National Institute for Health and Care Excellence

Draft for consultation

Type 2 diabetes in adults: management (medicines update)

[F1.2] Evidence reviews for subsequent pharmacological management of type 2 diabetes: sections 1.1.7 to 1.1.14

NICE guideline GID-NG10336

Evidence reviews underpinning recommendations 1.8.6-1.8.32, 1.8.34,1.8.38-1.8.60 and recommendations for research in the NICE guideline

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Draft for Consultation

This evidence review was developed by NICE

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1.1.7. Summary of the effectiveness evidence (pairwise meta-analysis)

1.1.7.1. The following tables report both the hazard ratios as reported by studies and also the absolute risk reduction per thousand people where the raw number of events for each outcome are available. Hazard ratio data have not been converted to absolute risk reduction. Model 1: People with type 2 diabetes and heart failure

1.1.7.1.1. Adding - A single therapy compared to placebo

Table 1: A summary matrix showing the outcomes for adding individual drugs (GLP-1 receptor agonists and SGLT-2 inhibitors) compared to adding placebo for people with type 2 diabetes with heart failure

Outcomes for drugs compared to placebo	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Health-related quality of life	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
All-cause mortality	No outcomes identified	1 study (n=1,667), Moderate quality, 16 fewer per 1000 (45 fewer to 20 more)	No outcomes identified	No outcomes identified	2 studies (n=2,113), Moderate quality, HR 0.78 (0.60 to 1.00)	1 study (n=1,724), Low quality, 15 fewer per 1000 (43 fewer to 20 more)	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
		HR 0.89 (0.70 to 1.13)				HR 0.87 (0.68 to 1.12)		
Cardiovascular mortality	No outcomes identified	1 study (n=1,1667), Moderate quality, 15 fewer per 1000 (38 fewer to 16 more) HR 0.85 (0.63 to 1.15)	No outcomes identified	No outcomes identified	1 study (n=1,461), Moderate quality, HR 0.72 (0.51 to 1.02)	1 study (n=1,724), Very low quality, 3 more per 1000 (20 fewer to 35 more) HR 1.01 (0.73 to 1.40)	No outcomes identified	No outcomes identified
3-item MACE	1 study (n=2,389), High quality, 3 more per 1000 (27 fewer to 37 more) HR 0.97 (0.81 to 1.16)	1 study (n=1,667), Moderate quality, 34 fewer per 1000 (54 fewer to 4 more) HR 0.81 (0.65 to 1.01)	No outcomes identified	1 study (n=573), Low quality, 5 more per 1000 (39 fewer to 73 more) HR 1.03 (0.64 to 1.66)	2 studies (n=2,119), Moderate quality, HR 0.84 (0.67 to 1.04)	1 study (n=1,724), Low quality, 6 more per 1000 (27 fewer to 47 more) HR 1.01 (0.81 to 1.26)	No outcomes identified	1 study (n=1,957), Moderate quality, 10 more per 1000 (21 fewer to 48 more) HR 1.05 (0.82 to 1.34)

Outcomes for drugs compared to placebo	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
4-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal stroke	No outcomes identified	1 study (n=1,667), Low quality, 4 fewer per 1000 (17 fewer to 18 more) HR 0.89 (0.53 to 1.49)	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=1,724), Very low quality, 8 more per 1000 (9 fewer to 34 more) HR 1.21 (0.77 to 1.90)	No outcomes identified	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified	1 study (n=1,1667), Moderate quality, 21 fewer per 1000 (39 fewer to 6 more)	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=1,724), Low quality, 10 fewer per 1000 (31 fewer to 19 more)	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
		HR 0.74 (0.52 to 1.05)				HR 0.85 (0.61 to 1.18)		
Unstable angina	No outcomes identified	1 study (n=1,667), Low quality, 10 fewer per 1000 (21 fewer to 9 more) Moderate quality HR 0.72 (0.42 to 1.23)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Hospitalisation for heart failure	No outcomes identified	1 study (n=1,667), Low quality, 0 fewer per 1000 (29 fewer to 36 more) HR 0.98 (0.75 to 1.28)	1 study (n=1,358), Low quality, 5 fewer per 1000 (32 fewer to 31 more) HR 0.93 (0.66 to 1.31)	No outcomes identified	2 studies, (n=2,113), Moderate quality, HR 0.62 (0.45 to 0.84)	1 study (n=1,724), Low quality, 30 fewer per 1000 (53 fewer to 1 more) HR 0.73 (0.55 to 0.97)	No outcomes identified	1 study (n=1,957), Moderate quality, 28 fewer per 1000 (44 fewer to 6 fewer)

Outcomes for drugs compared to placebo	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
								HR 0.63 (0.44 to 0.90)
Acute kidney injury	No outcome identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=652), Low quality, HR 0.75 (0.40 to 1.41)	No outcomes identified	No outcomes identified	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=599), Moderate quality, 78 fewer (117 fewer to 22 fewer) High quality, HR 0.5 (0.33 to 0.76)	No outcomes identified
Development of end stage kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Cardiac arrhythmia	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=1,724), Low quality, 16 fewer per 1000 (34 fewer to 10 more) HR 0.78 (0.55 to 1.11)	No outcomes identified	No outcomes identified
Diabetic ketoacidosis	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Falls requiring hospitalisation	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Hypoglycaemia episodes	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Severe hypoglycaemic episodes	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
HbA1c change	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Weight change	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
BMI change	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

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Table 2: A summary matrix showing the outcomes for adding individual drugs (DPP-4 inhibitors) compared to adding placebo for people with type 2 diabetes with heart failure

Outcomes for drugs compared to placebo	Alogliptin	Linagliptin	Sitagliptin	Vildagliptin
Health-related quality of life	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
All-cause mortality	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=254), Moderate quality, 54 more per 1000 (4 fewer to 231 more)
Cardiovascular mortality	1 study (n=1,533), Very low quality, 19 fewer per 1000 (40 fewer to 10 more) HR 0.77 (0.54 to 1.10)	1 study (n=1,1873), Low quality, HR 0.96 (0.73 to 1.26)	No outcomes identified	1 study (n=254), Low quality, 23 more per 1000 (15 fewer to 150 more)
3-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
4-item MACE	1 study (n=1,533), Very low quality, 20 fewer per 1000 (53 fewer to 20 more)	No outcomes identified	1 study (n=2,643), Moderate quality, HR 0.97 (0.80 to 1.18)	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal stroke	1 study (n=1,533), Very low quality, 6 more per 1000 (3 fewer to 31 more)	No outcomes identified	No outcomes identified	1 study (n=254), Low quality, 24 fewer per 1000 (31 fewer to 37 more)

Outcomes for drugs compared to placebo	Alogliptin	Linagliptin	Sitagliptin	Vildagliptin
Non-fatal myocardial infarction	1 study (n=1,533), Very low quality, 3 more per 1000 (22 fewer to 37 more)	No outcomes identified	No outcomes identified	No outcomes identified
Unstable angina	1 study (n=1,533), Very low quality, 8 fewer per 1000 (12 fewer to 4 more) HR 0.89 (0.70 to 1.13)	No outcomes identified	No outcomes identified	No outcomes identified
Hospitalisation for heart failure	1 study (n=1,533), Very low quality, 4 fewer per 1000 (27 fewer to 29 more) HR 1.00 (0.71 to 1.41)	1 study (n=1,873), Moderate quality, 14 fewer per 1000 (39 fewer to 18 more) HR 0.88 (0.68 to 1.14)	1 study (n=2,643), Moderate quality, 4 more per 1000 (14 fewer to 28 more) Low quality HR 1.05 (0.79 to 1.40)	1 study (n=254), High quality, 22 more per 1000 (33 fewer to 144 more)
Acute kidney injury	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Development of end stage kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Alogliptin	Linagliptin	Sitagliptin	Vildagliptin
Cardiac arrhythmia	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=254), Low quality, 39 more per 1000 (10 fewer to 191 more)
Diabetic ketoacidosis	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Falls requiring hospitalisation	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=254), Low quality, 9 fewer per 1000 (39 fewer to 80 more)
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Severe hypoglycaemic episodes	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
HbA1c change	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=227), Very low quality, MD 0.36% lower (0.71 lower to 0.01 lower)
Weight change	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Alogliptin	Linagliptin	Sitagliptin	Vildagliptin
BMI change	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

1.1.7.1.2. Adding - A single therapy compared to insulin

Table 3: A summary matrix showing the outcomes for adding individual drugs compared to adding insulin for people with type 2 diabetes with heart failure

Outcomes for drugs compared to insulin	Sitagliptin	Exenatide	Liraglutide
Health-related quality of life	No outcomes identified	No outcomes identified	No outcomes identified
All-cause mortality	No outcomes identified	1 study (n=26), Very low quality, 72 more per 1000 (63 fewer to 206 more)	No outcomes identified
Cardiovascular mortality	No outcomes identified	No outcomes identified	No outcomes identified
3-item MACE	No outcomes identified	No outcomes identified	No outcomes identified
4-item MACE	No outcomes identified	No outcomes identified	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal stroke	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified	No outcomes identified	No outcomes identified
Unstable angina	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to insulin	Sitagliptin	Exenatide	Liraglutide
Hospitalisation for heart failure	1 study (n=22), Very low quality, 0 fewer per 1000 (161 fewer to 161 more)	No outcomes identified	1 study (n=22), Very low quality, 0 fewer per 1000 (161 fewer to 161 more)
Acute kidney injury	No outcomes identified	No outcomes identified	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified	No outcomes identified
Development of end stage kidney disease	No outcomes identified	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified	No outcomes identified
Cardiac arrhythmia	No outcomes identified	No outcomes identified	No outcomes identified
Diabetic ketoacidosis	No outcomes identified	No outcomes identified	No outcomes identified
Falls requiring hospitalisation	No outcomes identified	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	No outcomes identified	No outcomes identified	No outcomes identified
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to insulin	Sitagliptin	Exenatide	Liraglutide
Severe hypoglycaemic episodes	1 study (n=22), Very low quality, 0 fewer per 1000 (161 fewer to 161 more)	No outcomes identified	1 study (n=22), Very low quality, 0 fewer per 1000 (161 fewer to 161 more)
HbA1c change	1 study (n=22), Very low quality, MD 1.30% higher (0.11 to 2.49 higher)	1 study (n=23), Very low quality, MD 0.3% higher (0.89 lower to 1.49 higher)	1 study (n=22), Very low quality, MD 0.20% higher (0.99 lower to 1.39 higher)
Weight change	No outcomes identified	No outcomes identified	No outcomes identified
BMI change	No outcomes identified	1 study (n=23), Very low quality, MD 2.40 kg/m^2 lower (5.14 lower to 0.34 higher)	No outcomes identified

1.1.7.2. Model 2: People with type 2 diabetes and cardiovascular disease

1.1.7.2.1. Adding - A single therapy compared to placebo

Table 6: A summary matrix showing the outcomes for adding individual drugs (GLP-1 receptor agonists and SGLT-2 inhibitors) compared to adding placebo for people with type 2 diabetes with cardiovascular disease

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Lixisenatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Health-related quality of life	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Lixisenatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
All-cause mortality	No outcomes identified	No outcomes identified	1 study (n=6,068), Moderate quality, 4 fewer per 1000 (15 fewer to 10 more) HR 0.94 (0.78 to 1.13)	1 study (n=6,656), Moderate quality, HR 0.9 (0.75, 1.07)	3 studies (n=8,861), Moderate quality, 4 fewer per 1000 (14 fewer to 7 more), Low quality HR 0.92 (0.79 to 1.07)	3 studies (n=7,210), Moderate quality, 25 fewer per 1000 (38 fewer to 12 fewer) HR 0.68 (0.57, 0.81)	1 study (n=8,246), High quality, 6 fewer per 1000 (18 fewer to 7 more), HR 0.93 (0.80 to 1.08)
Cardiovascular mortality	No outcomes identified	No outcomes identified	1 study (n=6,068), Moderate quality, 1 fewer per 1000 (11 fewer to 12 more) HR 0.98 (0.78, 1.22)	1 study (n=6,656), Moderate quality, HR 0.86 (0.70, 1.06)	3 studies (n=8,861), Low quality, 2 fewer per 1000 (8 fewer to 7 more), HR 0.94 (0.76 to 1.16)	3 studies (n=7,210), Moderate quality, 20 fewer per 1000 (31 fewer to 10 fewer) Moderate quality HR 0.62 (0.49, 0.78)	1 study (n=8,246), Moderate quality, 5 fewer per 1000 (15 fewer to 7 more), HR 0.92 (0.77 to 1.10)
3-item MACE	1 study (n=3,114), Low quality, 23 fewer per 1000	1 study (n=10,782), High quality, 12 fewer per	No outcomes identified	1 study (n=6,656), Moderate	1 study (n=6,974), Moderate quality, 14	1 study (n=97), Moderate quality, 0 fewer per 1000 (39	No outcomes identified

