully monitoring immunosuppressant agent levels. SGLT2 inhibitors could be considered cautiously as add-on therapy,

especially in the setting of concurrent immunosuppressant agents. However, glycaemic lowering may be modest, and adverse events, including euglycaemic diabetic ketoacidosis, urinary tract infections, as well as changes in immunosuppressant trough levels, should be vigilantly monitored for.

Implications for research

Given the lack of high certainty evidence, large scale RCTs investigating and comparing the safety and efficacy of a wider range of glucose-lowering agents are urgently required to guide glycaemic management in kidney transplant recipients with pre-existing or new-onset diabetes.

As both SGLT2 inhibitors and DPP-4 inhibitors have the highest certainty evidence (which is only of moderate to low certainty) and appear to be a promising treatments in kidney transplant recipients, high quality, larger double blind RCTs are required to confirm safety and efficacy, especially with respect to graft survival outcomes, glycaemic lowering efficacy, kidney function markers, hypoglycaemia and other adverse effects such as urinary tract infections and euglycaemic diabetic ketoacidosis.

In addition, high quality RCTs investigating different insulin regimens are required to determine appropriate acute inpatient treatment in the peri-transplant period and appropriate long-term outpatient treatment to improve outcomes such as graft survival and graft function.

Appropriately blinded RCTs are needed to evaluate and compare the safety and efficacy of other classes of contemporary glucose-lowering agents in the kidney transplant population such as GLP-1 agonists, glinides, metformin, and sulphonylureas.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Arashnia 2015

Study characteristics

Methods	<ul style="list-style-type: none"> Study design: double blind, parallel RCT Study duration: date of first recruitment to last follow-up was not documented Study follow-up period: 4 months
Participants	<ul style="list-style-type: none"> Country: Iran Setting: not reported Inclusion criteria: kidney transplant recipients with diabetes Number: treatment group (29); control group (29) Mean age $\pm$ SD (years): 44.2 $\pm$ 13.8 years Sex: (M/F): 38/20 Exclusion criteria: cigarette smokers; heart failure; hepatitis B and C; GFR < 30 mL/min; pregnancy; acute rejection with progressive kidney impairment; creatinine > 88.4 μmol/L
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Insulin therapy with oral pioglitazone 15 mg/day <p>Control group</p> <ul style="list-style-type: none"> Insulin therapy with placebo tablet/day <p>Baseline immunosuppression</p> <ul style="list-style-type: none"> Not reported <p>Co-interventions</p> <ul style="list-style-type: none"> Not reported
Outcomes	<p>Outcomes from the study registry</p> <ul style="list-style-type: none"> Primary outcomes <ul style="list-style-type: none"> * FBG * Blood uric acid * Blood hsCRP * Blood cholesterol, TG, HDL, LDL Secondary outcomes <ul style="list-style-type: none"> * Weight * BMI * Waist <p>Outcomes for this systematic review</p> <ul style="list-style-type: none"> Primary outcomes <ul style="list-style-type: none"> * Transplant or graft survival: not reported * Delayed graft function: not reported * HbA1c: not reported * FBG * Kidney function markers (including creatinine, eGFR, albuminuria): not reported

Arashnia 2015 (Continued)

- Secondary outcomes
 - * Death (any cause): not reported
 - * Macrovascular events (cardiovascular death, non-fatal MI, non-fatal stroke): not reported
 - * Microvascular events (new or worsening kidney disease, or retinopathy): not reported
 - * Systolic and diastolic BP: not reported.
 - * Lipids (HDL, LDL, TG)
 - * Body weight
 - * Safety/adverse events (including hypoglycaemia): not reported
 - * QoL: not reported

Notes

- Conflict of interest: none declared. The study was extracted from residential thesis of Dr Arashnia. The study was supported by a grant from Shahid-Beheshti University of Medical Sciences (grant#135)
- Waiting for contact from authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients divided randomly into two groups by closed label method."
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients divided randomly into two groups by closed label method."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blind randomised clinical trial." Quote: "First group received insulin therapy with daily one 15 mg pioglitazone tablet (A) for four months and second group received insulin therapy with placebo tablet (B). Placebo tablets were produced identical in shape and size with pioglitazone by its manufacturer."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "drug prescriber, those who visit the patients and filled the checklists in all stages as well as the person who performed the analysis were unaware of drug compounds of both groups."
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no drop-outs from the study
Selective reporting (reporting bias)	Low risk	They reported all outcomes registered on the study registry
Other bias	Low risk	Authors declared no conflicts of interest. The study was extracted from the residential thesis of Dr Arashnia. The study was supported by a grant from Shahid-Beheshti University of Medical Sciences (grant#135)

Barbosa 1983

Study characteristics

Methods	<ul style="list-style-type: none"> • Study design: prospective RCT • Study duration: 2 years • Study follow-up period: 13 months
Participants	<ul style="list-style-type: none"> • Country: USA

Barbosa 1983 (Continued)

- Setting: University of Minnesota Hospital and Clinic and Hennepin County Medical Center, Minneapolis. Referral population from all 50 US states, although approximately 90% came from the upper Midwest and all were white
- Caucasian patients with T1DM who are about to receive a kidney transplant
- Number: treatment group (33); control group (16)
- Mean age $\pm$ SD (years): not reported
- Sex: (M/F): not reported
- Exclusion criteria: not reported

Interventions
Treatment group

- Intensive insulin therapy
 - * Insulin administered via insulin pumps, mixtures of ultralente and regular or lente (NPH) and regular insulin 2 to 4 times/day
 - * BGL monitoring 2 to 10 times/day, with target sugars between 3.33 and 8.33 mmol/L before meals and at bedtime and < 10 mmol/L, 1 hour after major meals
 - * Weight maintaining or reducing diet with 20% protein, 50 to 60% carbohydrate, 20 to 30% fats and increased fibre content

Control group

- Less intensive insulin therapy
 - * Slow acting insulin (lente or NPH) before breakfast supplemented with regular insulin
 - * Home BGL monitoring 4 times/week; target glycaemic range no more than 60% of readings above 11.11 mmol/L and no more than 20% over 16.67 mmol/L
 - * Weight maintaining or reducing diabetes diet as appropriate at the time of discharge from the hospital after transplantation

Baseline immunosuppression

- AZA and prednisolone, CSA and prednisolone or CSA and AZA and prednisolone

Co-interventions

- Further dietary advice at the time of clinic visits

Outcomes
Outcomes from the study registry

- Primary outcomes
 - * Fasting and non-FBG, and 24 hour urine glucose
 - * glycosylated haemoglobin
- Secondary outcomes
 - * Death (any cause)
 - * Rejection

Outcomes for this systematic review

- Primary outcomes
 - * Transplant or graft survival: rejection (including graft loss)
 - * DGF/dialysis within 7 days: not reported
 - * HbA1c: not reported
 - * FBG: not reported
 - * Kidney function markers (including creatinine, eGFR, albuminuria): not reported

Barbosa 1983 (Continued)

- Secondary outcomes
 - * Death (any cause)
 - * Macrovascular events (cardiovascular death, non-fatal MI, non-fatal stroke, heart failure): not reported
 - * Microvascular events (new or worsening kidney disease, doubling of SCr, retinopathy): not reported
 - * Systolic and diastolic BP: not reported
 - * Lipids (HDL, LDL, TG): not reported
 - * Body weight: not reported
 - * Safety/adverse events (including hypoglycaemia): not reported
 - * QoL: not reported

Notes

- Conflict of interest: none declared
- Contact with authors: corresponding author contacted but data requested was not supplied by the time the review was finalised

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	Blinding was not possible due to the nature of the treatment
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 were a much larger number of patients who dropped out of the intensive group (5/33 or 15.15%) due to noncompliance compared with the standard group (1/16 or 6.25%). Conversely there was a larger number of patients who dropped out of the standard group due to kidney graft rejection (3/16 or 18.75%) compared with the intensive group (4/33 or 12.12%) However, overall the proportion of people dropping out due to all causes (including kidney rejection, death and lack of compliance) was equivalent between the standard (31.25%) and the intensive groups (30.61%). Furthermore, although not stated, it seemed that a per protocol analysis was done, increasing the risk of attrition bias
Selective reporting (reporting bias)	High risk	The study did not list any pre-specified primary outcomes, but had prespecified objectives, none of which were reported
Other bias	High risk	There was an additional risk of selection or allocation bias as the authors mentioned that during the study, due to the high attrition rate in the first year of the study, they introduced more stringent selection criteria which led to fewer dropouts in subsequent years Funding source: NIH grant, Eli Lilly, Ames Company, Minnesota Medical Foundation, Squibb/Novo, Minnesota Mining and Manufacturing