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Lixisenatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
	(47 fewer to 5 more), HR 0.87 (0.74 to 1.02)	1000 (24 fewer to 1 more), HR 0.9 (0.82 to 0.99)		quality, HR 0.83 (0.72, 0.95)	fewer per 1000 (29 fewer to 2 more), Low quality, HR 0.90 (0.79 to 1.03)	fewer to 39 more)	
4-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=7,020), Moderate quality, 15 fewer per 1000 (30 fewer to 2 more) HR 0.89 (0.8, 0.99)	1 study (n=8,246), High quality, 10 fewer per 1000 (25 fewer to 7 more), HR 0.92 (0.82 to 1.03)
5-item MACE	No outcomes identified	No outcomes identified	1 study (n=6,068), High quality, 4 fewer per 1000 (21 fewer to 15 more) HR 0.97 (0.85, 1.10)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Lixisenatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Non-fatal stroke	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=6,656), Moderate quality, HR 0.88 (0.67, 1.16)	1 study (n=6,974), Low quality, 1 fewer per 1000 (9 fewer to 9 more), HR 0.97 (0.76 to 1.24)	2 studies (n=7,117), Very low quality, 6 more per 1000 (2 fewer to 14 more) Moderate quality, HR 1.24 (0.92, 1.67)	1 study (n=8,246), Low quality, 0 more per 1000 (7 fewer to 9 more), HR 1.00 (0.76 to 1.32)
Non-fatal myocardial infarction	No outcomes identified	No outcomes identified	No outcomes identified	1 outcome, 1 study (n=6,656), Moderate quality, HR 0.79 (0.63, 0.99)	2 studies (n=7,896), Very low quality, 10 fewer per 1000 (22 fewer to 2 more) Low quality, HR 0.87 (0.74 to 1.02)	2 studies (n=7,117), Very low quality, 6 fewer per 1000 (17 fewer to 4 more) Moderate quality (1 study) HR 0.87 (0.70, 1.80)	1 study (n=8,246), Moderate quality, 2 more per 1000 (7 fewer to 14 more), HR 1.04 (0.86 to 1.26)
Unstable angina	No outcomes identified	No outcomes identified	1 study (n=6,068), Low quality, 0 more per 1000 (3 fewer to 3 more)	No outcomes identified	1 study (n=922), Very low quality, 9 fewer per 1000 (22 fewer to 5 more)	2 studies (n=7,113), Low quality, 0 fewer per 1000 (8 fewer to 9 more)	1 study (n=8,238), Moderate quality, 6 fewer per 1000 (12

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Lixisenatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
			HR 1.11 (0.47, 2.59)			HR 0.99 (0.74, 1.32)	fewer to 2 more)
Hospitalisation for heart failure	No outcomes identified	No outcomes identified	1 study (n=6,068), Moderate quality, 2 fewer per 1000 (10 fewer to 9 more) HR 0.96 (0.75, 1.23)	1 study (n=6,656), Moderate quality, HR 0.68 (0.51, 0.90)	2 studies (n=7,896), Low quality, 10 fewer per 1000 (17 fewer to 1 fewer), HR 0.78 (0.63 to 0.97)	2 studies (n=7,117), Moderate quality, 14 fewer per 1000 (23 fewer to 4 fewer) HR 0.65 (0.50, 0.85)	1 study (n=8,246), Moderate quality, 11 fewer per 1000 (16 fewer to 3 fewer) HR 0.7 (0.54 to 0.91)
Acute kidney injury	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=922), Very low quality, 7 more per 1000 (1 fewer to 14 more)	1 study (n=7,020), Moderate quality, 6 fewer per 1000 (10 fewer to 1 fewer)	1 study (n=8,238), Moderate quality, 3 fewer per 1000 (8 fewer to 3 more)

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Lixisenatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=6,656), Moderate quality, clinically important benefit, HR 0.74 (0.67, 0.82)	2 studies (n=1,887), Low quality, 22 more per 1000 (5 more to 53 more)	2 studies (n=6,369), Moderate quality, 45 fewer per 1000 (59 fewer to 30 fewer) High quality, HR 0.62 (0.54, 0.71)	1 study (n=8,246), Moderate quality, 8 fewer per 1000 (14 fewer to 1 more)
Development of end stage kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=6,656), Low quality, HR 0.69 (0.18, 2.64)	1 study (n=922), Very low quality, 7 more per 1000 (6 fewer to 19 more)	1 study (n=7,020), Low quality, 0 fewer per 1000 (2 fewer to 2 more)	1 study (n=8,246), Very low quality, 0 more per 1000 (1 fewer to 2 more)
Death from renal cause	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=8,246), Low quality, 0 fewer per 1000 (1 fewer to 1 more)
Cardiac arrhythmia	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study. (n=6,974), Low	1 study (n=97), Low quality, 20	1 study (n=8,238),

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Lixisenatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
					quality, 8 fewer per thousand (16 fewer to 2 more), HR 0.83 (0.66 to 1.04)	more per 1000 (19 fewer to 60 more)	Moderate quality, 2 fewer per 1000 (6 fewer to 3 more)
Diabetic ketoacidosis	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=6,656), Low quality, HR 4.62 (0.56, 38.04)	No outcomes identified	2 studies (n=7,117), Very low quality, 0 more per 1000 (1 fewer to 2 more)	1 study (n=8,238), Very low quality, 3 more per 1000 (1 more to 5 more)
Falls requiring hospitalisation	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=922), Very low quality, 0 more per 1000 (12 fewer to 29 more)	1 study (n=97), Moderate quality, 0 fewer per 1000 (39 fewer to 39 more)	No outcomes identified
Remission	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	No outcomes identified	No outcomes identified	1 study (n=6,068),	1 study (n=6,656),	2 studies (n=1,887), Low	1 study (n=7,020), High	1 study (n=8,238),

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Lixisenatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
			High quality, 14 more per 1000 (4 fewer to 34 more)	Moderate quality, HR 1.19 (0.94, 1.50)	quality, 20 fewer per 1000 (55 fewer to 21 more)	quality, 1 fewer per 1000 (22 fewer to 23 more)	High quality, 15 fewer per 1000 (35 fewer to 5 more)
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Severe hypoglycaemic episodes	No outcomes identified	No outcomes identified	1 study (n=6,068), Moderate quality, 3 fewer per 1000 (7 fewer to 1 more)	No outcomes identified	1 study (n=922), Low quality, 0 fewer per 1000 (4 fewer to 4 more)	1 study (n=7,020), Low quality, 2 fewer per 1000 (6 fewer to 5 more)	1 study (n=8,238), Moderate quality, 7 fewer per 1000 (16 fewer to 3 more)
HbA1c change	No outcomes identified	No outcomes identified	1 study (n=6,068), High quality, MD 0.27 % lower (0.31 lower to 0.23 lower)	No outcomes identified	1 outcome, 2 studies (n=897), Very low quality, MD 0.58% lower (0.74% lower to 0.42% lower)	4 studies (n=7,292), Very low quality, MD 0.24 % lower (0.75 lower to 0.26 higher)	1 study (n=8,246), Low quality, MD 0.17% lower (0.26% lower to 0.08% lower)
Weight change	No outcomes identified	No outcomes identified	1 study (n=6,068) High	No outcomes identified	2 studies (n=1,651), Low	2 studies (n=190) Very	1 study (n=8,246),

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Lixisenatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
			quality, MD 0.70 kg lower (0.90 lower to 0.50 lower)		quality, MD 2.24 kg lower (2.93 lower to 1.56 lower)	low quality, MD 1.87 kg lower (3.01 lower to 0.73 lower)	Very low quality, MD 2.6 kg lower (3.05 lower to 2.15 lower)
BMI change	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=97), Low quality, MD 0.9 kg/m^2 higher (1.28 lower to 3.08 higher)	No outcomes identified

Table 6: A summary matrix showing the outcomes for adding individual drugs (DPP-4 inhibitors and thiazolidinediones) compared to adding placebo for people with type 2 diabetes with cardiovascular disease

Outcomes for drugs compared to placebo	Alogliptin	Saxagliptin	Sitagliptin	Pioglitazone
Health-related quality of life	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
All-cause mortality	1 study (n=5,380), Very low quality, 8 fewer per 1000 (19 fewer to 5 more), HR 0.88 (0.71 to 1.09)	No outcomes identified	1 study (n=14,671), High quality, 1 more per 1000 (7 fewer to 10 more), HR 1.01 (0.90 to 1.13)	2 studies (n=5,359), Very low quality, 3 fewer per 1000 (15 fewer to 12 more) HR 0.96 (0.78, 1.18)

Outcomes for drugs compared to placebo	Alogliptin	Saxagliptin	Sitagliptin	Pioglitazone
Cardiovascular mortality	1 study (n=5,380), Very low quality, 7 fewer per 1000 (16 fewer to 5 more), HR 0.85 (0.66 to 1.10)	No outcomes identified	1 study (n=14,671), High quality, 2 more per 1000 (5 fewer to 10 more), HR 1.03 (0.89 to 1.19)	1 study (n=5,238), Very low quality, 3 fewer per 1000 (13 fewer to 10 more) HR 0.94 (0.74, 1.19)
3-item MACE	No outcomes identified	1 study (n=6,494), Low quality, 1 fewer per 1000 (10 fewer to 9 more) HR 0.97 (0.86 to 1.09)	No outcomes identified	1 study (n=5,238), Very low quality, 20 fewer per 1000 (34 fewer to 4 fewer**)** HR 0.82 (0.70, 0.96)
4-item MACE	1 study (n=5,380), Low quality, 7 fewer per 1000 (23 fewer to 12 more)	No outcomes identified	1 study (n=14,671), High quality, 2 fewer per 1000 (11 fewer to 9 more), HR 0.98 (0.89 to 1.08)	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal stroke	1 study (n=5,380), Very low quality, 1 fewer per 1000 (5 fewer to 6 more), HR 0.91 (0.55 to 1.51)	No outcomes identified	No outcomes identified	1 study (n=5,238), Very low quality, 8 fewer per 1000 (16 fewer to 3 more) HR 0.81 (0.61, 1.08)

Outcomes for drugs compared to placebo	Alogliptin	Saxagliptin	Sitagliptin	Pioglitazone
Non-fatal myocardial infarction	1 study (n=5,380), Very low quality, 5 more per 1000 (8 fewer to 20 more), HR 1.08 (0.88 to 1.33)	No outcomes identified	1 study (n=14,671), High quality, 2 fewer per 1000 (7 fewer to 5 more)	2 studies (n= 5,359), Very low quality, 8 fewer per 1000 (18 fewer to 4 more) HR 0.83 (0.65, 1.06)
Unstable angina	1 study (n=5,380), Very low quality, 2 fewer per 1000 (7 fewer to 6 more)	No outcomes identified	1 study (n=14,671), Moderate quality, 2 fewer per 1000 (5 fewer to 3 more), HR 0.90 (0.70 – 1.16)	No outcomes identified
Hospitalisation for heart failure	1 study (n=5,380), Very low quality, 6 more per 1000 (3 fewer to 19 more), HR 1.19 (0.90 to 1.57)	No outcomes identified	1 study (n=14,671), High quality, 0 fewer per 1000 (5 fewer to 6 more), HR 1.00 (0.83 to 1.20)	1 study (n=5,238), Very low quality, 16 more per 1000 (4 more to 32 more) Add HR?
Acute kidney injury	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified	1 study (n=14,671), High quality, 0 fewer per 1000 (8 fewer to 9 more)	No outcomes identified
Development of end stage kidney disease	1 study (n=5,380), Very low quality, 1 more per	No outcomes identified	1 study (n=14,671), Moderate quality, 1	No outcomes identified

Outcomes for drugs compared to placebo	Alogliptin	Saxagliptin	Sitagliptin	Pioglitazone
	1000 (4 fewer to 6 more)		fewer per 1000 (5 fewer to 3 more)	
Death from renal cause	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Cardiac arrhythmia	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=5,238), Very low quality, 3 fewer per 1000 (9 fewer to 5 more)
Diabetic ketoacidosis	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Falls requiring hospitalisation	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	1 study (n=5,380), Very low quality, 2 more per 1000 (10 fewer to 17 more)	No outcomes identified	No outcomes identified	1 study (n=5,238), Low quality, 78 more per 1000 (52 more to 107 more)
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Severe hypoglycaemic episodes	1 study (n=5,380), Very low quality, 1 more per 1000 (4 fewer to 5 more)	No outcomes identified	1 study (n=14,671), Moderate quality, 2 more per 1000 (2 fewer to 8 more), HR 1.12 (0.89 – 1.41)	No outcomes identified

Outcomes for drugs compared to placebo	Alogliptin	Saxagliptin	Sitagliptin	Pioglitazone
HbA1c change	1 study (n=5,380), Low quality, MD 0.33% lower (0.43 lower to 0.29 lower)	No outcomes identified	1 study (n=2820), Low quality, MD 0.32% lower (0.35 lower to 0.29 lower)	1 study (n=121), Very low quality, MD 0.84% lower (1.55 lower to 0.13 lower)
Weight change	1 study (n=5,380), Low quality, MD 0.06 higher (0.25lower to 0.37 higher)	No outcomes identified	No outcomes identified	No outcomes identified
BMI change	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

1.1.7.2.2. Adding - A single therapy compared to insulin

Table 4 A summary matrix table showing the outcomes for adding drugs compared to adding insulin for people with type 2 diabetes with cardiovascular disease

Outcomes for drugs compared to Insulin	Sitagliptin	Exenatide	Liraglutide	Tirzepatide	Glimepiride
Health-related quality of life	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
All-cause mortality	No outcomes identified	1 study (n=26), Very low quality, 72 more	No outcomes identified	1 study (n=1991), Moderate quality, 10	No outcomes identified

Outcomes for drugs compared to Insulin	Sitagliptin	Exenatide	Liraglutide	Tirzepatide	Glimepiride
		per 1000 (63 fewer to 206 more)		fewer per 1000 (20 fewer to 7 more) HR 0.70 (0.42, 1.17)	
Cardiovascular mortality	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=1995), Low quality, 5 fewer per 1000 (13 fewer to 10 more)	No outcomes identified
3-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
4-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=1995), Moderate quality, 15 fewer per 1000 (29 fewer to 6 more) HR 0.74 (0.51, 1.07)	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal stroke	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=1995), Low quality, 2 fewer per 1000 (8 fewer to 12 more)	No outcomes identified

Outcomes for drugs compared to Insulin	Sitagliptin	Exenatide	Liraglutide	Tirzepatide	Glimepiride
Non-fatal myocardial infarction	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=1995), Low quality, 7 fewer per 1000 (15 fewer to 8 more)	No outcomes identified
Unstable angina	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=1995), Low quality, 4 fewer per 1000 (7 fewer to 5 more)	No outcomes identified
Hospitalisation for heart failure	1 study (n=22), Very low quality, 0 fewer per 1000 (161 fewer to 161 more)	No outcomes identified	1 study (n=22), Very low quality, 0 fewer per 1000 (161 fewer to 161 more)	1 study (n=1995) Low quality, 2 fewer per 1000 (5 fewer to 8 more)	No outcomes identified
Acute kidney injury	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Development of end stage kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to Insulin	Sitagliptin	Exenatide	Liraglutide	Tirzepatide	Glimepiride
Cardiac arrhythmia	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Diabetic ketoacidosis	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Falls requiring hospitalisation	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=1995), High quality, 293 fewer per 1000 (325 fewer to 258 fewer)	1 study (n=58), High quality, 414 fewer per 1000 (535 fewer to 170 fewer)
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Severe hypoglycaemic episodes	1 study (n=22), Very low quality, 0 fewer per 1000 (161 fewer to 161 more)	No outcomes identified	1 study (n=22), Very low quality, 0 fewer per 1000 (161 fewer to 161 more)	1 study (n=1995) Moderate quality, 7 fewer per 1000 (10 fewer to 2 more)	No outcomes identified

Outcomes for drugs compared to Insulin	Sitagliptin	Exenatide	Liraglutide	Tirzepatide	Glimepiride
HbA1c change	1 study (n=22), Very low quality, MD 1.3% higher (0.11 higher to 2.49 higher)	1 study (n=23), Very low quality, MD 0.3% higher (0.89 lower to 1.49 higher)	1 study (n=22), Very low quality, MD 0.2% higher (0.99 lower to 1.39 higher)	1 study (n=1,959), High quality, MD 0.98% lower (1.06 lower to 0.90 lower)	1 study (n=55), Moderate quality, MD 0.6% lower (1.29 lower to 0.09 lower)
Weight change	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=1,959), High quality, MD 11.35 kg lower (11.90 lower to 10.80 lower)	1 study (n=55), Low quality, MD -2.9 kg lower (11.66 lower to 5.86 lower)
BMI change	No outcomes identified	1 study (n=23), Very low quality, MD 2.40 lower (5.14 lower to 0.34 higher)	No outcomes identified	No outcomes identified	No outcomes identified

1.1.7.2.3. Adding - A single therapy compared to glimepiride

Table 5: A summary matrix table showing the outcomes for adding drugs compared to adding glimepiride for people with type 2 diabetes with cardiovascular disease

Outcomes for drugs compared to glimepiride	Linagliptin
Health-related quality of life	No outcomes identified
All-cause mortality	No outcomes identified

Outcomes for drugs compared to glimepiride	Linagliptin
Cardiovascular mortality	No outcomes identified
3-item MACE	1 study (n=3,925), Moderate quality, 11 fewer per 1000 (41 fewer to 25 more), HR 0.94 (0.77 to 1.15)
4-item MACE	No outcomes identified
5-item MACE	No outcomes identified
Non-fatal stroke	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified
Unstable angina	No outcomes identified
Hospitalisation for heart failure	No outcomes identified
Acute kidney injury	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified
Development of end stage kidney disease	No outcomes identified
Death from renal cause	No outcomes identified
Cardiac arrhythmia	No outcomes identified
Diabetic ketoacidosis	No outcomes identified
Falls requiring hospitalisation	No outcomes identified

Outcomes for drugs compared to glimepiride	Linagliptin
Progression of liver disease	No outcomes identified
Remission	No outcomes identified
Hypoglycaemia episodes	No outcomes identified
At night hypoglycaemic episodes	No outcomes identified
Severe hypoglycaemic episodes	No outcomes identified
HbA1c change	No outcomes identified
Weight change	No outcomes identified
BMI change	No outcomes identified

1.1.7.2.4. Adding - a single therapy compared to sitagliptin

Table 7: A summary matrix showing the outcomes for adding individual drugs compared to adding sitagliptin for people with type 2 diabetes with cardiovascular disease

Outcomes for drugs compared to placebo	Liraglutide	Empagliflozin
Health-related quality of life	No outcomes identified	No outcomes identified
All-cause mortality	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Liraglutide	Empagliflozin
Cardiovascular mortality	No outcomes identified	No outcomes identified
3-item MACE	No outcomes identified	No outcomes identified
4-item MACE	No outcomes identified	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified
Non-fatal stroke	No outcomes identified	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified	No outcomes identified
Unstable angina	No outcomes identified	No outcomes identified
Hospitalisation for heart failure	1 study (n=20), Very low quality, 0 fewer per 1000 (174 fewer to 174 more)	No outcomes identified
Acute kidney injury	No outcomes identified	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified
Development of end stage kidney disease	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified
Cardiac arrhythmia	No outcomes identified	No outcomes identified
Diabetic ketoacidosis	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Liraglutide	Empagliflozin
Falls requiring hospitalisation	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	No outcomes identified	No outcomes identified
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified
Severe hypoglycaemic episodes	1 study (n=20), Very low quality, 0 fewer per 1000 (174 fewer to 174 more)	No outcomes identified
HbA1c change	1 study (n=20), Very low quality**,** MD 1.10% lower (1.98 lower to 0.22 lower)	1 study (n=97), Moderate quality**,** MD 0.10% higher (0.14 lower to 0.34 lower)
Weight change	No outcomes identified	1 study (n=97), Very low quality**,** MD 0.20 kg higher (4.16 lower to 4.56 higher)
BMI change	No outcomes identified	No outcomes identified

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1.1.7.2.5. Adding – A single therapy compared to vildagliptin

Table 6 A summary matrix showing the outcomes for adding individual drugs compared to adding vildagliptin for people with type 2 diabetes with cardiovascular disease

Outcomes for drugs compared to vildagliptin	Dapagliflozin
Health-related quality of life	No outcomes identified
All-cause mortality	1 study, (n=49), Low quality, 0 fewer per 1000 (76 fewer to 76 more)
Cardiovascular mortality	1 study, (n=49), Low quality, 0 fewer per 1000 (76 fewer to 76 more)
3-item MACE	No outcomes identified
4-item MACE	No outcomes identified
5-item MACE	No outcomes identified
Non-fatal stroke	1 study, (n=49), Low quality, 0 fewer per 1000 (76 fewer to 76 more)
Non-fatal myocardial infarction	1 study, (n=49), Low quality, 40 more per 1000 (37 fewer to 117 more)
Unstable angina	No outcomes identified
Hospitalisation for heart failure	1 study, (n=50), Low quality, 0 fewer per 1000 (75 fewer to 75 more)
Acute kidney injury	No outcome identified
Persistent signs of worsening kidney disease	No outcomes identified

Outcomes for drugs compared to vildagliptin	Dapagliflozin
Development of end stage kidney disease	No outcomes identified
Death from renal cause	No outcomes identified
Cardiac arrhythmia	No outcomes identified
Diabetic ketoacidosis	No outcomes identified
Falls requiring hospitalisation	No outcomes identified
Progression of liver disease	No outcomes identified
Remission	No outcomes identified
Hypoglycaemia episodes	No outcomes identified
At night hypoglycaemic episodes	No outcomes identified
Severe hypoglycaemic episodes	No outcomes identified
HbA1c change	1 study, (n=43), Very low quality, MD 0.21% higher (0.53 lower to 0.95 higher)
Weight change	1 study, (n=43), Low quality, MD 2.99 kg lower (4.16 lower to 1.82 lower)
BMI change	1 study, (n=43), Low quality, MD 1.20 kg/m^2 lower (1.68 lower to 0.72 lower)

1.1.7.2.6. Adding - A single therapy compared to pioglitazone

Table 8: A summary matrix showing the outcomes for adding individual drugs compared to adding pioglitazone for people with type 2 diabetes with cardiovascular disease

Outcomes for drugs compared to pioglitazone	Glimepiride
Health-related quality of life	No outcomes identified
All-cause mortality	1 study (n=543), Very low quality, 4 fewer per 1000 (20 fewer to 12 more)
Cardiovascular mortality	1 study (n=543), Very low quality, 7 fewer per 1000 (22 fewer to 7 more)
3-item MACE	No outcomes identified
4-item MACE	No outcomes identified
5-item MACE	1 study (n=543), Very low quality, 7 more per 1000 (19 fewer to 64 more)
Non-fatal stroke	1 study (n=543), Very low quality, 4 more per 1000 (3 fewer to 11 more)
Non-fatal myocardial infarction	1 study (n=543), Very low quality, 7 more per 1000 (5 fewer to 72 more)
Unstable angina	1 study (n=543), Very low quality, 7 fewer per 1000 (13 fewer to 25 more)
Hospitalisation for heart failure	1 study (n=543), Very low quality, 4 more per 1000 (10 fewer to 53 more)
Acute kidney injury	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified
Development of end stage kidney disease	No outcomes identified
Death from renal cause	No outcomes identified

Outcomes for drugs compared to pioglitazone	Glimepiride
Cardiac arrhythmia	No outcomes identified
Diabetic ketoacidosis	No outcomes identified
Falls requiring hospitalisation	No outcomes identified
Progression of liver disease	No outcomes identified
Remission	No outcomes identified
Hypoglycaemia episodes	1 study (n=543), Moderate quality, 218 more per 1000 (116 more 358 more)
At night hypoglycaemic episodes	No outcomes identified
Severe hypoglycaemic episodes	No outcomes identified
HbA1c change	1 study (n=543), Moderate quality, MD 0.19% higher (0.01 higher to 0.37 higher)
Weight change	1 study (n=543), Low quality, MD 2.9kg lower (7.06 lower to 1.26 higher)
BMI change	No outcomes identified

1.1.7.3. Model 3: People with type 2 diabetes and chronic kidney disease

1.1.7.3.1. Adding - A single therapy compared to placebo

Table 7: Summary matrix table for adding drugs compared to adding placebo for people with type 2 diabetes with chronic kidney disease

Outcomes for drugs compared to placebo	Liraglutide	Semaglutide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Health-related quality of life	No outcomes identified	1 study (n=324), Moderate quality, (SF-36 – subscale physical component) MD 1.98 higher (0.57 higher to 3.39 higher) High quality, (SF-36 – subscale mental component MD 1.98 higher (0.57 higher to 3.39 higher)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
All-cause mortality	1 study (n=277), Very low quality, 21 more per 1000 (10 fewer to 52 more)	1 study (n=3533), Moderate quality, HR 0.80 (0.67, 0.96	3 studies (n=4,798), Moderate quality, 6 fewer per 1000	4 studies (n=6750), Very low quality, 8 fewer per 1000	2 studies (n=2988), Moderate quality, 21 fewer per 1000	1 study (n=467), Very low quality, 3 more per 1000 (14 fewer to 66 more)