Barbosa 1994

Study characteristics

Methods	<ul style="list-style-type: none"> Study design: prospective RCT Study duration: 1978 to 1992 Study follow-up period: 5 years
Participants	<ul style="list-style-type: none"> Country: USA Setting: single centre; University of Minnesota Hospital and Clinic and Hennepin County Medical Center, Minneapolis. Referral population from all 50 USA states, although approximately 90% came from the upper Midwest and all were white Inclusion criteria: patients with T1DM who had received a kidney allograft as treatment for end-stage diabetic kidney disease Number: treatment group (52); control group (47) Mean age $\pm$ SD (years): treatment group (35 $\pm$ 6); control group (36 $\pm$ 8) Sex: (M/F): treatment group (41/11); control group (34/13) Exclusion criteria: not reported
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Intensive insulin therapy <ul style="list-style-type: none"> * Aiming for HbA1 levels within normal limits (i.e. 0.051 to 0.071) * Study nurses contacted patients 2 to 3 times/week, and study dietitian contacted the patient frequently * Home BGL 4 to 6 times/day, allowing frequent readjustment of the insulin dose * Diet and exercise to meet the study goals * Various forms of insulin used; continuous SC infusions, multi-dose injections commonly consisting of a mixture of beef/pork isophane insulin and crystalline regular insulin before breakfast, crystalline regular insulin before supper and isophane insulin at bedtime. Some also took crystalline regular insulin at lunch and a few were treated with extended insulin zinc once or twice a day and crystalline regular insulin at the 3 main meals. During the last 5 years of the study, many people used human insulin <p>Control group</p> <ul style="list-style-type: none"> Less intensive insulin therapy <ul style="list-style-type: none"> * Aimed to alleviate hyperglycaemic symptoms or reduce HbA1 levels to $\leq$ 0.12 * Study nurses contacted patients every 2 to 4 months (more often if subjects had concerns such as symptomatic hyperglycaemia HbA1 > 0.12 or hypoglycaemic episodes) and study dietitian contacted patient once annually * Home BGL 1 to 4 times/day * Exercise was recommended to participants in general terms * Patients received 1 daily injection of a mixture of isophane insulin and crystalline regular insulin (beef/pork) 30 minutes before breakfast. About a third of patients had 2 injections of a mixture of isophane insulin and crystalline regular insulin daily but attempts were made to return to 1 injection/day <p>Baseline immunosuppression</p> <ul style="list-style-type: none"> AZA and prednisolone, CSA and prednisolone, or CSA and AZA and prednisolone <p>Co-interventions</p> <ul style="list-style-type: none"> None
Outcomes	Outcomes from the study registry

Barbosa 1994 (Continued)

- Primary outcomes
 - * GBM widening, mesangial expansion, and changes in mesangial matrix
- Secondary outcomes
 - * HbA1c
 - * Death (any cause)
 - * Rejection and graft loss
 - * Hypoglycaemia

Outcomes for this systematic review

Primary outcomes

- Transplant or graft survival: graft loss and rejection
- Delayed graft function/dialysis within 7 days: not reported
- HbA1c: not reported
- FBG: not reported
- Kidney function markers (including creatinine, eGFR, albuminuria): not reported
- Secondary outcomes
 - * Death (any cause)
 - * Macrovascular events (cardiovascular death, non-fatal MI, non-fatal stroke, heart failure): not reported
 - * Microvascular events (new or worsening kidney disease, doubling of SCr, retinopathy): not reported
 - * Systolic and diastolic BP: not reported
 - * Lipids (HDL, LDL, TG): not reported
 - * Body weight: not reported
 - * Safety/adverse events (including hypoglycaemia): number of visits to hospital for treatment of severe hypoglycaemia
 - * QoL: not reported

Notes

- Comparison groups were well matched for age, sex, and duration of diabetes
- Conflict of interest: none declared
- Contact with authors: corresponding author contacted but data requested was not supplied by the time the review was finalised

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	Blinding was not possible due to the nature of the treatment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	A large number of patients did not complete the study, however, all the withdrawals and losses to follow-up were described. Although dropout rate was high, the authors wrote that there was no significant difference in dropout

Barbosa 1994 (Continued)

rates between groups, and no obvious source of bias that would affect conclusions, regarding maximised versus standard glycaemic control. However, with regard to the breakdown of causes of drop-out, the intensive insulin therapy group had a higher rate of voluntary withdrawals 9/27 or 33.33% (i.e. people who could not tolerate the intensive insulin therapy) compared with the less intensive insulin therapy group 4/24 or 16.67%. This could lead to attrition bias, given that the authors did a per protocol analysis for outcomes shown

Selective reporting (reporting bias)	Low risk	The prespecified primary outcome of glomerular mesangial expansion as determined by electron microscopy was reported
Other bias	High risk	<p>There was an additional risk of selection bias because there was a change in the randomisation method - initially investigators randomised 2:1 in favour of the intensive group as investigators hypothesised that this group would have more withdrawals from the study than the standard group. As this was not the case, in the seventh year of recruiting, they randomised 2:1 in favour of the standard group</p> <p>Funding source: Grants from the National Institute of Health and the National Centre for Research Resources. Also funding from Eli Lilly and Boehringer Mannheim Diagnostics, Minnesota Medical Foundation and the American Diabetes Association</p>

EMPA-Renal Tx 2019

Study characteristics

Methods	<ul style="list-style-type: none"> Study design: single centre, prospective, controlled, double-blind, RCT Study duration: 7 November 2016 to 28 June 2018 Study follow-up period: 24 weeks
Participants	<ul style="list-style-type: none"> Country: Norway. Setting: single centre in Oslo Inclusion criteria: kidney transplant recipient transplanted more than 1 year ago and NODAT after transplantation (FBG ≥ 7.0 mmol/L and/or 2-hour plasma glucose ≥ 11.1 mmol/L following an oral glucose tolerance test); ≥ 18 years with the following features: stable kidney function ($< 20\%$ deviation in SCr within last 2 months); stable immunosuppressive therapy ≥ 3 months before inclusion; signed informed consent and expected to cooperate. Number: 49 recruited; 44 completed the study; 49 included in safety analyses <ul style="list-style-type: none"> * Treatment group (22); control group (22) Median age and range (years): treatment group (63, 31 to 72); control group (59, 21 to 75) Sex: (M/F): treatment group (17/5); control group (17/5) Exclusion criteria: eGFR < 30 mL/min/1.73 m²; pregnant or nursing mothers; hypersensitivity to the active substance or to any of the excipients; any reason why, in the opinion of the investigator, the patient should not participate
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Empagliflozin: 10 mg/day <p>Control group</p> <ul style="list-style-type: none"> Placebo: tablet/day
Outcomes	Outcomes from study registry

EMPA-Renal Tx 2019 (Continued)

- Primary outcome
 - * Weighted mean glucose estimated with continuous glucose monitoring
- Secondary outcomes
 - * FBG
 - * 2-hour glucose concentration
 - * HbA1c
 - * Body weight
 - * Waist-hip-ratio
 - * Body composition
 - * Blood pressure
 - * Arterial stiffness
 - * Kidney function
- Other outcomes
 - * Incidence of abnormal trough levels of immunosuppressive drugs
 - * Adverse event
 - * Urinary glucose excretion

Outcomes for this systematic review

- Primary outcomes
 - * Transplant or graft survival; graft loss and rejection
 - * Delayed graft function/dialysis within 7 days: not reported
 - * HbA1c
 - * FBG
 - * Kidney function markers (including creatinine, eGFR, albuminuria): eGFR
- Secondary outcomes
 - * Death (any cause): not reported
 - * Macrovascular events (cardiovascular death, non-fatal MI, non-fatal stroke, heart failure): not reported
 - * Microvascular events (new or worsening kidney disease, doubling of SCr, retinopathy): not reported
 - * Systolic and diastolic BP
 - * Lipids (HDL, LDL, TG): not reported
 - * Body weight
 - * Safety/adverse events (including hypoglycaemia): hypoglycaemia, discontinuation of medication due to adverse events, other adverse events
 - * QoL: not reported

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation was performed by the R package "blockrand" using simple randomisation, one block, and equal probabilities of each sequence"
Allocation concealment (selection bias)	Low risk	Quote: "A person not directly involved in the practical implementation of the study performed the allocation. For each new patient entering the study, a study number was assigned with a prelisted drug package"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Both patient and investigator/study personnel were blinded with regards to study drug (active/placebo) until statistical analyses were performed"

EMPA-Renal Tx 2019 (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Both patient and investigator/study personnel were blinded with regards to study drug (active/placebo) until statistical analyses were performed"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Five patients dropped out from the study. Two were from the empagliflozin group (2/24, 8.3%) due to repeated urinary tract infections and urosepsis. Three were from the placebo group (3/25, 12%), due to withdrawal of consent, colon cancer, and no longer fulfilling Post-transplant diabetes criteria, respectively. However, data from these patient were included in the safety outcomes
Selective reporting (reporting bias)	Low risk	All preplanned outcomes were reported. Of note, data for the primary outcome of weighted mean glucose was not analysed or reported. However, this was due to a study technical error
Other bias	Low risk	The study was initiated and funded by the investigators and supported by grants from the South-Eastern Norway Regional Health Authority, the Norwegian Diabetes Association, Oslo Diabetes Research Centre and supported by an unrestricted grant from Boehringer Ingelheim, Norway. One of the authors, T.J., had received lecture honoraria from Boehringer Ingelheim