Outcomes for drugs compared to placebo	Liraglutide	Semaglutide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
		2 studies (n=3857), Moderate quality, 28 fewer per 1000 (45 fewer to 7 fewer)	(20 fewer to 10 more) 2 studies (n=4709), Moderate quality, HR 0.84 (0.69 to 1.02)	(30 fewer to 15 more)	(36 fewer to 2 fewer) 1 study (n=2250), Moderate quality, HR 0.76 (0.59 to 0.98)	
Cardiovascular mortality	1 study (n=277), Very low quality, 7 more per 1000 (17 fewer to 31 more)	1 study (n=3533), Moderate quality, HR 0.71 (0.56, 0.90) 2 studies (n=3857), Moderate quality, 24 fewer per 1000 (37 fewer to 8 fewer	2 studies (n= 4,709), Moderate quality, 12 fewer per 1000 (22 fewer to 1 more) Moderate quality, HR 0.79 (0.62 to 1.01)	3 studies (n=6,457), Very low quality, 4 fewer per 1000 (14 fewer to 6 more)	1 study (n=2250), Moderate quality, 24 fewer per 1000 (40 fewer to 1 fewer) HR 0.71 (0.52 to 0.97)	No outcomes identified
3-item MACE	No outcomes identified	1 study (n=3533), Moderate quality, HR 0.82 (0.68, 0.99)	No outcomes identified	1 study (n=5,884), Moderate quality, 9 fewer per 1000 (24 fewer to 9 more)	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Liraglutide	Semaglutide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
		1 study (n=3533), Moderate quality, 24 fewer per 1000 (43 fewer to 2 fewer)				
4-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified	2 studies (n=4,709), Moderate quality, 36 fewer per 1000 (52 fewer to 18 fewer), Moderate quality, HR 0.75 (0.64 to 0.88)	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Liraglutide	Semaglutide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Non-fatal stroke	No outcomes identified	1 study (n=3533), Moderate quality, HR 1.22 (0.84, 1.77) 7 more per 1000 (4 fewer to 22 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified	1 study (n=3533), Moderate quality, HR 0.80 (0.55, 1.15) 7 fewer per 1000 (16 fewer to 6 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Unstable angina	No outcomes identified	1 study (n=3533), Moderate quality, 6 fewer per 1000 (12 fewer to 1 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Hospitalisation for heart failure	No outcomes identified	1 study (n=324), Low quality, 6 fewer per 1000	2 studies (n=4,709) Moderate quality,	1 study (n=5,884), Low quality, 15 fewer per 1000	1 study (n=2250) Moderate quality, 26 fewer per 1000	No outcomes identified

Outcomes for drugs compared to placebo	Liraglutide	Semaglutide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
		(18 fewer to 6 more)	23 fewer (32 fewer to 12 fewer), High quality, HR 0.61 (0.47 to 0.79)	(23 fewer to 4 fewer)	(39 fewer to 8 fewer) Moderate quality, HR 0.61 (0.42 – 0.89)	
Acute kidney injury	No outcomes identified	2 studies (n=3857), Low quality, 1 more per 1000 (13 fewer to 19 more)	1 study (n=4,397) Moderate quality, 6 fewer per 1000 (15 fewer to 7 more), HR 0.85 (0.64 to 1.13)	1 study (n=252), Very low quality, 12 fewer per 1000 (35 fewer to 11 more)	No outcomes identified	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified	1 study (n=3533), Moderate quality, HR 0.73 (0.59, 0.89) 27 fewer per 1000 (44 fewer to 7 fewer)	1 study (n=4,401) High quality, 32 fewer per 1000 (43 fewer to 19 fewer) HR 0.60 (0.48 to 0.75)	2 studies (n=545), Very low quality, 1 fewer per 1000 (23 fewer to 20 more)	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Liraglutide	Semaglutide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Development of end stage kidney disease	No outcomes identified	1 study (n=3533), Moderate quality, HR 0.84 (0.63, 1.12) 7 fewer per 1000 (19 fewer to 8 more)	1 study (n=4,401), Moderate quality, 22 fewer per 1000 (33 fewer to 9 fewer), HR 0.68 (0.54 to 0.86)	1 study (n=252), Very low quality, 12 fewer per 1000 (22 fewer to 59 more)	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	1 study (n=3533), Low quality, HR 0.97 (0.27, 3.48) 0 fewer per 1000 (4 fewer to 4 fewer)	1 study (n=4,401), Low quality, 1 fewer per 1000 (4 fewer to 1 more)	No outcomes identified	No outcomes identified	No outcomes identified
Cardiac arrhythmia	No outcomes identified	1 study (n=3533), Moderate quality, 5 more per 1000 (2 fewer to 18 more)	No outcome identified	No outcomes identified	1 study (n=738), Low quality, 9 fewer per 1000 (14 fewer to 14 more)	No outcomes identified

Outcomes for drugs compared to placebo	Liraglutide	Semaglutide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Diabetic ketoacidosis	1 study (n=277), Very low quality, 7 more per 1000 (17 fewer to 31 more)	1 study (n=3533), Very low quality, 2 more per 1000 (3 fewer to 6 more)	2 studies (n=4,705), Very low quality, 4 more per 1000 (1 fewer to 48 more) 1 study (n=4397), High quality, HR 10.8 (1.39 to 83.92)	3 studies (n=6,498), Very low quality, 0 fewer per 1000 (2 fewer to 3 more)	No outcomes identified	No outcomes identified
Falls requiring hospitalisation	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified.	No outcomes identified
Hypoglycaemia episodes	1 outcome, 1 study (n=277), Low quality, 56 fewer per 1000 (128 fewer to 55 more)	1 outcome, 1 study (n=324), Moderate quality, 37 more per 1000 (3 fewer to 182 more)	2 studies (n=4705), High quality, 7 fewer per 1000 (23 fewer to 13 more) 1 study (n=4397), Moderate quality,	3 studies (n=866), Very low quality, 9 fewer per 1000 (53 fewer to 46 more)	1 study. (n=738), Moderate quality, 4 fewer per 1000 (61 fewer to 69 more)	1 study (n=467), Very low quality, 13 fewer per 1000 (78 fewer to 80 more)

Outcomes for drugs compared to placebo	Liraglutide	Semaglutide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
			HR 0.92 (0.77 to 1.10)			
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Severe hypoglycaemic episodes	1 study (n=277), Very low quality, 7 more per 1000 (7 fewer to 21 more)	1 study (n=3533), Low quality, HR 1.02 (0.62, 1.68) 2 studies (n=3857), Very low quality, 1 more per 1000 (9 fewer to 10 more)	No outcomes identified	4 studies (n=6,750), Low quality, 7 fewer per 1000 (12 fewer to 2 fewer)	1 study (n=738), Low quality, 4 fewer per 1000 (14 fewer to 25 more)	No outcomes identified
HbA1c change	1 study (n=277), Low quality, MD 0.66% lower (0.90 lower to 0.42 lower)	2 studies (n=3857), High quality, MD 0.81% lower (0.89 lower to 0.72 lower)	3 studies (n=4,921), High quality, MD 0.2% lower (0.32 lower to 0.08 lower)	3 studies (n=627), Low quality, MD 0.23% lower (0.4 lower to 0.07 lower)	1 study, (n=738), Moderate quality, MD 0.46 lower (0.59 lower to 0.33% lower)	2 studies (n=1,172), Low quality, MD 0.14% lower (0.3 lower to 0.02 higher)

Outcomes for drugs compared to placebo	Liraglutide	Semaglutide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Weight change	1 study (n=277), Moderate quality, MD 1.32 kg lower (2.24 lower to 0.40 lower)	2 studies (n=3857), Very low quality, MD 3.72 kg lower (4.13 lower to 3.32 lower)	3 studies (n=4,921), High quality, MD 0.90 kg lower (1.38 lower to 0.43 lower)	2 studies (n=454), Low quality, MD 2.15 kg lower (4.22 lower to 0.08 lower) 1 study (n=292), Low quality, MD 0.87 lower (2.17 lower to 0.43 higher)	1 study (n=738), High quality, MD 1.55 kg lower (2.0 lower to 1.1 lower)	2 studies (n=1,009), Very low quality, MD 2.05 kg lower (2.53 lower to 1.57 lower)
BMI change	1 study (n=277), Low quality, MD 0.50 kg/m^2 lower (0.83 lower to 0.17 lower)	1 study (n=324), Moderate quality, MD 0.9 kg/m2 lower (1.2 lower to 0.6 lower)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Table 8: Summary matrix table for adding drugs (DPP-4 inhibitors and thiazolidinediones) compared to adding placebo for people with type 2 diabetes with chronic kidney disease

Outcomes for drugs compared to placebo	Linagliptin	Saxagliptin	Pioglitazone
Health-related quality of life	No outcomes identified	No outcomes identified	No outcomes identified
All-cause mortality	2 studies (n=493), Very low quality, 3 more per 1000 (11 fewer to 56 more)	1 study (n=170), Very low quality, 12 fewer per 1000 (39 fewer to 106 more)	No outcomes identified
Cardiovascular mortality	1 study, (n=360), Low quality, 11 more per 1000 (4 fewer to 26 more)	No outcomes identified	No outcomes identified
3-item MACE	No outcomes identified	No outcomes identified	No outcomes identified
4-item MACE	No outcomes identified	No outcomes identified	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Linagliptin	Saxagliptin	Pioglitazone
Non-fatal stroke	2 studies (n=493), Very low quality, 0 fewer per 1000 (14 fewer to 14 more)	No outcomes identified	No outcomes identified
Non-fatal myocardial infarction	2 studies (n=493), Very low quality, 9 more per 1000 (4 fewer to 68 more)	No outcomes identified	No outcomes identified
Unstable angina	No outcomes identified	No outcomes identified	No outcomes identified
Hospitalisation for heart failure	2 studies (n=4543), Very low quality, 13 fewer per 1000 (28 fewer to 3 more), 1 study (n=4183), Moderate quality, HR 0.84 (0.68 to 1.04)	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Linagliptin	Saxagliptin	Pioglitazone
Acute kidney injury	1 study (n=133), Very low quality, 12 more per 1000 (41 fewer to 200 more)	No outcomes identified	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified	No outcomes identified
Development of end stage kidney disease	1 study (n=360), High quality, 0 fewer per 1000 (11 fewer to 11 more)	1 study (n=170), Very low quality, 24 fewer per 1000 (56 fewer to 9 more)	No outcomes identified

Outcomes for drugs compared to placebo	Linagliptin	Saxagliptin	Pioglitazone
Death from renal cause	No outcomes identified	No outcomes identified	No outcomes identified
Cardiac arrhythmia	No outcomes identified	No outcomes identified	No outcomes identified
Diabetic ketoacidosis	No outcomes identified	No outcomes identified	No outcomes identified
Falls requiring hospitalisation	No outcomes identified	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	2 studies (n=493), Very low quality, 93 more per 1000 (24 more to 184 more)	1 study (n=170), Very low quality, 47 more per 1000 (18 fewer to 254 more)	1 study (n=39), Very low quality, 5 fewer per 1000 (90 fewer to 535 more)
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Linagliptin	Saxagliptin	Pioglitazone
Severe hypoglycaemic episodes	2 studies (n= 493), Very low quality, 0 fewer per 1000 (21 fewer to 20 more)	No outcomes identified	1 study (n=39), Very low quality, 0 fewer per 1000 (95 fewer to 95 more)
HbA1c change	3 studies (n=556), Moderate quality, MD 0.6% lower (0.75 lower to 0.45 lower)	1 study (n=60), Very low quality, MD 0.63% lower (1.24 lower to 0.02 lower)	1 study (n=39), Low quality, MD 0.81% lower (1.46 lower to 0.16 lower)
Weight change	2 studies (n=249), Very low quality, MD 0.95 kg lower (3.23 lower to 1.33 higher)	No outcomes identified	No outcomes identified
BMI change	No outcomes identified	No outcomes identified	No outcomes identified

1.1.7.3.2. Adding - A single therapy compared to insulin

Table 9: Summary matrix table for adding drugs compared to adding insulin for people with type 2 diabetes with chronic kidney disease

Outcomes for drugs compared to insulin	Glimepiride	Dulaglutide	Exenatide
Health-related quality of life	No outcomes identified	No outcomes identified	No outcomes identified
All-cause mortality	No outcomes identified	1 study (n=576), Very low quality, 0 more per 1000 (14 fewer to 48 more)	No outcomes identified
Cardiovascular mortality	No outcomes identified	1 study (n=576), Very low quality, 0 more per 1000 (14 fewer to 48 more)	No outcomes identified
3-item MACE	No outcomes identified	No outcomes identified	No outcomes identified
4-item MACE	No outcomes identified	No outcomes identified	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal stroke	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to insulin	Glimepiride	Dulaglutide	Exenatide
Unstable angina	No outcomes identified	No outcomes identified	No outcomes identified
Hospitalisation for heart failure	No outcomes identified	No outcomes identified	No outcomes identified
Acute kidney injury	No outcomes identified	No outcomes identified	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified	1 study (n=576), Very low quality, 71 fewer per 1000 (141 fewer to 14 more)	No outcomes identified
Development of end stage kidney disease	No outcomes identified	1 study (n=576), Very low quality, 25 fewer per 1000 (52 fewer to 25 more)	No outcomes identified
Death from renal cause	No outcomes identified	1 study (n=576), Low quality, 0 fewer per 1000 (8 fewer to 8 more)	No outcomes identified
Cardiac arrhythmia	No outcomes identified	No outcomes identified	No outcomes identified
Diabetic ketoacidosis	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to insulin	Glimepiride	Dulaglutide	Exenatide
Falls requiring hospitalisation	No outcomes identified	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	1 study (n=58), High quality, 414 fewer per 1000 (535 fewer to 170 fewer)	1 study (n=576), Low quality, 51 fewer per 1000 (67 fewer to 17 fewer)	1 study (n=92), Very low quality, 217 fewer per 1000 (320 fewer to 23 fewer)
At night hypoglycaemic episodes	No outcomes identified	1 study (n=576), Low quality, 259 fewer per 1000 (306 fewer to 200 fewer)	No outcomes identified
Severe hypoglycaemic episodes	No outcomes identified	1 study (n=576), Low quality, 54 fewer per 1000 (62 fewer to 31 fewer)	1 study (n=92), Very low quality, 44 fewer per 1000 (102 fewer to 15 more)
HbA1c change	1 study (n=55), Moderate quality, MD 0.6% lower (1.29 lower to 0.09% higher)	1 study (n=576), Low quality, MD 0.1% lower (0.34 lower to 0.14 higher)	1 study (n=92), Very low quality, MD 0.22% higher (0.43 lower to 0.87 higher)

Outcomes for drugs compared to insulin	Glimepiride	Dulaglutide	Exenatide
Weight change	1 study (n=55), Low quality, MD 2.9 kg lower (11.66 lower to 5.86 higher)	1 study (n=576), Low quality, MD 3.8 kg lower (4.81 lower to 2.79 lower)	1 study (n=92), Very low quality, MD 2.68 kg lower (4.47 lower to 0.89 lower)
BMI change	No outcomes identified	No outcomes identified	No outcomes identified

1.1.7.3.3. Adding a single therapy compared to linagliptin

Table 10: Summary matrix table for adding drugs compared to adding linagliptin for people with type 2 diabetes with chronic kidney disease (adding to insulin)

Outcomes for drugs compared to linagliptin	Empagliflozin
Health-related quality of life	No outcomes identified
All-cause mortality	No outcomes identified
Cardiovascular mortality	No outcomes identified
3-item MACE	No outcomes identified
4-item MACE	No outcomes identified
5-item MACE	No outcomes identified

Outcomes for drugs compared to linagliptin	Empagliflozin
Non-fatal stroke	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified
Unstable angina	No outcomes identified
Hospitalisation for heart failure	No outcomes identified
Acute kidney injury	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified
Development of end stage kidney disease	No outcomes identified
Death from renal cause	No outcomes identified
Cardiac arrhythmia	No outcomes identified
Diabetic ketoacidosis	No outcomes identified
Falls requiring hospitalisation	No outcomes identified
Progression of liver disease	No outcomes identified
Remission	No outcomes identified
Hypoglycaemia episodes	1 study (n=107), Very low quality, 151 more per 1000 (26 fewer to 448 more)
At night hypoglycaemic episodes	No outcomes identified
Severe hypoglycaemic episodes	No outcomes identified
HbA1c change	1 study (n=107), Very low quality, MD 0.34% lower (0.67 lower to 0.01 lower)

Outcomes for drugs compared to linagliptin	Empagliflozin
Weight change	No outcomes identified
BMI change	No outcomes identified

Table 11: Summary matrix table for switching from or adding to drugscompared to switching or adding to linagliptin for people with type 2 diabetes with chronic kidney disease

Outcomes for drugs compared to linagliptin	Sitagliptin
Health-related quality of life	No outcomes identified
All-cause mortality	1 study (n=94), Very low quality, 4 fewer per 1000 (38 fewer to 233 more)
Cardiovascular mortality	No outcomes identified
3-item MACE	No outcomes identified
4-item MACE	No outcomes identified
5-item MACE	No outcomes identified
Non-fatal stroke	No outcomes identified
Non-fatal myocardial infarction	1 study (n=94), Very low quality, 17 more per 1000 (34 fewer to 305 more)
Unstable angina	No outcomes identified
Hospitalisation for heart failure	1 study (n=94), Very low quality, 5 fewer per 1000 (54 fewer to 221 more)
Acute kidney injury	No outcomes identified

Outcomes for drugs compared to linagliptin	Sitagliptin
Persistent signs of worsening kidney disease	No outcomes identified
Development of end stage kidney disease	1 study (n=94), Very low quality, 35 more per 1000 (41 fewer to 336 more)
Death from renal cause	No outcomes identified
Cardiac arrhythmia	1 study (n=94), Very low quality, 4 fewer per 1000 (38 fewer to 233 more)
Diabetic ketoacidosis	No outcomes identified
Falls requiring hospitalisation	No outcomes identified
Progression of liver disease	No outcomes identified
Remission	No outcomes identified
Hypoglycaemia episodes	No outcomes identified
At night hypoglycaemic episodes	No outcomes identified
Severe hypoglycaemic episodes	No outcomes identified
HbA1c change	1 study (n=66), Very low quality, MD 0.34% higher (0.02 lower to 0.70 higher)
Weight change	1 study (n=66), Very low quality, MD 1.10 kg higher (1.05 lower to 3.25 higher)
BMI change	No outcomes identified

1.1.7.3.4. Adding – A single therapy compared to sitagliptin

Table 12: Summary matrix table for adding drugs compared to adding sitagliptin for people with type 2 diabetes with chronic kidney disease (adding to other glucose-lowering drugs)

Outcomes for drugs compared to sitagliptin	Vildagliptin
Health-related quality of life	No outcomes identified
All-cause mortality	1 study (n=148), Low quality, 7 fewer per 1000 (27 fewer to 136 more)
Cardiovascular mortality	1 study (n=148), Very low quality, 12 more per 1000 (11 fewer to 36 more)
3-item MACE	No outcomes identified
4-item MACE	No outcomes identified
5-item MACE	No outcomes identified
Non-fatal stroke	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified
Unstable angina	No outcomes identified
Hospitalisation for heart failure	No outcomes identified
Acute kidney injury	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified
Development of end stage kidney disease	No outcomes identified
Death from renal cause	No outcomes identified

Outcomes for drugs compared to sitagliptin	Vildagliptin
Cardiac arrhythmia	No outcomes identified
Diabetic ketoacidosis	No outcomes identified
Falls requiring hospitalisation	No outcomes identified
Progression of liver disease	No outcomes identified
Remission	No outcomes identified
Hypoglycaemia episodes	1 study (n=148), Low quality, 3 more per 1000 (80 fewer to 180 more)
At night hypoglycaemic episodes	No outcomes identified
Severe hypoglycaemic episodes	No outcomes identified
HbA1c change	1 study (n=140), Moderate quality, MD 0.02% higher (0.33 lower to 0.37 higher)
Weight change	No outcomes identified
BMI change	No outcomes identified

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1.1.7.3.5. Adding – A single therapy compared to dulaglutide

Table 13: Summary matrix table for adding drugs compared to adding dulaglutide for people with type 2 diabetes with chronic kidney disease

Outcomes for drugs compared to dulaglutide	Semaglutide
Health-related quality of life	1 study (n=107), overall score, DTR-QoL, Low quality, MD 0.9 (4.35 lower, 6.15 higher)
All-cause mortality	No outcomes identified
Cardiovascular mortality	No outcomes identified
3-item MACE	No outcomes identified
4-item MACE	No outcomes identified
5-item MACE	No outcomes identified
Non-fatal stroke	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified
Unstable angina	No outcomes identified
Hospitalisation for heart failure	1 study (n=107), Very low quality, 19 more per 1000 (17 fewer to 54 more)
Acute kidney injury	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified
Development of end stage kidney disease	No outcomes identified
Death from renal cause	No outcomes identified

Outcomes for drugs compared to dulaglutide	Semaglutide
Cardiac arrhythmia	No outcomes identified
Diabetic ketoacidosis	1 study (n=107), Low quality, 0 fewer per 1000 (36 fewer to 36 more)
Falls requiring hospitalisation	No outcomes identified
Progression of liver disease	1 study (n=107), Very low quality, 88 more per 1000 (63 fewer to 365 more)
Remission	No outcomes identified
Hypoglycaemia episodes	No outcomes identified
At night hypoglycaemic episodes	No outcomes identified
Severe hypoglycaemic episodes	1 study (n=107), Low quality, 0 fewer per 1000 (36 fewer to 36 more)
HbA1c change	1 study (n=107), Low quality, MD 0.4% lower (0.63 lower to 0.17 lower)
Weight change	1 study (n=107), Low quality, MD 2.5 kg lower (3.36 lower to 1.64 lower)
BMI change	1 study (n=107), Low quality, MD 1.0 kg/m^2 lower (1.33 lower to 0.67 lower)

Table 14: Summary matrix table for switching drugs monotherapy compared to dulaglutide for people with type 2 diabetes with chronic kidney disease (switching from dulaglutide)

Outcomes for drugs compared to dulaglutide	Semaglutide
Health-related quality of life	No outcomes identified
All-cause mortality	No outcomes identified

Outcomes for drugs compared to dulaglutide	Semaglutide
Cardiovascular mortality	No outcomes identified
3-item MACE	No outcomes identified
4-item MACE	No outcomes identified
5-item MACE	No outcomes identified
Non-fatal stroke	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified
Unstable angina	No outcomes identified
Hospitalisation for heart failure	No outcomes identified
Acute kidney injury	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified
Development of end stage kidney disease	No outcomes identified
Death from renal cause	No outcomes identified
Cardiac arrhythmia	No outcomes identified
Diabetic ketoacidosis	No outcomes identified
Falls requiring hospitalisation	No outcomes identified
Progression of liver disease	No outcomes identified
Remission	No outcomes identified

Outcomes for drugs compared to dulaglutide	Semaglutide
Hypoglycaemia episodes	1 study (n=70), Very low quality, 29 more per 1000 (23 fewer to 573 more)
At night hypoglycaemic episodes	No outcomes identified
Severe hypoglycaemic episodes	1 study (n=70), Very low quality, 0 fewer per 1000 (54 fewer to 54 more)
HbA1c change	1 study (n=63), Low quality, MD 0.6% lower (0.91 lower to 0.29 lower)
Weight change	1 study (n=63), Low quality, MD 2.7 kg lower (3.55 lower to 1.85 lower)
BMI change	1 study (n=63), Low quality, MD 1.0 kg/m^2 lower (1.34 lower to 0.66 lower)

1.1.7.3.6. Switching or adding - A single therapy compared to liraglutide

Table 15: Summary table for switching from or adding to a drug compared to switching to or adding liraglutide for people with type 2 diabetes with chronic kidney disease

Outcomes for drugs compared to liraglutide	Linagliptin	Sitagliptin
Health-related quality of life	No outcomes identified	No outcomes identified
All-cause mortality	1 study (n=90), Very low quality, 0 fewer per 1000 (38 fewer to 257 more)	1 study (n=94), Very low quality, 4 fewer per 1000 (38 fewer to 233 more)
Cardiovascular mortality	No outcomes identified	No outcomes identified
3-item MACE	No outcomes identified	No outcomes identified
4-item MACE	No outcomes identified	No outcomes identified

Outcomes for drugs compared to liraglutide	Linagliptin	Sitagliptin
5-item MACE	No outcomes identified	No outcomes identified
Non-fatal stroke	No outcomes identified	No outcomes identified
Non-fatal myocardial infarction	1 study (n=90), Very low quality, 22 more per 1000 (18 fewer to 451 more)	1 study (n=94), Very low quality, 39 more per 1000 (16 fewer to 545 more)
Unstable angina	No outcomes identified	No outcomes identified
Hospitalisation for heart failure	1 study (n=90), Very low quality, 0 fewer per 1000 (52 fewer to 246 more)	1 study (n=94), Very low quality, 5 fewer per 1000 (54 fewer to 221 more)
Acute kidney injury	No outcomes identified	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified
Development of end stage kidney disease	1 study (n=90), Very low quality, 0 fewer per 1000 (52 fewer to 246 more)	1 study (n=94), Very low quality, 35 more per 1000 (41 fewer to 336 more)
Death from renal cause	No outcomes identified	No outcomes identified
Cardiac arrhythmia	1 study (n=90), Very low quality, 22 more per 1000 (18 fewer to 451 more)	1 study (n=94), Very low quality, 19 more per 1000 (18 fewer to 413 more)
Diabetic ketoacidosis	No outcomes identified	No outcomes identified
Falls requiring hospitalisation	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified

Outcomes for drugs compared to liraglutide	Linagliptin	Sitagliptin
Remission	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	No outcomes identified	No outcomes identified
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified
Severe hypoglycaemic episodes	No outcomes identified	No outcomes identified
HbA1c change	1 study (n=64), Low quality, MD 0.05% lower (0.34 lower to 0.24 higher)	1 study (n=66), Very low quality, MD 0.29% higher (0.11 lower to 0.69 higher)
Weight change	No outcomes identified	No outcomes identified
BMI change	1 study (n=64), Very low quality, MD 0.1 kg/m^2 higher (1.84 lower to 2.04 higher)	1 study (n=66), Very low quality, MD 1.2 kg/m^2 higher (0.62 lower to 3.02 higher)