Haidinger 2010
Study characteristics

Methods	<ul style="list-style-type: none"> Study design: phase 2 RCT Study duration: March 2009 to July 2012 Study follow-up period: 16 weeks; 3 months of treatment, and primary and secondary outcomes reported at 3 months, and secondary outcomes at 4 months.
Participants	<ul style="list-style-type: none"> Country: Austria Setting: single centre outpatient clinic, Department of Nephrology and Dialysis from Vienna General Hospital/Medical University of Vienna Patients with NODAT, transplant vintage > 6 months; stable graft function (no clinically meaningful change in kidney function within the last 3 months) and informed consent Number: treatment group (16); control group (16) Mean age $\pm$ SD (years): treatment group (64.25 $\pm$ 27); control group (63 $\pm$ 8.4) Sex: (M/F): treatment group (10/6); control group (14/2) Exclusion criteria: prior history of T1DM or T2DM; pregnancy; severe kidney impairment with eGFR $\leq$ 30 mL/min/1.73 m²; severe liver impairment with AST and ALT 3x upper limit of normal
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Vildagliptin (oral): 50 mg/day for 3 months <p>Control group</p> <ul style="list-style-type: none"> Placebo <p>Baseline immunosuppression</p> <ul style="list-style-type: none"> TAC or CSA, MMF or MPA or AZA, and prednisolone <p>Co-interventions</p> <ul style="list-style-type: none"> None

Haidinger 2010 (Continued)

Outcomes

Outcomes from the study registry

- Primary outcomes
 - * 2-hour blood glucose
- Secondary outcomes
 - * HbA1c
 - * FBG
 - * Kidney function markers including creatinine, (eGFR, albuminuria: eGFR
 - * Systolic and diastolic BP
 - * Lipids (HDL, LDL, TG)
 - * Liver function parameters
 - * BMI
 - * Immunosuppressant serum level
 - * Safety/adverse events (including hypoglycaemia)

Outcomes for this systematic review

- Primary outcomes
 - * Transplant or graft survival: reported on correspondence
 - * DGF/dialysis within 7 days: not reported
 - * HbA1c
 - * FBG
 - * Kidney function markers including creatinine, estimated glomerular filtration rate (eGFR), albuminuria: eGFR
- Secondary outcomes
 - * Death (any cause): reported on correspondence
 - * Macrovascular events (cardiovascular death, non-fatal MI, non-fatal stroke, heart failure): cardiovascular events were reported on correspondence
 - * Microvascular events (new or worsening kidney disease, doubling of SCr, retinopathy): not reported
 - * Systolic and diastolic BP
 - * Lipids (HDL, LDL, TG)
 - * Body weight: not reported
 - * Safety/adverse events (including hypoglycaemia): Severe hypoglycaemia (i.e. hypoglycaemia requiring third party assistance), discontinuation of medication due to adverse events, liver abnormalities/failure, angina pectoris, elevated pancreas enzymes, elevated triglycerides, cough, conjunctivitis, urinary tract infections, and leukopenia were reported.
 - * QoL: not reported

Notes

- Groups were well matched for nearly all baseline characteristics including gender, age, BMI (28.4 ± 4.5 versus 27.9 ± 6 kg/m², $P = 0.78$), HbA1c ($6.7 \pm 0.73\%$ versus $6.7 \pm 0.82\%$, $P = 0.95$), eGFR (58.3 ± 16.3 versus 53.6 ± 14.4 mL/min/1.73 m², $P = 0.40$), time since transplantation (69.9 ± 63.9 versus 51.4 ± 47.2 months, $P = 0.38$) and prednisolone dose (3.6 ± 1.8 versus 4.1 ± 2.6 mg/d, $P = 0.52$). However, use of MPA (8 participants in the intervention versus 4 in the control arm, $P = 0.02$) and MMF (7 participants in the intervention versus 2 in the control arm, $P = 0.049$) at baseline was significantly different
- Conflict of interest: none declared
- Contact with authors: authors contacted

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	On correspondence, randomisation was reported to be performed by the pharmaceutical department via a computer randomisation program

Haidinger 2010 (Continued)

Allocation concealment (selection bias)	Low risk	On correspondence, allocation concealment and blinding were reported to be maintained until the end of the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding was done at the local pharmacy; study was also double blind and a placebo pill was used
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout rate, with 1/33 not completing the study
Selective reporting (reporting bias)	Low risk	The main prespecified primary and secondary outcomes of interest were reported
Other bias	Low risk	Funding source: Medical University of Vienna, Austria

Hermayer 2012
Study characteristics

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: not reported Study follow-up period: 3-day post kidney transplant treatment; the study followed episodes of rejection to 3 years
Participants	<ul style="list-style-type: none"> Country: USA Setting: kidney transplant candidates admitted to the Medical University of South Carolina. Most were African American (60%), with T2DM (89%); 10% had T1DM, and 1 patient had impaired fasting glycaemia Inclusion criteria: ≥ 18 years, T1DM or T2DM, FPG > 5.56 mmol/L and random BGL > 6.67 mmol/L; willing and able to provide informed consent; awaiting living or cadaveric kidney transplant Number (randomised/transplanted and analysed): treatment group (52/44); control group (52/49) Mean age $\pm$ SD (years): treatment group (58 ± 9.8); control group (56.3 ± 9.6) Sex: (M/F): treatment group (30/14); control group (35/14) Exclusion criteria: active gastrointestinal tract bleed 3 months before; scheduled to receive a simultaneous pancreas transplant; history of a functioning pancreatic transplant; currently managed on an insulin pump; unable or unwilling to provide informed consent; unable to commit to the study protocol including the outpatient follow-up phase of care
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Intensive insulin therapy <ul style="list-style-type: none"> * First 72 hours post-transplant <ul style="list-style-type: none"> ☐ IV insulin infusion with BGL checked 1 to 2 hourly aiming for BGL 3.89 to 6.11 mmol/L ☐ Oral glucose-lowering agents were discontinued * After 72 hours <ul style="list-style-type: none"> ☐ Long acting and rapid-acting SC insulin aiming for BGL between 3.89 to 6.71 mmol/L <p>Control group</p>

Hermayer 2012 (Continued)

- Less intensive insulin therapy
 - * First 72 hours post-transplant
 - ☐ SC long and rapid-acting insulin aiming for a target BGL between 3.89 to 10 mmol/L
 - ☐ BGL checked 4 hourly
 - ☐ On commencing dietary intake, BGL checked pre meals, bedtime and at 3 am. BGL maintained at 3.90 to 10 mmol/L
 - * After 72 hours
 - ☐ a minimum of 1 to 2 insulin SC injections to maintain BGL between 5 and 10 mmol/L

Baseline immunosuppression

- TAC, MMF and prednisolone

Co-interventions

- None

Outcomes	<p>Outcomes from the study registry</p> <ul style="list-style-type: none"> • Primary outcomes <ul style="list-style-type: none"> * DGF: either day-10 SCR > 221 µmol/L or need for dialysis within first 7 days • Secondary outcomes <ul style="list-style-type: none"> * Mean blood glucose * Graft survival and acute rejection episode * Safety/adverse events (including hypoglycaemia): severe hypoglycaemia (BG < 2.2 mmol/L) and severe hyperglycaemia (BG > 19.4 mmol/L) <p>Outcomes for this systematic review</p> <ul style="list-style-type: none"> • Primary outcomes <ul style="list-style-type: none"> * Transplant or graft survival: rejection (including graft loss) * DGF/dialysis within 7 days: either day-10 SCR > 221 µmol/L or need for dialysis within first 7 days * HbA1c: not reported * FBG: not reported * Kidney function markers (including creatinine, eGFR, albuminuria): not reported • Secondary outcomes <ul style="list-style-type: none"> * Death (any cause): not reported * Macrovascular events (cardiovascular death, non-fatal MI, non-fatal stroke, heart failure): not reported * Microvascular events (new or worsening kidney disease, doubling of SCR, retinopathy): not reported * Systolic and diastolic BP: not reported * Lipids (HDL, LDL, TG): not reported * Body weight: not reported * Safety/adverse events (including hypoglycaemia): severe hypoglycaemia (BG < 2.2 mmol/L) and severe hyperglycaemia (BG > 19.4 mmol/L) * QoL: not reported
Notes	<ul style="list-style-type: none"> • At baseline, both groups were well matched for ethnicity, male gender, age, HbA1c (7 ± 1.8 versus $7.2 \pm 1.7\%$, $P = 0.65$), duration of dialysis (3.1 ± 1.9 versus 2.8 ± 1.9 years, $P = 0.44$), as well as cardiovascular disease and donor and graft history. One patient with impaired fasting glycaemia was included in the active treatment group compared to none in the control group • Conflict of interest: none declared • Contact with authors: corresponding author contacted but data requested was not supplied by the time the review was finalised

Risk of bias

Hermayer 2012 (Continued)

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	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	High risk	The study was unblinded and subjects were randomised before transplant. Losses to follow-up mainly occurred if people were not transplanted. Reasons for not being transplanted included a positive cross match, poor graft quality, patient health, and "other" and "unspecified". There was a higher dropout rate i.e. 8/52 or 15.38% rate in the intensive group and 3/52 = 5.77% in the standard group. Given that there was no allocation concealment, the higher dropout rate in the intensive group could potentially be related to investigator bias
Selective reporting (reporting bias)	Low risk	All the prespecified primary and secondary outcomes were reported
Other bias	Low risk	Funding source: American Diabetes Association Clinical Investigator Award

HiRT 2016
Study characteristics

Methods	<ul style="list-style-type: none"> Study design: single-centre, open-label, RCT Study duration: recruited between 15 August 2012, and 20 March 2014, all of whom underwent transplant and were successfully followed at our centre through 18 June 2014 Study follow-up period: 1 year
Participants	<ul style="list-style-type: none"> Country: USA Setting: University of California San Francisco Medical Center Inclusion criteria: adult patients with a diagnosis of diabetes mellitus who were admitted for deceased donor kidney transplantation Number: treatment group (30); control group (30) Mean age $\pm$ SD (years): treatment group (60.9 $\pm$ 9.1); control group (60.7 $\pm$ 11) Sex: (M/F): treatment group (20/10); control group (20/10) Exclusion criteria: children and adult candidates enrolled in a concurrent study evaluating the effect of a medication or other intervention on graft function
Interventions	Treatment group

HiRT 2016 (Continued)

- Moderate intense glucose control
 - * Insulin infusion if blood glucose > 6.7 mmol/L. To avoid prolonged treatment, the infusion was started no earlier than four hours before the anticipated start of the transplant
 - * Intra-operatively, blood glucose checked every 30 to 45 minutes with the goal of keeping it between 4.4 to 8.9 mmol/L
 - * Use of bolus therapy or insulin infusion was left to the discretion of the anaesthesia team
 - * Postoperatively, all recipients were placed on an insulin infusion with a target blood glucose level of 5.5 to 10 mmol/L for 24 hours postoperatively
 - * After 24 hours of the infusion, the primary transplant team was given complete control over glucose management

Control group

- Standard glucose control
 - * Standard insulin sliding scale when serum blood glucose > 11.1 mmol/L perioperatively, at time of reperfusion, and postoperatively for 24 hours
 - * After 24 hours, the primary transplant team was given complete control of glucose management and allowed to start insulin as they deemed appropriate

Outcomes	Outcomes from the study registry
	<ul style="list-style-type: none"> • Primary outcomes <ul style="list-style-type: none"> * Poor initial graft function defined by the occurrence of DGF (defined by a decrease in SCr < 10%/day for 3 consecutive days after transplant) or slow graft function (SCR > 3 mg/dL 5 days after transplant without dialysis) * Acute rejection at 90 days and graft survival/kidney function at 3 months, 6 months and then yearly • Secondary outcomes <ul style="list-style-type: none"> * Wound infection * Length of hospital stay * Death at 30 days. * Hypoglycaemic episodes (glucose < 70 mg/dL or < 3.9 mmol/L) * Stroke
	Outcomes for this systematic review
	<ul style="list-style-type: none"> • Primary outcomes <ul style="list-style-type: none"> * Transplant or graft survival: Biopsy proven rejection and graft loss * DGF/dialysis within 7 days: poor graft function defined as need for dialysis within 7 days of transplant or failure of the SCr to drop by > 10% for 3 consecutive days. DGF (need for dialysis within 7 days of transplant) * HbA1c: not reported * FBG: not reported * Kidney function markers (including creatinine, eGFR, albuminuria): not reported • Secondary outcomes <ul style="list-style-type: none"> * Death (any cause): perioperative death. * Macrovascular events (cardiovascular death, non-fatal MI, non-fatal stroke, heart failure, peripheral vascular disease): stroke * Microvascular events (new or worsening kidney disease, doubling of SCr or retinopathy): not reported * Systolic and diastolic BP: not reported. * Lipids (HDL, LDL, TG): not reported * Body weight: not reported * Safety/adverse events (including hypoglycaemia): the primary safety measure was the number of severe hypoglycaemic events (blood glucose < 2.2 mmol/L). Also reported seizures. * QOL: not reported
Notes	<ul style="list-style-type: none"> • Funding source: not reported

HiRT 2016 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation strategy (block size of four) to ensure equal distribution of patients between study arms was used Quote: "The randomisation was generated per computer algorithm."
Allocation concealment (selection bias)	Low risk	Quote: "The randomisation scheme was hidden in an electronic file until each patient was enrolled."
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study was a "single-center, open-label, randomised controlled trial comparing standard and moderately intense glucose control."
Blinding of outcome assessment (detection bias) All outcomes	High risk	The study was a "single-center, open-label, randomised controlled trial comparing standard and moderately intense glucose control."
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no drop-outs from either study group
Selective reporting (reporting bias)	High risk	In the manuscript, the primary outcome was "primary outcome was poor graft function (dialysis within seven days of transplant or failure of serum creatinine to fall by 10% for three consecutive days)." In the ClinicalTrials.gov (NCT01643382), the poor graft function was defined as "Our primary endpoint will be poor initial graft function defined by the occurrence of DGF (defined by a decrease in serum creatinine of <10%/day for 3 consecutive days after transplant) or slow graft function (serum creatinine >3 mg/dL 5 days after transplant without dialysis)"
Other bias	Low risk	No conflicts of interest declared

Kharazmkia 2014
Study characteristics

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: September 2012 to May 2013 Study follow-up period: 16 weeks
Participants	<ul style="list-style-type: none"> Country: Iran Setting: University Hospital Transplant Unit Inclusion criteria: diabetes, received kidney transplantation at least 1 month prior to study; stable graft function within the past 2 weeks Number (randomised/analysed): treatment group (35/31); control group (36/31). However, 35 treatment and 36 control used for safety and followed-up Mean age $\pm$ SD (years): treatment group (50.2 $\pm$ 12.6); control group (54.8 $\pm$ 8.7) Sex: (M/F): treatment group (24/7); control group (16/15) Exclusion criteria: history of febrile episodes; hepatitis B or C infection; eGFR < 30 mL/min/1.73 m² (based on MDRD at baseline); history of CHF (NYHA 2-4); pregnancy; those who received steroid pulse

Kharazmkia 2014 (Continued)

or had an acute episode of allograft dysfunction (decrement of eGFR by at least 30 mL/min/1.73 m²) during follow-up

Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • Pioglitazone (oral): 30 mg/day for 4 months • Insulin <p>Control group</p> <ul style="list-style-type: none"> • Placebo • Insulin <p>Baseline immunosuppression</p> <ul style="list-style-type: none"> • CSA-based immunosuppressive protocol which consisted of MMF and prednisolone <p>Co-interventions</p> <ul style="list-style-type: none"> • All participants continued their insulin therapy • Glycaemic targets were pre-prandial plasma glucose 5 to 7.2 mmol/L and HbA1c < 7%
Outcomes	<p>Outcomes from the study registry</p> <ul style="list-style-type: none"> • Primary outcomes <ul style="list-style-type: none"> * FBG * HbA1c • Secondary outcomes <ul style="list-style-type: none"> * Lipids * Inflammatory markers including C-reactive protein, erythrocyte sedimentation rate, Interleukin-18 * SCr * Body weight * Safety/adverse events (including hypoglycaemia): lower extremity oedema, insomnia, transient elevation of liver enzyme levels 2 or more times the upper limits, and severe congestive heart failure <p>Outcomes for this systematic review</p> <ul style="list-style-type: none"> • Primary outcomes <ul style="list-style-type: none"> * Transplant or graft survival: not reported * DGF/dialysis within 7 days: not reported * HbA1c * FBG: not reported * Kidney function markers (including creatinine, eGFR, albuminuria): creatinine • Secondary outcomes <ul style="list-style-type: none"> * Death (any cause): not reported * Macrovascular events (cardiovascular death, non-fatal MI, non-fatal stroke, heart failure): not reported * Microvascular events (new or worsening kidney disease, doubling of SCr, retinopathy): not reported * Systolic and diastolic BP: not reported * Lipids (HDL, LDL, TG) * Body weight * Safety/adverse events (including hypoglycaemia): lower extremity oedema, insomnia, transient elevation of liver enzyme levels ≥ 2 times the upper limits, and severe congestive heart failure * QoL: not reported
Notes	<ul style="list-style-type: none"> • Errors in flow diagram • Conflict of interest: none declared

Kharazmkia 2014 (Continued)

- Contact with authors: corresponding author contacted but data requested was not supplied by the time the review was finalised

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised random number method
Allocation concealment (selection bias)	Low risk	Quote: "...concealment of randomisation was adhered to"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double blind; clinician researchers, participants and data analysts remained blinded to the random allocations during the study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Described as double blind; clinician researchers, participants and data analysts remained blinded to the random allocations during the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	10/71 participants (14.29%) did not complete the study. 5/35 (14.3%) pioglitazone group participants dropped out because one did not receive the intervention and four discontinued the intervention; 5/36 placebo arm participants (13.9%) dropped out because they did not continue the intervention
Selective reporting (reporting bias)	High risk	Reported all major outcomes according to the study registry. Several errors were detected in the published report
Other bias	Low risk	Funding source: grant from the Deputy of Research and Technology of Shahid Behesti University of Medical Sciences