Table 16: Summary table for monotherapy compared to liraglutide for people with type 2 diabetes with chronic kidney disease (switching from liraglutide)

Outcomes for drugs compared to liraglutide	Semaglutide
Health-related quality of life	Overall (DTSQ), 1 study (n=37), Low quality, MD 8.20 higher (2.30 higher to 14.10 higher)
All-cause mortality	No outcomes identified
Cardiovascular mortality	No outcomes identified
3-item MACE	No outcomes identified

Outcomes for drugs compared to liraglutide	Semaglutide
4-item MACE	No outcomes identified
5-item MACE	No outcomes identified
Non-fatal stroke	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified
Unstable angina	No outcomes identified
Hospitalisation for heart failure	No outcomes identified
Acute kidney injury	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified
Development of end stage kidney disease	No outcomes identified
Death from renal cause	No outcomes identified
Cardiac arrhythmia	No outcomes identified
Diabetic ketoacidosis	No outcomes identified,
Falls requiring hospitalisation	No outcomes identified
Progression of liver disease	No outcomes identified
Remission	No outcomes identified
Hypoglycaemia episodes	1 study (n=40), Very low quality, 100 fewer per 1000 (144 fewer to 291 more)
At night hypoglycaemic episodes	No outcomes identified

Outcomes for drugs compared to liraglutide	Semaglutide
Severe hypoglycaemic episodes	1 study (n=40), Very low quality, 0 fewer per 1000 (92 fewer to 92 more)
HbA1c change	1 study (n=37), Low quality, MD 0.5% lower (0.86 lower to 0.14 lower)
Weight change	1 study (n=37), Moderate quality, MD 0.2 kg lower (1.87 lower to 1.47 higher)
BMI change	1 study (n=37), Moderate quality, MD 0 kg/m^2 (0.65 lower to 0.65 higher)

1.1.7.3.1. Combination therapy compared to placebo

Table 17: Summary table for combination therapy compared to placebo for people with type 2 diabetes with chronic kidney disease (adding to glucose-lowering drugs)

Outcomes for drugs compared to placebo	Dapagliflozin + Saxagliptin
Health-related quality of life	No outcomes identified
All-cause mortality	1 study (n=300), Very low quality, 7 more per 1000 (6 fewer to 19 more)
Cardiovascular mortality	No outcomes identified
3-item MACE	No outcomes identified
4-item MACE	No outcomes identified
5-item MACE	No outcomes identified
Non-fatal stroke	No outcomes identified

Outcomes for drugs compared to placebo	Dapagliflozin + Saxagliptin
Non-fatal myocardial infarction	No outcomes identified
Unstable angina	No outcomes identified
Hospitalisation for heart failure	No outcomes identified
Acute kidney injury	No outcomes identified
Persistent signs of worsening kidney disease	1 study (n=300), Very low quality, 13 more per 1000 (13 fewer to 39 more)
Development of end stage kidney disease	No outcomes identified
Death from renal cause	No outcomes identified
Cardiac arrhythmia	No outcomes identified
Diabetic ketoacidosis	1 study (n=300), Very low quality, 0 fewer per 1000 (13 fewer to 13 more)
Falls requiring hospitalisation	No outcomes identified
Progression of liver disease	No outcomes identified
Remission	No outcomes identified
Hypoglycaemia episodes	1 study (n=300), Very low quality, 133 more per 1000 (25 more to 294 more)
At night hypoglycaemic episodes	No outcomes identified
Severe hypoglycaemic episodes	1 study (n=300), Very low quality, 6 more per 1000 (16 fewer to 29 more)
HbA1c change	1 study (n=296), Very low quality, MD 0.58% lower (0.8 lower to 0.36 lower)
Weight change	1 study (n=300), Low quality, MD 0.04 kg lower (1.32 lower to 1.24 higher)

Outcomes for drugs compared to placebo	Dapagliflozin + Saxagliptin
BMI change	No outcomes identified

1.1.7.3.2. Combination therapy compared to dapagliflozin

Table 18: Summary table for combination therapy compared to dapagliflozin for people with type 2 diabetes with chronic kidney disease (adding to glucose-lowering drugs)

Outcomes for drugs compared to dapagliflozin	Dapagliflozin + Saxagliptin
Health-related quality of life	No outcomes identified
All-cause mortality	1 study (n=297), Very low quality, 0 fewer per 1000 (19 fewer to 18 more)
Cardiovascular mortality	No outcomes identified
3-item MACE	No outcomes identified
4-item MACE	No outcomes identified
5-item MACE	No outcomes identified
Non-fatal stroke	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified
Unstable angina	No outcomes identified
Hospitalisation for heart failure	No outcomes identified
Acute kidney injury	No outcomes identified

Outcomes for drugs compared to dapagliflozin	Dapagliflozin + Saxagliptin
Persistent signs of worsening kidney disease	1 study (n=297), Very low quality, 20 more per 1000 (2 fewer to 42 more)
Development of end stage kidney disease	No outcomes identified
Death from renal cause	No outcomes identified
Cardiac arrhythmia	No outcomes identified
Diabetic ketoacidosis	1 study (n=297), Very low quality, 7 fewer per 1000 (20 fewer to 7 more)
Falls requiring hospitalisation	No outcomes identified
Progression of liver disease	No outcomes identified
Remission	No outcomes identified
Hypoglycaemia episodes	1 study (n=297), Very low quality, 88 more per 1000 (14 fewer to 234 more)
At night hypoglycaemic episodes	No outcomes identified
Severe hypoglycaemic episodes	1 study (n=297), Very low quality, 13 more per 1000 (5 fewer to 31 more)
HbA1c change	No outcomes identified
Weight change	No outcomes identified
BMI change	No outcomes identified

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1.1.7.4. Model 5: People with type 2 diabetes at high cardiovascular risk with no other comorbidities

1.1.7.4.1. Adding — A single therapy compared to adding placebo

Table 19: A summary matrix showing the outcomes for adding individual drugs (GLP-1 receptor agonists, dual GIP/GLP-1 receptor co-agonists and SGLT-2 inhibitors) compared to adding placebo for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Health-related quality of life	Overall (EQ-5D-5L UK Index) 1 study (n=300), Very low quality, MD 0.01 lower (0.07 lower to 0.05 higher)	Overall (IWQOL-Lite) 1 study (n=242), Low quality, MD 1.00 lower (5.13 lower to 3.13 higher)	18 outcomes[a] 4 studies (n = 66, n=80, n=476 and n=826) Very low to high quality,	Mental component (SF-12) 1 study (n=348) Moderate quality, MD 0.33 higher (1.57 lower to 2.23 higher)	Mental component (SF-36) 5 studies (n=5715) High quality, MD 0.75 higher (0.28 lower to 1.22 higher)	Physical functioning (SF-36) 1 study (n=938) High quality, MD 2.00 higher (1.04 lower to 2.96 higher)	No outcomes identified	Overall (EQ-5D) 2 studies (n=354), Very low quality, MD 0.00 higher (0.03 lower to 0.04 higher)	Overall (EQ-5D-5L) 1 study (n=129) Moderate quality, MD 0.05 higher (0.01 higher to 0.09 higher)	No outcomes identified

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
		Subscale barriers to activity (Diabetes Health Profile) 1 study (n=46), Low quality, MD 4.30 lower (9.75 lower to 1.15 higher)	),	Physical component (SF-12) 1 study (n=348) High quality, MD 1.73 higher (0.01 lower to 3.45 higher)	Physical subscale (SF-36) 5 studies (n=5715) High quality, MD 0.55 higher (0.17 lower to 0.93 higher)					

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
		Subscale disinhibited eating (Diabetes Health Profile) 1 study (n=46), Low quality, MD 8.09 lower (19.75 lower to 3.57 higher)								

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
		Subscale psychological distress (Diabetes Health Profile) 1 study (n=46), Low quality, MD 2.73 higher (3.04 lower to 8.50 higher)								

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
		Subscale well being (DMSAT) 1 study (n=242), Very low quality, MD 7.10 higher (0.95 lower to 15.15 higher)								

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
All-cause mortality	8 studies (n=12124), Moderate quality, 5 fewer per 1000 (14 fewer to 3 more)	8 studies (n=16741), Moderate quality, 9 fewer per 1000 (17 fewer to 2 fewer)	11 studies (n=13096), Very low quality, 1 fewer per 1000 (9 fewer to 6 more) 1 study (n=9360), Moderate quality, HR 0.85 (0.74, 0.98)	10 studies (n=4944) Very low quality, 3 fewer per 1000 (7 fewer to 1 more)	10 studies (n=10303), Moderate quality, 4 fewer per 1000 (9 fewer to 2 more) 2 studies (n=6480) Very low quality, HR 0.75 (0.37, 1.52)	4 studies (n=1744), Very low quality, 0 fewer per 1000 (8 fewer to 7 more)	6 studies (n=2797, Very low quality, 2 more per 1000 (3 fewer to 6 more)	11 studies (n=21414), Low quality, 4 fewer per 1000 (10 fewer to 3 more)	9 studies (n=3742) Very low quality, 1 more per 1000 (4 fewer to 5 more)	3 studies (n=1589), High quality, 0 fewer per 1000 (5 fewer to 5 more)

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
	1 study (n=9901), Moderate quality, HR 0.90 (0.80, 1.01)	1 study (n=14752), Moderate quality, HR 0.86 (0.77, 0.97)					1 study (n=10142), Moderate quality, HR 0.87 (0.75, 1.01)	1 study (n=17160), Moderate quality, HR 0.98 (0.82, 1.17)		

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Cardiovascular mortality	8 studies (n=12124), Moderate quality, 10 fewer per 1000 (20 fewer to 1 more)	8 studies (n=16741), Moderate quality, 5 fewer per 1000 (11 fewer to 1 more)	9 studies (n=12566), Moderate quality, 1 fewer per 1000 (9 fewer to 7 more) 1 study (n=9360), Moderate quality, HR 0.78 (0.66, 0.92)	9 studies (n=4462) Very low quality, 0 fewer per 1000 (4 fewer to 3 more)	7 studies (n=8306), Moderate quality, 4 fewer per 1000 (10 fewer to 2 more) 2 studies (n=6480) Very low quality, HR 0.72 (0.37, 1.41)	2 studies (n=548), High quality, 0 fewer per 1000 (14 fewer to 14 more)	5 studies (n=1879), Very low quality, 2 more per 1000 (4 fewer to 7 more)	7 studies (n=20041), Very low quality, 0 fewer per 1000 (5 fewer to 4 more)	5 studies (n=2067) Very low quality, 1 more per 1000 (4 fewer to 7 more)	3 studies (n=1589),, High quality, 0 fewer per 1000 (5 fewer to 5 more)

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
	1 study (n=9901), Moderate quality, HR 0.91 (0.78, 1.06)	1 study (n=14752), Moderate quality, HR 0.88 (0.76, 1.02)					1 study (n=10142), Moderate quality, HR 0.87 (0.71, 1.06)	1 study (n=17160), Moderate quality, HR 0.92 (0.82, 1.04)		

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
3-item MACE	1 study (n=9901), High quality, 14 fewer per 1000 (26 fewer to 1 fewer)	1 study (n=14752), High quality, 8 fewer per 1000 (18 fewer to 2 more)	1 study (n=9340), Moderate quality, 18 fewer per 1000 (31 fewer to 4 fewer) 1 study (n=9340),	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=10142), Moderate quality, HR 0.85 (0.75, 0.97)	1 study (n=17160), Moderate quality, 6 fewer per 1000 (13 fewer to 3 more)	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
	1 study (n=9901), Moderate quality, HR 0.88 (0.79, 0.99)	1 study (n=14752), High quality, HR 0.91 (0.83, 1.00)	Moderate quality, HR 0.87 (0.78, 0.97)					1 study (n=17160) Moderate quality, HR 0.93 (0.84, 1.03)		

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
4-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=475) Low quality, 3 fewer per 1000 (8 fewer to 53 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
5-item MACE	No outcomes identified	No outcomes identified	No outcome	No outcomes identified	2 studies (n=6480)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
			s identified		Moderate quality, 25 fewer per 1000 (37 fewer to 12 fewer) HR 0.76 (0.65, 0.88)					

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Non-fatal stroke	3 studies (n=10500), Low quality, 7 fewer per 1000 (13 fewer to 1 fewer)	No outcomes identified	2 studies (n=9766), Lowquality, 4 fewer per 1000 (10 fewer to 4 more) 1 study (n=9340), Moderate quality, HR 0.89	2 studies (n=701) Low quality, 9 more per 1000 (1 fewer to 18 more)	6 studies (n=8663) Low quality, 8 fewer per 1000 (13 fewer to 3 fewer) 2 studies (n=6480) Moderate quality, HR 0.64 (0.43, 0.96)	No outcomes identified	1 study (n=10142), Moderate quality, HR 0.90 (0.71, 1.15)	2 studies (n=17756), Low quality, 0 fewer per 1000 (5 fewer to 4 more)	1 study (n=275) Low quality, 11 fewer per 1000 (32 fewer to 10 more)	No outcomes identified