Soliman 2013

Study characteristics

Methods	<ul style="list-style-type: none"> • Study design: open-label RCT • Study duration: date of first recruitment to last follow-up not documented • Study follow-up period: 12 weeks
Participants	<ul style="list-style-type: none"> • Country: Egypt • Setting: University Hospital in Cairo • Inclusion criteria: NODAT defined by BGL > 11.1 after an oral glucose tolerance test; stable graft function for more than 6 months after transplant • Number (randomised/analysed): treatment group (31/28); control group (31/17). No drop-outs due to medications, serious adverse clinical events. • Mean age, range: 38.5, 31 to 62 years • Sex: (M/F): 26/19 • Exclusion criteria: prior history of T1DM or T2DM; BMI > 40; pregnancy; severe kidney impairment (GFR < 30 mL/min/1.73 m²); severe liver impairment; severe blood glucose elevation (HbA1c > 8.5%)
Interventions	Treatment group

Soliman 2013 (Continued)

- Sitagliptin (oral): 100 mg but adjusted according to participant's eGFR
 - * eGFR > 50 50 mL/min/1.73 m²: 100 mg/d
 - * GFR 25 to 49 50 mL/min/1.73 m²: 50 mg/d

Control group

- Glargine (SC)
 - * Dosages adjusted according to SC sliding scale pattern, titrated to target a fasting BGL ≤ 5.5 mmol/L

Baseline immunosuppression

- Triple therapy of TAC or CSA, MMF or AZA, and prednisolone

Co-interventions

- All participants received metformin
- Glycaemic targets were pre-prandial plasma glucose 5 to 7.2 mmol/L and HbA1c < 7%

Outcomes	<p>Outcomes from the study registry</p> <ul style="list-style-type: none"> • Primary outcomes <ul style="list-style-type: none"> * HbA1c • Secondary outcomes <ul style="list-style-type: none"> * FBG * Lipids * Body weight * Safety/adverse events including hypoglycaemia and gastrointestinal side effects <p>Outcomes for this systematic review</p> <ul style="list-style-type: none"> • Primary outcomes <ul style="list-style-type: none"> * Transplant or graft survival: not reported * DGF/dialysis within 7 days: not reported * HbA1c * FBG * Kidney function markers (including creatinine, eGFR, albuminuria): not reported • Secondary outcomes <ul style="list-style-type: none"> * Death (any cause): not reported * Macrovascular events (cardiovascular death, non-fatal MI, non-fatal stroke, heart failure): not reported * Microvascular events (new or worsening kidney disease, doubling of SCr, retinopathy): not reported * Systolic and diastolic BP: not reported * Lipids (HDL, LDL, TG) * Body weight * Safety/adverse events (including hypoglycaemia): hypoglycaemia and gastrointestinal side effects * QoL: not reported
Notes	<ul style="list-style-type: none"> • Multiple errors in publication especially for the tables, with errors in calculations • Conflict of interest: no conflicts of interest were reported • Contact with authors: corresponding author contacted due to contradictions in the results reported in the table compared to the text, but clarification and data required were not supplied by the time the review was finalised

Risk of bias

Bias	Authors' judgement	Support for judgement
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Soliman 2013 (Continued)

Random sequence generation (selection bias)	Unclear risk	Study described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
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 but many endpoints requiring assay were performed by technicians blinded to the treatment sequence. Therefore, most efficacy outcomes were blinded except for weight. For safety outcomes, it was unclear if researchers were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	17/62 (27.4%) participants dropped out. Rates were higher in the glargine group (insulin) (14/31; 45%) compared with sitagliptin (3/31; 9.68%) In the insulin group 6 patients who required multiple short acting dosages of insulin were excluded; 3 were lost to follow-up, and 5 did not want to continue insulin due to the fear of the long-term need for insulin In the sitagliptin group, all dropouts occurred 1 week after randomisation. 3/31 patients needed multiple short acting dosages of insulin and were excluded A PP analysis was conducted
Selective reporting (reporting bias)	Low risk	Prespecified primary outcomes of interest were reported
Other bias	Low risk	Funding source: no grants were received for the study

Strom Halden 2014

Study characteristics

Methods	<ul style="list-style-type: none"> Study design: cross-over RCT Study duration: not reported Study follow-up period: 8 weeks
Participants	<ul style="list-style-type: none"> Country: Norway Setting: Oslo University Hospital at Rikshospitalet Inclusion criteria: adult kidney transplant recipients with NODAT who received a transplant more than 1 year ago and had stable kidney function (< 20% variation in serum creatinine over last 2 months); stable maintenance dose prednisolone for the preceding 3 months; unchanged doses of other oral glucose-lowering treatment Number: 19 Median age, IQR: 67, 62 to 72 years Sex: (M/F): 12/7 Exclusion criteria: severe liver disease; eGFR < 25 mL/min/1.73 m²; pregnant/nursing mothers; patients on insulin therapy
Interventions	Treatment group

Strom Halden 2014 (Continued)

- Sitagliptin (oral): 100 mg but adjusted according to eGFR
 - * eGFR > 50 mL/min/1.73 m²: 100 mg
 - * eGFR 25 to 49 mL/min/1.73 m²: 50 mg

Control group

- Placebo

Baseline immunosuppression

- CSA, TAC or everolimus
- Prednisolone

Co-interventions

- None reported, besides pre-existing prescription of sulphonylureas: glipizide or glimepiride

Outcomes

Outcomes from the study registry

- Primary outcomes
 - * Insulin secretion, insulin release index (SecrHOMA), C-peptide/glucose creatinine ratio (CPGCR)
- Secondary outcomes
 - * FBG
 - * Insulin sensitivity index
 - * Systolic and diastolic BP
 - * BMI
 - * Endothelial function: Area under the flux versus time curve including the fourth iontophoretic stimulation and after the Rh-test
 - * Cardiovascular markers: μ CRP, VCAM-1, adiponectin, and sTNFR-1
 - * Transplant or graft survival: reported to be 100% on correspondence
 - * Safety/adverse events (including hypoglycaemia): sweating

Outcomes for this systematic review

- Primary outcomes
 - * Transplant or graft survival: reported to be 100% on correspondence
 - * DGF/dialysis within 7 days: not reported
 - * HbA1c
 - * FBG: not reported
 - * Kidney function markers (including creatinine, eGFR, albuminuria): not reported
- Secondary outcomes
 - * Death (any cause): not reported
 - * Macrovascular events (cardiovascular death, non-fatal MI, non-fatal stroke, heart failure): not reported
 - * Microvascular events (new or worsening kidney disease, doubling of SCr, retinopathy): not reported
 - * Systolic and diastolic BP
 - * Lipids (HDL, LDL, TG): not reported
 - * Body weight: not reported
 - * Safety/adverse events (including hypoglycaemia): sweating
 - * QoL: not reported

Notes

- 12 patients had drug-naïve NODAT; 7 were on sulphonylureas (either glipizide or glimepiride)
- Conflict of interest: none declared
- Contact with authors: authors contacted, but first phase data were not supplied

Risk of bias

Strom Halden 2014 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by use of a pre-made list of treatment sequence, and the consecutively included patients were assigned the next number on the list, which was not available to the physicians recruiting the patients
Allocation concealment (selection bias)	High risk	No allocation concealment as confirmed by the authors. The study was unblinded and not placebo controlled. This was confirmed with the authors
Blinding of participants and personnel (performance bias) All outcomes	High risk	Reported to be unblinded and not placebo controlled
Blinding of outcome assessment (detection bias) All outcomes	High risk	Reported to be unblinded and not placebo controlled
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	One patient (5.26%) dropped out and did not complete the study due to side effects (night sweats) from sitagliptin
Selective reporting (reporting bias)	Unclear risk	All prespecified primary and secondary outcomes were reported, however first phase data were not available
Other bias	Unclear risk	The authors confirmed in writing that there was no washout period for patients who stopped sitagliptin and then crossed-over to no treatment. This may dilute out the effect of sitagliptin compared with no treatment. However, only first phase data was considered for this systematic review Funding source: investigator initiated; grant from Southeast Norway Regional Health Authority and Laboratory for renal physiology at Rikshospitalet

ALT - alanine aminotransferase; AST - aspartate aminotransferase; AZA - azathioprine; BG(L) - blood glucose (level); BMI - body mass index; BP - blood pressure; CHF - congestive heart failure; CSA - cyclosporin; DGF - delayed graft function; FBG - fasting blood glucose; GBM - glomerular basement membrane; (e)GFR - (estimated) glomerular filtration rate; HBA1c - glycated haemoglobin A1c; HDL - high density lipoprotein; LDL - low density lipoprotein; M/F - male/female; MI - myocardial infarction; MMF - mycophenolate mofetil; MPA - mycophenolic acid; NODAT - new-onset diabetes after transplant; PP - per protocol; QoL - quality of life; RCT - randomised controlled trial; SC - subcutaneous; SCr - serum creatinine; SD - standard deviation; T1DM - type 1 diabetes mellitus; T2DM - type 2 diabetes mellitus; TAC - tacrolimus; TG - triglyceride