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
	1 study (n=9901), Moderate quality, HR 0.76 (0.61, 0.95)		(0.72, 1.10)					1 study (n=17160), Moderate quality, HR 1.01 (0.84, 1.21)		

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Non-fatal myocardial infarction	3 studies (n=10624), Low quality, 2 fewer per 1000 (8 fewer to 6 more)	2 studies (n=619), Very low quality, 3 fewer per 1000 (5 fewer to 9 more) 2 studies (n=619), Very low quality, 3 fewer per 1000 (15 fewer to 8 more)	2 studies (n=9766), Low quality, 7 fewer per 1000 (16 fewer to 2 more) 1 study (n=9340), Moderate quality,	1 study (n=390), Low quality, 5 more per 1000 (5 fewer to 15 more)	5 studies (n=8267), Low quality, 3 fewer per 1000 (10 fewer to 4 more) 2 studies (n=6480), Very low quality, HR 0.91 (0.58, 1.43)	No outcomes identified	1 study (n=10142), Moderate quality, HR 0.85 (0.69, 1.05)	1 study (n=17160), Low quality, 6 fewer per 1000 (11 fewer to 1 more)	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
	1 study (n=9901), Moderate quality, HR 0.96 (0.79, 1.16)		HR 0.88 (0.75, 1.03)					1 study (n=17160), Low quality, HR 0.89 (0.77, 1.02)		

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Unstable angina	3 studies (n=10624), Low quality, 2 more per 1000 (3 fewer to 8 more)	1 study (n=14752), Low quality, 3 more per 1000 (2 fewer to 8 more)	2 studies (n=9766), Very low quality, 0 fewer per 1000 (7 fewer to 6 more) 1 study (n=9340), Low quality, HR 0.98 (0.76, 1.26)	No outcomes identified	3 studies (n=6907) Very low quality, 0 fewer per 1000 (5 fewer to 4 more) 2 studies (n=6480), Low quality, HR 0.97 (0.60, 1.56)	No outcomes identified	No outcomes identified	1 study (n=17160), Moderate quality, 1 more per 1000 (4 fewer to 6 more)	1 study (n=266) Low quality, 11 fewer per 1000 (33 fewer to 11 more)	No outcomes identified

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
	1 study (n=9901), Moderate quality, HR 1.14 (0.84, 1.54)									

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Hospitalisation for heart failure	1 study (n=9901), Moderate quality, 3 fewer per 1000 (10 fewer to 6 more)	2 studies (n=14798), Low quality, 1 fewer per 1000 (6 fewer to 5 more)	1 study (n=9340), Moderate quality, 6 fewer per 1000 (14 fewer to 3 more) 1 study (n=9340), Moderat	No outcomes identified	4 studies (n=7606) Very low quality, 0 more per 1000 (6 fewer to 8 more) 2 studies (n=6480), Low quality, HR 1.03 (0.76, 1.41)	No outcomes identified	1 study (n=10142), Moderate quality, HR 0.67 (0.52, 0.87)	1 study (n=17160), Low quality, 9 fewer per 1000 (13 fewer to 4 fewer)	1 study (n=275), Moderate quality, 0 fewer per 1000 (17 fewer to 17 more)	No outcomes identified

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
	1 study (n=9901), Moderate quality, HR 0.93 (0.77, 1.12)	1 study (n=14752), Moderate quality, HR 0.94 (0.78, 1.13)	e quality, HR 0.87 (0.73, 1.04)					1 study (n=17160), Low quality, HR 0.73 (0.61, 0.88)		

Acute kidney injury	2 studies (n=10192), Very low quality, 1 fewer per 1000 (5 fewer to 4 more)	1 study (n=463), Low quality, 4 more per 1000 (4 fewer to 13 more)	3 studies (n=10068), Low quality, 2 more per 1000 (3 fewer to 9 more)	No outcomes identified	6 studies (n=9144), Very low quality, 1 fewer per 1000 (8 fewer to 5 more)	No outcomes identified	No outcomes identified	1 study (n=17160), Low quality, 6 fewer per 1000 (9 fewer to 2 fewer) 1 study (n=17160), Low quality, HR 0.69 (0.55, 0.87)	2 studies (n=494), Very low quality, 9 more per 1000 (8 fewer to 26 more)	No outcomes identified

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Persistent signs of worsening kidney disease	1 study (n=9901), High quality, 9 fewer per 1000 (20 fewer to 2 more)	No outcomes identified	2 studies (n=9420), Low quality, 15 fewer per 1000 (23 fewer to 5 fewer)	No outcomes identified	1 study (n=3297), Moderate quality, 23 fewer per 1000 (33 fewer to 9 fewer)	1 study (n=938), Low quality, 2 more per 1000 (3 fewer to 43 more)	1 study (n=10142), High quality, HR 0.73 (0.67, 0.79)	4 studies (n=19109), Moderate quality, 11 fewer per 1000 (14 fewer to 7 fewer)	2 studies (n=286), Moderate quality, 0 fewer per 1000 (19 fewer to 19 more)	No outcomes identified

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
	1 study (n=9901), Moderate quality, HR 0.89 (0.78, 1.01)		1 study (n=9340), Moderate quality, HR 0.78 (0.67, 0.91)		1 study (n=3297), Moderate quality, HR 0.64 (0.46, 0.89)			1 study (n=17160), Moderate quality, HR 0.54 (0.43, 0.67)		

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Development of end stage kidney disease	1 study (n=9901), Low quality, 1 fewer per 1000 (2 fewer to 1 more)	1 study (n=14752), Moderate quality, 1 fewer per 1000 (4 fewer to 2 more)	2 studies (n=10184), Very low quality, 2 fewer per 1000 (5 fewer to 3 more)	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=10142), Low quality, HR 0.77 (0.30, 1.97)	3 studies (n=17874), Low quality, 1 fewer per 1000 (3 fewer to 0 more)	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
			1 study (n=9340), Moderate quality, HR 0.87 (0.61, 1.24)					1 study (n=17160), Moderate quality, HR 0.31 (0.13, 0.78)		

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Death from renal cause	No outcomes identified	1 study (n=14752), Low quality, 0 more per 1000 (1 fewer to 1 more)	2 studies (n=10185), Very low quality, 1 more per 1000 (1 fewer to 2 more) 1 study (n=9340), Very low quality, HR 1.59 (0.52, 4.86)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=17160), Very low quality, 0 more per 1000 (0 more to 1 more) 1 study (n=17160), Very low quality, HR 0.60 (0.22, 1.65)	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Cardiac arrhythmia	2 studies (n=10006), Very low quality, 5 more per 1000 (3 fewer to 13 more)	1 study (n=14752), Moderate quality, 4 fewer per 1000 (10 fewer to 3 more)	No outcomes identified	No outcomes identified	1 study (n=3297), Low quality, 5 fewer per 1000 (14 fewer to 9 more)	1 study (n=938), Low quality, 5 more per 1000 (2 fewer to 65 more)	1 study (n=10142), Moderate quality, 2 more per 1000 (3 fewer to 9 more)	1 study (n=17160), Low quality, 3 fewer per 1000 (6 fewer to 0 more)	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
							1 study (n=10142), Moderate quality, HR 0.84 (0.64, 1.12)			

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Diabetic ketoacidosis	2 studies (n=528), High quality, 0 fewer per 1000 (12 fewer to 12 more)	2 studies (n=209), Very low quality, 5 more per 1000 (38 fewer to 49 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	2 studies (n=354), Low quality, 0 fewer per 1000 (16 fewer to 16 more)	3 studies (n=17498), Low quality, 2 more per 1000 (0 more to 3 more)	7 studies (n=1872) Very low quality, 2 fewer per 1000 (9 fewer to 5 more)	1 study (n=462), High quality, 0 fewer per 1000 (10 fewer to 10 more)

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
							1 study (n=3486, Low quality, HR 1.57 (0.40, 6.16)	1 study (n=17160), Low quality, HR 2.18 (1.10, 4.30)		
Falls requiring hospitalisation	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Progression of liver disease	1 study (n=9901), Moderate quality, 3 fewer per 1000 (6 fewer to 0 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=938), Low quality, 3 more per 1000 (1 fewer to 8 more)	No outcomes identified	1 study (n=17160), Very low quality, 1 fewer per 1000 (4 fewer to 2 more) 1 study (n=17160), Low quality, HR 0.92 (0.68, 1.25)	1 study (n=129), Low quality, 31 more per 1000 (11 fewer to 73 more)	No outcomes identified

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Remission	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	6 studies (n=1523), Moderate quality, 38 more per 1000 (5 fewer to 91 more)	13 studies (n=3878), Low quality, 56 more per 1000 (10 more to 102 more)	13 studies (n=13945), Low quality, 69 more per 1000 (6 more to 142 more)	10 studies (n=4944) Moderate quality, 44 more per 1000 (18 more to 76 more)	7 studies (n=3426), Very low quality, 26 more per 1000 (19 fewer to 102 more)	4 studies (n=1748), Very low quality, 136 more per 1000 (45 fewer to 556 more)	4 studies (n=1537), Very low quality, 45 more per 1000 (32 fewer to 121 more)	11 studies (n=4320), Low quality, 13 more per 1000 (8 fewer to 34 more)	12 studies (n=4476) ModerateHigh quality, 13 more per 1000 (7 fewer to 34 more)	3 studies (n=1589), Moderate quality, 25 more per 1000 (0 more to 64 more)

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
							1 study (n=3486, Low quality, HR 1.04 (0.78, 1.39)			
At night hypoglycaemic episodes	3 studies (n=890), Low quality, 11 fewer per 1000 (56 fewer to 51 more)	1 study (n=259), Low quality, 94 fewer per 1000 (158 fewer to 8 more)	2 studies (n=601), Low quality, 16 fewer per 1000 (95 fewer to 63 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Severe hypoglycaemic episodes	7 studies (n=11424), Very low quality, 1 fewer per 1000 (6 fewer to 3 more)	11 studies (n=17877), Very low quality, 3 more per 1000 (2 fewer to 8 more)	13 studies (n=14184), Moderate quality, 5 fewer per 1000 (10 fewer to 0 more)	10 studies ,(n=4944), Moderate quality, 2 more per 1000 (1 fewer to 6 more)	7 studies (n=8609), Very low quality, 11 more per 1000 (1 fewer to 23 more)	4 studies (n=1748), Very low quality, 2 more per 1000 (4 fewer to 9 more)	3 studies (n=1399), Very low quality, 5 fewer per 1000 (20 fewer to 9 more)	11 studies (n=21414), Low quality, 2 fewer per 1000 (5 fewer to 0 more)	9 studies (n=3463), Very low quality, 0 more per 1000 (5 fewer to 6 more)	1 study (n=462), Low quality, 7 fewer per 1000 (19 fewer to 6 more)
HbA1c change	9 studies (n=12907), Low quality, MD 0.90% lower (1.08 lower to 0.73 lower)	13 studies (n=18502), Very low quality, MD 0.72% lower (0.82 lower to 0.63 lower) 1 study (n=30), Moderate	19 studies (n=13820), Very low quality, MD 0.88% lower (1.03 lower to	10 studies (n=4866), Low quality, MD 0.51% lower (0.63 lower to 0.40 lower)	7 studies (n=6899), Low quality, MD 1.04 % lower (1.26 lower to 0.82 lower)	3 studies (n=1675), High quality, MD 1.53% lower (1.65 lower to 1.42 lower)	8 studies (n=12824), Very low quality, MD 0.71% lower (0.87 lower to 0.54 lower)	12 studies (n=20714), Very low quality, MD 0.54% lower (0.62 lower to 0.45 lower)	14 studies (n=3785), Very low quality, MD 0.74% lower (0.99 lower to 0.49 lower)	3 studies (n=1589), High quality, MD 0.73% lower (0.81 lower to 0.64 lower)

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
		quality, MD 0.52 mmol/mol lower (0.86 lower to 0.17 lower)	0.72 lower) 1 study (n=49), Very low quality, MD 2.90 mmol/mol lower (8.09 lower to		2 studies (n=121), Very low quality, MD 14.67 mmol/mol lower (27.41 lower to 1.94 lower)	1 study (n=65), Moderate quality, MD 25.50 mmol/mol lower (26.02 lower to 24.98 lower)		1 study (n=66), Moderate quality, MD 5.49 mmol/mol lower (10.13 lower to 0.85 lower)		

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
			2.29 higher)							