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Clodi 1997	Wrong population: did not involve patients with diabetes
Halden 2016	Wrong study design: Is a mechanistic rather than an interventional study. The study was examining the effect of a hormone, GLP-1, rather than the effects of a pharmacological agent such as a GLP-1 agonist
Han 2010	Wrong population: did not involve patients with diabetes
Hecking 2012	Wrong population: did not involve patients with diabetes
Kim 1997a	Wrong intervention/control: did not use glucose-lowering agents

Study	Reason for exclusion
LANDMARK 2 2009	Wrong intervention/control: did not use glucose-lowering agents
Orazio 2011	Wrong intervention/control: did not use glucose-lowering agents
Re 2010	Wrong population: did not involve patients with diabetes
SAPT-NODAT 2012	Wrong population: did not involve patients with diabetes
Sharif 2009	Wrong intervention/control: did not use glucose-lowering agents
TransDiab 2017	Wrong population: did not involve patients with diabetes
TRIMECO 2018	Wrong intervention/control: did not use glucose-lowering agents
Werzowa 2013	Wrong population: did not involve patients with diabetes
Yates 2014	Wrong population: did not involve patients with diabetes

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

[Lakhani 2016](#)

Methods	<ul style="list-style-type: none"> Prospective, open labelled pilot RCT
Participants	<ul style="list-style-type: none"> Country: India Setting: Sr Ganga Ram Hospital, New Delhi, India Inclusion criteria: hospitalised patients with NODAT Number: 28 – only 12 patients had kidney transplant, 6 in each group Median age, IQR: Sex: (M/F): ? Exclusion criteria: ?
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Insulin according to a novel algorithm including insulin NPH given along with prednisolone in appropriate doses to negate the effects of prednisolone, and insulin Glargine given once a day to negate the effects of Tacrolimus. <p>Control group</p> <ul style="list-style-type: none"> Insulin according to standard basal-bolus insulin algorithm followed in the hospital
Outcomes	Study outcomes: ?
Notes	<ul style="list-style-type: none"> Contacted authors: Awaiting further information from authors

[NCT00507494](#)

Methods	<ul style="list-style-type: none"> Double-blind, placebo controlled, cross-over RCT; phase 3 study Time frame: 12 weeks
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NCT00507494 (Continued)

Participants	<ul style="list-style-type: none"> Inclusion criteria: kidney transplantation (> 6 months ago); stable graft function; DMT2; acceptable glycaemia (HbA1c < 8%); CrCl (> 30 mL/min/1.73 m²); proteinuria > 30 mg/24 hours Males and females aged 30 to 70 years Exclusion criteria: type 1 diabetes; pregnant or breast feeding women; congestive heart failure (>stage 1 NYHA); creeping creatinine, treatment for rejection within 3 months prior to inclusion; ALT, AST > 2.5 fold the upper limit of normal; uncontrolled hypertension; hypo- or hyperthyroidism
Interventions	<ul style="list-style-type: none"> Pioglitazone: 30 mg once daily tablet for 12 weeks or placebo once daily tablet for 12 weeks in random order. After 12-week treatment there is a 4-week washout out which is followed by switch of study medication in a cross over fashion and a further 12-week treatment
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> Proteinuria <p>Secondary outcomes</p> <ul style="list-style-type: none"> Filtration fraction Renal nitric oxide bioavailability Insulin resistance Platelet function Safety: tolerability, plasma glucose, body weight, oedema
Notes	<ul style="list-style-type: none"> Start date: 2007 Peter Gross, Nephrology Department, Department of Medicine, University hospital Dresden Study completed in 2009, however no results posted in 2016 - authors contacted but no reply at time of review completion.

BP - blood pressure; CrCl - creatinine clearance; DMT2- diabetes mellitus type 2; eGFR - estimated glomerular filtration rate; FBG - fasting blood glucose; HbA1c - glycated haemoglobin A1c; HDL - high density lipoprotein. LDL - low density lipoprotein; M/F - male/female; MI - myocardial infarction; NODAT - new-onset diabetes after transplant; SD - standard deviation

Characteristics of ongoing studies [ordered by study ID]

NCT03642184

Study name	Efficacy and safety of empagliflozin in new onset diabetes after kidney transplantation (NODAT)
Methods	<ul style="list-style-type: none"> Open label, RCT Study follow-up period: 24 weeks
Participants	<ul style="list-style-type: none"> Country: China Setting: Ren Ji Hospital (Shanghai Jiao Tong University School of Medicine), Shanghai, China Inclusion criteria adults (aged 18 to 65 years); single kidney transplantation; normal glucose tolerance or pre-diabetes mellitus before transplantation; diagnosis of NODAT based on oral glucose tolerance test results; standard triple immunosuppression therapy; HbA1c ≤ 10%; steady hormone usage; BMI 18.5 to 30 kg/m²; patient informed consent Exclusion criteria: prevalent diabetes prior to transplantation; pregnancy; diagnosis of type 1 diabetes following transplantation; severe liver function impairment (AST/ALT 3 times standard value); severely impaired kidney function (eGFR < 45); history of cancer in the past 5 years (except basal cell carcinoma) and/or cancer treatment; participating in another trial involving the study drug within 30 days; premenopausal women (1 year before the last menstrual period ≤ informed consent); alcohol or drug abuse within 3 months of informed consent, affecting compliance; need for other drugs to control NODAT
Interventions	Treatment group

NCT03642184 (Continued)

- Empagliflozin: 10 to 25 mg once/day (dosage adjustment based on glucose targets)

Comparator group

- Linagliptin: 5 mg once/day (dose adjustment based on glucose targets)

Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> • Change in eGFR from baseline <p>Secondary outcomes</p> <ul style="list-style-type: none"> • Graft loss • Death • Acute rejection • Progression to albuminuria • Progression to macroalbuminuria • FBG • HbA1c • Adverse events
Starting date	14 July 2018
Contact information	<p>Shan Mou: +8613918221242; shan_mou@126.com</p> <p>Yaomin Hu: +8613651617002; amin99@163.com</p>
Notes	

VAT 2013

Study name	
Methods	<ul style="list-style-type: none"> • Study design: single-centre, open-label RCT • Study duration: Participants were recruited between 15 August 2012, and 20 March 2014, all of whom underwent transplant and were successfully followed at our centre through 18 June 2014 • Study follow-up period: 1 year.
Participants	<ul style="list-style-type: none"> • Country: Australia • Setting: Renal transplant department of Royal Prince Alfred Hospital, NSW • Inclusion criteria: kidney transplant recipient; adult (≥ 18 years); NODAT (OGTT or random or fasting BSL > WHO recommendation); HbA1c < 8.0% • Number: 48 patients to be recruited • Mean age $\pm$ SD (years): ? • Sex: (M/F): ? • Exclusion criteria: diabetic at time of transplant; Less than 3 months post-transplant; treatment with diabetic medications; eGFR < 30 mL/min/m²; severe hyperglycaemia HbA1c > 8.0%; active infection or inflammatory process; unstable cardiac disease; elevated alanine aminotransferase, aspartate aminotransferase, or creatine phosphokinase (more than 2 times upper limit of normal); inability to give informed consent; pregnancy or breastfeeding, or, woman of child-bearing age not willing to use contraception during the study period; patient is participating or has participated in another clinical trial and/or is taking or has taken an investigational drug in the past 28 days; patient is unlikely or unable to comply with the visits scheduled in the protocol (e.g. due to excessive travel requirements); exclusion criteria will comply with local label product information sheet; allergy to vildagliptin

VAT 2013 (Continued)

Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • Vildagliptin: 50 mg once or twice/day <p>Comparator group</p> <ul style="list-style-type: none"> • Gliclazide modified release 60 mg once/day
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> • Hypoglycaemic events, defined as blood glucose < 3.9 mmol/L (with or without symptoms) <p>Secondary outcomes</p> <ul style="list-style-type: none"> • 24 hour CGM done at baseline and in the last week of each 120-day treatment period to measure the composite endpoints of Vildagliptin compare with sulphonylureas <ul style="list-style-type: none"> * Mean afternoon blood glucose (1300 to 1900 pm) * Percentage time of glucose > 11mmol/L * Percentage time of glucose < 3.9 mmol/L (hypoglycaemia) • Efficacy <ul style="list-style-type: none"> * Difference of glycaemic control markers from baseline to endpoint between Vildagliptin and sulphonylureas arms • HbA1c: measured via whole blood assay • Fasting plasma glucose: measured via a plasma assay • Fructosamine - measured via serum assay <ul style="list-style-type: none"> * Difference of fasting insulin (serum assay), c-peptide (serum assay) and glucagon (plasma assay) level from baseline to endpoint between Vildagliptin and sulphonylureas arms • Safety <ul style="list-style-type: none"> * Symptomatic episodes of hypoglycaemia * BGL confirmed hypoglycaemia (< 3.9 mmol/L) * eGFR * Urine albumin:creatinine ratio * Haemoglobin, white cell count * Lipids * Liver function tests * Biopsy-proven acute rejection * Graft loss * Immunosuppressive drug levels
Starting date	1/3/2013
Contact information	Steve.Chadban@health.nsw.gov.au
Notes	<ul style="list-style-type: none"> • Contacted authors: Awaiting further information from authors.

BMI - body mass index; BGL - blood glucose level; BSL - blood sugar level; (eGFR) - (estimated) glomerular filtration rate; FBG - fasting blood glucose; HbA1c - glycated haemoglobin A1c; NODAT- new onset diabetes after transplantation; OGTT - oral glucose tolerance test; RCT - randomised controlled trial

DATA AND ANALYSES

Comparison 1. More intensive versus less intensive insulin therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Graft loss or rejection	4	301	Risk Ratio (IV, Random, 95% CI)	1.12 [0.32, 3.94]
1.1.1 Graft loss	1	60	Risk Ratio (IV, Random, 95% CI)	0.20 [0.01, 4.00]
1.1.2 Rejection	2	142	Risk Ratio (IV, Random, 95% CI)	1.77 [0.24, 13.14]
1.1.3 Graft loss or rejection	1	99	Risk Ratio (IV, Random, 95% CI)	0.90 [0.13, 6.16]
1.2 Delayed graft function	2	153	Risk Ratio (IV, Random, 95% CI)	0.63 [0.42, 0.93]
1.3 Dialysis within 7 days	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
1.4 eGFR [mL/min/1.73 m²]	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.5 Serum creatinine [μmol/L]	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.6 Death (any cause)	3	208	Risk Ratio (IV, Random, 95% CI)	0.68 [0.29, 1.58]
1.7 Non-fatal stroke	1	60	Risk Ratio (IV, Random, 95% CI)	Not estimable

Analysis 1.1. Comparison 1: More intensive versus less intensive insulin therapy, Outcome 1: Graft loss or rejection

Analysis 1.2. Comparison 1: More intensive versus less intensive insulin therapy, Outcome 2: Delayed graft function

Footnotes

(1) Delayed graft function was defined as either day-10 sCr over 221 umol/L or need for dialysis within first 7 days.

(2) Delayed graft function was defined as need for dialysis within 7 days of transplant with at least two sessions of dialysis needed

Analysis 1.3. Comparison 1: More intensive versus less intensive insulin therapy, Outcome 3: Dialysis within 7 days

Analysis 1.4. Comparison 1: More intensive versus less intensive insulin therapy, Outcome 4: eGFR [mL/min/1.73 m²]

Analysis 1.5. Comparison 1: More intensive versus less intensive insulin therapy, Outcome 5: Serum creatinine [μmol/L]

Analysis 1.6. Comparison 1: More intensive versus less intensive insulin therapy, Outcome 6: Death (any cause)

Analysis 1.7. Comparison 1: More intensive versus less intensive insulin therapy, Outcome 7: Non-fatal stroke

Comparison 2. DPP-4 inhibitors versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 HbA1c	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.2 Fasting blood glucose	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.3 eGFR [mL/min/1.73 m ²]	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

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

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

Analysis 2.3. Comparison 2: DPP-4 inhibitors versus placebo, Outcome 3: eGFR [mL/min/1.73 m²]

Comparison 3. DPP-4 inhibitors versus insulin glargine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Gastrointestinal side effects	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3: DPP-4 inhibitors versus insulin glargine, Outcome 1: Gastrointestinal side effects

Comparison 4. Glitazones and insulin versus placebo and insulin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Total cholesterol [mmol/L]	2	120	Mean Difference (IV, Random, 95% CI)	-0.49 [-0.75, -0.23]
4.2 HDL cholesterol [mmol/L]	2	120	Mean Difference (IV, Random, 95% CI)	0.12 [0.01, 0.24]
4.3 LDL cholesterol [mmol/L]	2	120	Mean Difference (IV, Random, 95% CI)	-0.27 [-0.47, -0.06]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.4 Triglyceride [mmol/L]	2	120	Mean Difference (IV, Random, 95% CI)	-0.30 [-0.49, -0.12]
4.5 Body weight [kg]	2	120	Mean Difference (IV, Random, 95% CI)	1.56 [-1.87, 4.99]

Analysis 4.1. Comparison 4: Glitazones and insulin versus placebo and insulin, Outcome 1: Total cholesterol [mmol/L]

Analysis 4.2. Comparison 4: Glitazones and insulin versus placebo and insulin, Outcome 2: HDL cholesterol [mmol/L]

Analysis 4.3. Comparison 4: Glitazones and insulin versus placebo and insulin, Outcome 3: LDL cholesterol [mmol/L]

Analysis 4.4. Comparison 4: Glitazones and insulin versus placebo and insulin, Outcome 4: Triglyceride [mmol/L]

Analysis 4.5. Comparison 4: Glitazones and insulin versus placebo and insulin, Outcome 5: Body weight [kg]

ADDITIONAL TABLES

Table 1. Adverse effects: more intensive versus less intensive insulin therapy

Outcome	Study	Intensive		Standard		Risk Ratio (95% CI)
		Events	Total	Events	Total	
Hypoglycaemia	HiRT 2016	0	30	0	30	Not estimable
Severe hypoglycaemia*	Hermayer 2012	7	44	2	49	3.90 (0.85 to 17.78)
Hypoglycaemia requiring 3rd party assistance	HiRT 2016	0	30	0	30	Not estimable
Discontinuation of medication due to adverse events	HiRT 2016	0	30	0	30	Not estimable

* Severe hypoglycaemia was defined as a blood glucose < 2.2 mmol/L

Table 2. Adverse effects: DPP-4 inhibitors versus placebo

Outcome	Study	DPP-4 inhibitors		Placebo		Risk Ratio
		Events	Total	Events	Total	
Hypoglycaemia	Haidinger 2010	0	16	Not available	16	Not estimable

Table 2. Adverse effects: DPP-4 inhibitors versus placebo (Continued)

	Strom Halden 2014	2*	19†	Not available	19	Not estimable
Discontinuation of medication due to adverse events	Haidinger 2010	0	16	0	16	Not estimable
	Strom Halden 2014	1	19	Not available	19	Not estimable

* Patients were receiving glipizide which can cause hypoglycaemia

† Patient numbers are reported for the entire study period because data was not available for the first phase of the study

Table 3. Adverse effects: DPP-4 inhibitors versus insulin glargine

Outcome	Study	DPP-4 inhibitors		Insulin glargine		Risk Ratio (95% CI)
		Events	Total	Events	Total	
Hypoglycaemia	Soliman 2013	5	28	3	17	1.01 (0.28 to 3.71)
Discontinuation of medication due to adverse events	Soliman 2013	0	28	0	17	Not estimable

Table 4. Adverse effects: SGLT2 inhibitors versus placebo

Outcome	Study	SGLT2 inhibitors		Placebo		Risk Ratio (95% CI)
		Events	Total	Events	Total	
Hypoglycaemia	EMPA-Renal Tx 2019	0	22	0	22	Not estimable
Discontinuation of medication due to adverse events	EMPA-Renal Tx 2019	2	24	1	25	2.08 (0.20 to 21.50)

Table 5. Adverse effects: glitazones and insulin versus placebo and insulin

Outcome	Study	Glitazones and insulin		Placebo and insulin		Risk Ratio (95% CI)]
		Events	Total	Events	Total	
Hypoglycaemia	Not reported					
Discontinuation of medication due to adverse events	Kharazmkia 2014	4	35	0	36	9.25 (0.52 to 165.69)

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	<ol style="list-style-type: none"> 1. MeSH descriptor: [Hypoglycemic Agents] explode all trees 2. MeSH descriptor: [Sulfonylurea Compounds] explode all trees 3. MeSH descriptor: [Dipeptidyl-Peptidase IV Inhibitors] this term only 4. MeSH descriptor: [Glucagon-Like Peptide 1] this term only 5. MeSH descriptor: [alpha-Glucosidases] this term only 6. MeSH descriptor: [Sodium-Glucose Transporter 2] this term only 7. (glucose lowering and (therap* or agent* or drug*)):ti,ab,kw in Trials 8. (hypoglycemi* and (agent* or drug* or therap*)):ti,ab,kw in Trials 9. (antidiabet* and (agent* or drug* or therap*)):ti,ab,kw in Trials 10.insulin*:ti,ab,kw in Trials 11.(metformin):ti,ab,kw in Trials 12.rosiglitazone:ti,ab,kw or rivoglitazone:ti,ab,kw or pioglitazone:ti,ab,kw or troglitazone:ti,ab,kw in Trials 13.MeSH descriptor: [Thiazolidinediones] this term only 14.acarbose:ti,ab,kw or miglitol:ti,ab,kw or voglibose:ti,ab,kw 15.(repaglinide or nateglinide or exenatide or pramlintide or benfluorex or liraglutide or mitiglinide):ti,ab,kw in Trials 16.(sitagliptin or vildagliptin or saxagliptin):ti,ab,kw in Trials 17.linagliptin:ti,ab,kw or alogliptin:ti,ab,kw in Trials 18."glucagon-like peptide-1":ti,ab,kw in Trials 19.Incretin mimetic*:ti,ab,kw in Trials 20.alpha-glucosidase inhibitor*:ti,ab,kw in Trials 21."ddp iv inhibitor" or "ddp iv inhibitors":ti,ab,kw in Trials 22.(exenatide):ti,ab,kw in Trials 23.MeSH descriptor: [Amylin Receptor Agonists] explode all trees 24.tak-875 or fasiglifam:ti,ab,kw (Word variations have been searched) 25.PPAR agonist*:ti,ab,kw (Word variations have been searched) 26.gpr40 agonist*:ti,ab,kw (Word variations have been searched) 27.bromocriptine*:ti,ab,kw (Word variations have been searched) 28.{or #1-#27} 29.MeSH descriptor: [Kidney Transplantation] this term only 30.(kidney transplant* or renal transplant*):ti,ab,kw (Word variations have been searched) 31.{or #29-#30} 32.{and #28, #31}
MEDLINE	<ol style="list-style-type: none"> 1. Kidney Transplantation/ 2. exp Diabetes Mellitus/ 3. (diabetes or diabetic).tw. 4. Diabetic Nephropathies/ 5. diabetic nephropath\$.tw. 6. (diabetic kidney\$ or diabetic renal\$).tw. 7. nodat.tw. 8. or/2-7 9. and/1,8 10.exp Hypoglycemic Agents/ 11.metformin.tw.

(Continued)

- 12.exp Sulfonylurea Compounds/
- 13.(glipizide or glimepride or gliclazide or glibenclamide or glyburide).tw.
- 14.insulin.tw.
- 15.Sodium-Glucose Transporter 2/
- 16.(Sodium glucose co-transporter 2 or Sodium glucose transporter 2).tw.
- 17.canagliflozin.tw.
- 18.ipragliflozin.tw.
- 19.dapagliflozin.tw.
- 20.empagliflozin.tw.
- 21.remogliflozin.tw.
- 22.sergliflozin.tw.
- 23.tofogliflozin.tw.
- 24.(ertugliflozin or luseogliflozin or sotagliflozin).tw.
- 25.alpha-Glucosidases/
- 26.acarbose.tw.
- 27.miglitol.tw.
- 28.voglibose.tw.
- 29.dipeptidyl-peptidase IV inhibitor\$.tw.
- 30.alogliptin.tw.
- 31.gemigliptin.tw.
- 32.linagliptin.tw.
- 33.saxagliptin.tw.
- 34.sitagliptin.tw.
- 35.vildagliptin.tw.
- 36.Glucagon-Like Peptide 1/
- 37.pramlintide.tw.
- 38.exenatide.tw.
- 39.liraglutide.tw.
- 40.taspoglutide.tw.
- 41.albiglutide.tw.
- 42.lixisenatide.tw.
- 43.Thiazolidinediones/
- 44.glitazone\$.tw.
- 45.pioglitazone.tw.
- 46.rivoglitazone.tw.
- 47.rosiglitazone.tw.
- 48.troglitazone.tw.
- 49.nateglinide.tw.
- 50.repaglinide.tw.
- 51.mitiglinide.tw.
- 52.Bromocriptine/
- 53.bromocriptine.tw.
- 54.(tak-875 or fasiglifam).tw.
- 55.gpr40 agonist\$.tw.
- 56.saroglitazar.tw.
- 57.aleglitazar.tw.
- 58.muraglitazar.tw.
- 59.tesaglitazar.tw.
- 60.exp Amylin Receptor Agonists/
- 61.amylin analog\$.tw.
- 62.ffar1.tw.

(Continued)

63.(Dual peroxisome proliferator-activated receptor agonist\$ or PPAR agonist\$.tw.
64.or/10-63
65.and/9,64

EMBASE

1. exp diabetes mellitus/
2. exp kidney transplantation/
3. exp antidiabetic agent/
4. exp sulphonylureas derivative/
5. glucose transporter 2/
6. exp dipeptidyl peptidase IV inhibitor/
7. alpha glucosidase/
8. exp glucagon like peptide/
9. exp glitazone derivative/
10.exp thiazole derivative/
11.bromocriptine/
12.peroxisome proliferator activated receptor agonist/
13.(tak-875 or fasiglifam).tw.
14."TAK 875"/
15.or/3-14
16.and/1-2,15

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	<p><i>Low risk of bias:</i> 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).</p> <p><i>High risk of bias:</i> 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.</p> <p><i>Unclear:</i> Insufficient information about the sequence generation process to permit judgement.</p>
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	<p><i>Low risk of bias:</i> Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).</p> <p><i>High risk of bias:</i> 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.</p> <p><i>Unclear:</i> Randomisation stated but no information on method used is available.</p>
Blinding of participants and personnel	<p><i>Low risk of bias:</i> 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.</p>

(Continued)

Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	<p><i>High risk of bias:</i> 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.</p> <p><i>Unclear:</i> Insufficient information to permit judgement</p>
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	<p><i>Low risk of bias:</i> 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.</p> <p><i>High risk of bias:</i> 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.</p> <p><i>Unclear:</i> Insufficient information to permit judgement.</p>
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	<p><i>Low risk of bias:</i> 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.</p> <p><i>High risk of bias:</i> 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.</p> <p><i>Unclear:</i> Insufficient information to permit judgement</p>
Selective reporting Reporting bias due to selective outcome reporting	<p><i>Low risk of bias:</i> 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).</p> <p><i>High risk of bias:</i> Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.</p> <p><i>Unclear:</i> Insufficient information to permit judgement</p>
Other bias Bias due to problems not covered elsewhere in the table	<p><i>Low risk of bias:</i> The study appears to be free of other sources of bias.</p> <p><i>High risk of bias:</i> 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.</p>

(Continued)

Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

WHAT'S NEW

Date	Event	Description
16 January 2020	New search has been performed	New search undertaken; new studies incorporated
16 January 2020	New citation required but conclusions have not changed	Three new included studies and interventions added

HISTORY

Protocol first published: Issue 8, 2012

Review first published: Issue 2, 2017

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: MJ, CL, SZ
2. Study selection: CL, TT
3. Extract data from studies: CL, TT, MO, MJ
4. Enter data into RevMan: CL,TT
5. Carry out the analysis: TT, MO, CL
6. Interpret the analysis: CL, TT, MO, MJ, KC, CH, SZ
7. Draft the final review: CL, TT, MJ, KC, CH, SZ
8. Disagreement resolution: SZ
9. Update the review: CL,TT, SZ

DECLARATIONS OF INTEREST

- Clement Lo: none known
- Tadashi Toyoma: none known
- Megumi Oshima: none known
- Min Jun: none known
- Ken L Chin: none known
- Carmel M 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.
- Sophia Zoungas has previously received speaker honoraria from Servier, MSD, Sanofi Aventis, Eli Lilly, Astra Zeneca, BMS, Takeda and Janssen. She has previously served on external advisory boards for MSD, Novo Nordisk, Sanofi Aventis, Amgen, Novartis, Janssen, Astra Zeneca and Eli Lilly.

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- Nil, Other

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This is an update of our original review published in 2017 ([Lo 2017](#)). At the request of Cochrane Kidney and Transplant, we have added in quality of life as a secondary outcome. In addition, we have added in delayed graft function/dialysis within 7 days as a primary outcome. Furthermore, systolic and diastolic BP, lipids and body weight have become secondary outcomes.

INDEX TERMS

Medical Subject Headings (MeSH)

Adamantane [adverse effects] [analogs & derivatives] [therapeutic use]; Bias; Cause of Death; Diabetes Mellitus, Type 1 [blood] [*drug therapy]; Diabetes Mellitus, Type 2 [blood] [*drug therapy]; Dipeptidyl-Peptidase IV Inhibitors [adverse effects] [*therapeutic use]; Fasting [blood]; Glycated Hemoglobin A [metabolism]; Graft Survival [drug effects]; Hypoglycemia [chemically induced]; Hypoglycemic Agents [adverse effects] [*therapeutic use]; Insulin [adverse effects] [therapeutic use]; Insulin Glargine [adverse effects] [therapeutic use]; Kidney Transplantation [*adverse effects]; Nitriles [adverse effects] [therapeutic use]; Pioglitazone; Postoperative Complications [*drug therapy] [etiology]; Pyrrolidines [adverse effects] [therapeutic use]; Randomized Controlled Trials as Topic; Sitagliptin Phosphate [adverse effects] [therapeutic use]; Sodium-Glucose Transporter 2 Inhibitors [adverse effects] [therapeutic use]; Thiazolidinediones [adverse effects] [therapeutic use]; Transplant Recipients; Vildagliptin

MeSH check words

Humans