Weight change	9 studies (n=12288), High quality, MD 1.44 kg lower (1.60 lower to 1.27 lower)	14 studies (n=18565), Very low quality, MD 1.58 kg lower (2.00 lower to 1.17 lower)	19 studies (n=1277 2), Very low quality, MD 2.02 kg lower (2.85 lower to 1.20 lower)	10 studies (n=4910), High quality, MD 0.74 lower (-1.02 lower to 0.46 lower)	9 studies (n=7022), Low quality, MD 3.59 kg lower (4.24 lower to 2.94 lower)	4 studies (n=1740), Very low quality, MD 6.55 kg lower (12.94 lower to 0.16 lower)	7 studies (n=12244), Very low quality, MD 2.16 kg lower (2.67 lower to 1.65 lower)1 study (n=595), Low quality, MD 2.93 % lower (3.89 lower to 1.97 lower)	13 studies (n=20546), Very low quality, MD 1.80 kg lower (2.12 lower to 1.49 lower)	14 studies (n=3866), Very low quality, MD 2.22 kg lower (2.62 lower to 1.81 lower)	2 studies (n=968), High quality, MD 1.94 kg lower (2.26 lower to 1.62 lower)

Outcomes for drugs compared to placebo	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
BMI change	3 studies (n=10111), High quality, MD 0.53 kg/m^2 lower (0.61 lower to 0.46 lower)	3 studies (n=239), Very low quality, MD 1.28 kg/m^2 lower (1.51 lower to 1.06 lower)	9 studies (n=4300), Very low quality, MD 1.08 kg/m2 lower (1.37 lower to 0.79 lower)	No outcomes identified	4 studies (n=2585), Low quality, MD 1.26 kg/m^2 lower (1.60 lower to 0.91 lower)	2 studies (n=1200), Very low quality, MD 0.83 kg/m^2 lower (6.76 lower to 5.10 higher)	No outcomes identified	2 studies (n=166), Very low quality, MD 0.45 kg/m^2 lower (2.85 lower to 1.94 higher)	2 studies (n=202), Moderate quality, MD 0.58 kg/m^2 lower (0.92 lower to 0.24 lower)	No outcomes identified

(a) Health-related quality of life outcomes for liraglutide compared to placebo: SF-36 physical functioning subscale, SF-36 vitality (energy/fatigue) subscale, SF-36 mental health (emotional wellbeing) subscale, IWQoL overall, MDQoL general health perception subscale, MDQoL treatment impact subscale, MDQoL current health perception subscale, MDQoL hypoglycaemia subscale, MDQoL treatment satisfaction subscale, MDQoL social or vocational worry subscale, MDQoL social stigma subscale, -36 physical role functioning (limitations) subscale, SF-36 emotional role functioning subscale, SF-36 general health subscale, MDQoL lifestyle flexibility subscale, MDQoL glycaemia control perception subscale, SF-36 bodily pain subscale, SF-36 social functioning subscale.

Table 20: A summary matrix showing the outcomes for adding individual drugs (biguanides, DPP-4 inhibitors, sulfonylureas and thiazolidinediones) compared to adding placebo for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone
Health-related quality of life	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	Overall (IWQOL) 1 study (n=183), Low quality, MD 0.30 higher (3.83 lower to 4.43 higher) Well being subscale (DMSAT)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone
					1 study (n=183), Low quality, MD 1.10 lower (9.37 lower to 7.17 higher)				

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone
All-cause mortality	2 studies (n=802) Very low quality, 12 more per 1000 (8 fewer to 32 more)	4 studies (n=1911), Very low quality, 2 more per 1000 (5 fewer to 10 more)	10 studies (n=10270) Very low quality, 2 fewer per 1000 (12 fewer to 8 more) 1 study (n=6979), High quality, HR 0.98 (0.84, 1.14)	7 studies (n=19289) Very low quality, 4 more per 1000 (2 fewer to 10 more) 1 study (n=16492) Very low quality, HR 1.11 (0.96, 1.28)	16 studies (n=6563), Very low quality, 1 fewer per 1000 (3 fewer to 2 more)	12 studies (n=3850) Very low quality, 1 fewer per 1000 (6 fewer to 3 more)	2 studies (n=300), Very low quality, 0 fewer per 1000 (18 fewer to 18 more)	1 study (n=180), Low quality, 0 fewer per 1000 (22 fewer to 22 more)	6 studies (n=2334), Very low quality, 2 fewer per 1000 (8 fewer to 5 more)

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone
Cardiovascular mortality	1 study (n=390) Very low quality, 10 more per 1000 (4 fewer to 141 more)	3 studies (n=1417), Very low quality, 2 more per 1000 (6 fewer to 10 more)	10 studies (n=10270) Very low quality, 2 more per 1000 (3 fewer to 6 more) 1 study (n=6979) High quality, HR 0.96 (0.81, 1.14)	5 studies (n=18519) Very low quality, 1 more per 1000 (4 fewer to 6 more) 1 study (n=16492) Low quality, HR 1.03 (0.87, 1.22)	11 studies (n=4392), Very low quality, 1 fewer per 1000 (5 fewer to 2 more)	8 studies (n=2275) Very low quality, 0 more per 1000 (6 fewer to 6 more)	2 studies (n=300),Very low quality, 0 fewer per 1000 (18 fewer to 18 more)	1 study (n=180), Low quality,0 fewer per 1000 (22 fewer to 22 more)	4 studies (n=1653), Very low quality, 0 more per 1000 (6 fewer to 6 more)

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone
3-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=16492) Low quality, 0 fewer per 1000 (8 fewer to 8 more) 1 study (n=16492) Low quality, HR 1.00 (0.89, 1.12	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	2 studies (n=1275), Very low quality, 8 more per 1000 (14 fewer to 89 more)

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone
4-item MACE	No outcomes identified	No outcomes identified	2 studies (n=7282) High quality, 1 more per 1000 (13 fewer to 18 more) 1 study (n=6980),	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone
			High quality, HR 1.00 (0.88, 1.14)						
5-item MACE	No outcomes identified	No outcomes identified	2 studies (n=1566)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone
			Very low quality, 9 more per 1000 (5 fewer to 23 more)						
Non-fatal stroke	No outcomes identified	No outcomes identified	4 studies (n=7794) Very low quality, 2 fewer per 1000 (8 fewer to 4 more) 1 study (n=6979), Moderate quality, HR 0.88 (0.63, 1.23)	2 studies (n=16983) Very low quality, 2 more per 1000 (2 fewer to 6 more) 1 study (n=16413), Very low quality, HR 1.11 (0.88, 1.40)	1 study (n=497) Very low quality, 4 fewer per 1000 (12 fewer to 4 more)	3 studies (n=1258) Very low quality, 5 fewer per 1000 (13 fewer to 2 more)	No outcomes identified	No outcomes identified	1 study (n=933), Very low quality, 1 more per 1000 (7 fewer to 10 more)

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone
Non-fatal myocardial infarction	No outcomes identified	1 study (n=494), Low quality, 8 more per 1000 (1 fewer to 16 more)	4 studies (n=7812) Very low quality, 6 more per 1000 (3 fewer to 14 more) 1 study (n=6979), Moderate quality, HR 1.15 (0.91, 1.45)	2 studies (n=16878) Very low quality, 2 fewer per 1000 (6 fewer to 4 more) 1 study (n=16413), Very low quality, HR 0.95 (0.80, 1.13)	3 studies (n=1391), Very low quality,1 fewer per 1000 (6 fewer to 4 more)	No outcomes identified	2 studies (n=300), Very low quality, 12 fewer per 1000 (19 fewer to 35 more)	No outcomes identified	2 studies (n=1141), Very low quality, 2 fewer per 1000 (8 fewer to 15 more)

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone
Unstable angina	No outcomes identified	No outcomes identified	3 studies (n=7491) Very low quality, 1 fewer per 1000 (6 fewer to 4 more) 1 study (n=6978), Low quality, HR 0.87 (0.57, 1.33)	1 study (n=16492) Very low quality, 2 more per 1000 (1 fewer to 6 more) 1 study (n=16492), Very low quality, HR 1.19 (0.89, 1.59)	2 studies (n=1138), Very low quality, 0 fewer per 1000 (5 fewer to 5 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone
Hospitalisation for heart failure	1 study (n=390) Very low quality, 5 fewer per 1000 (17 fewer to 47 more)	No outcomes identified	4 studies (n=7858) Very low quality, 5 fewer per 1000 (15 fewer to 5 more) 1 study (n=6978), Moderate quality, HR 0.90 (0.74, 1.09)	1 study (n=16413) Very low quality, 7 more per 1000 (2 more to 14 more) 1 study (n=16413) Very low quality, HR	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	2 studies (n=1232), Very low quality, 2 more per 1000 (4 fewer to 9 more)

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone
				1.27 (1.07, 1.51)					

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone
Acute kidney injury	No outcomes identified	No outcomes identified	1 study (n=6979), Moderate quality, 2 fewer per 1000 (8 fewer to 7 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified	1 study (n=6979), High quality, 17 fewer per 1000 (35 fewer to 3 more)	1 study (n=16492), Very low quality, 2 more per 1000 (2 fewer to 7 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=933), Very low quality, 17 fewer per 1000 (28 fewer to 9 more)

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone
			1 study (n=6979), Moderate quality, HR 0.86 (0.78, 0.95)	1 study (n=16492), Very low quality, HR 1.10 (0.89, 1.36)					

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone
Development of end stage kidney disease	No outcomes identified	No outcomes identified	2 studies (n=7284), Very low quality, 0 fewer per 1000 (6 fewer to 6 more)	1 study (n=16492), Very low quality, 1 fewer per 1000 (3 fewer to 2 more) 1 study (n=16492) Very low quality, HR 0.90 (0.61, 1.33)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone
Death from renal cause	No outcomes identified	No outcomes identified	1 study (n=6979) Low quality, 0 fewer per 1000 (1 fewer to 1 more)	1 study (n=16492) Very low quality, 1 more per 1000 (0 more to 2 more)	No outcomes identified	No outcomes identified	1 study (n=363), Low quality, 0 fewer per 1000 (13 fewer to 13 more)	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone
Cardiac arrhythmia	No outcomes identified	No outcomes identified	1 study (n=241), Low quality, 6 more per 1000 (6 fewer to 18 more)	1 study (n=315), Very low quality, 6 fewer per 1000 (18 fewer to 6 more)	No outcomes identified	No outcomes identified	No outcome identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone
Diabetic ketoacidosis	No outcomes identified	No outcomes identified	2 studies (n=478), High quality, 0 fewer per 1000 (12 fewer to 12 more)	No outcomes identified	1 study (n=467), Very low quality,3 fewer per 1000 (4 fewer to 30 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone
Falls requiring hospitalisation	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Progression of liver disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=278), Low quality, 0 fewer per 1000 (14 fewer to 14 more)	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone
Remission	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	4 studies (n=789) High quality, 21 more per 1000 (70 fewer to 125 more)	4 studies (n=1910), Very low quality, 9 more per 1000 (23 fewer to 51 more)	12 studies (n=12025) Very low quality, 4 more per 1000 (11 fewer to 20 more)	8 studies (n=19862) Very low quality, 2 more per 1000 (10 fewer to 15 more)	20 studies (n=7467), Very low quality, 18 more per 1000 (1 more to 35 more)	15 studies (n=5260) Very low quality, 4 more per 1000 (6 fewer to 15 more)	4 studies (n=1071),Very low quality, 172 more per 1000 (15 more to 641 more)	1 study (n=180), Moderate quality,65 more per 1000 (15 more to 115 more)	7 studies (n=1340), Very low quality, 198 more per 1000 (21 more to 529 more)

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Severe hypoglycaemic episodes	2 studies (n=562), Very low quality, 46 more per 1000 (21	3 studies (n=1417), Very low quality, 6 fewer per 1000 (17	12 studies (n=12025), Very low quality, 1 fewer per 1000 (6	6 studies (n=19040), Very low quality, 4 more per 1000 (0	16 studies (n=6253), Very low quality, 1 more per	13 studies (n=4482) Very low quality, 3 fewer per	4 studies (n=1272), Very low quality, 1 fewer per 1000 (9	1 study (n=180), Low quality, 1 fewer per 1000 (11	2 studies (n=1325), Very low quality, 7 more per

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone
	fewer to 704 more)	fewer to 6 more)	fewer to 4 more)	more to 7 more) 1 study (n=16492), Very low quality, HR 1.22 (0.82, 1.82)	1000 (5 fewer to 6 more)	1000 (8 fewer to 2 more)	fewer to 8 more)	fewer to 158 more)	1000 (1 more to 14 more)
HbA1c change	6 studies (n=1221), Very low quality, MD 0.47% lower (0.80 lower to 0.13 lower)	3 studies (n=1417), Very low quality, MD 0.53% lower (0.63 lower to 0.42 lower)	12 studies (n=11690), Low quality, MD 0.53 % lower (0.62 lower to 0.44 lower)	8 studies (n=19721), Very low quality, MD 0.50% lower (0.67 lower to 0.33 lower)	23 studies (n=7623), Very low quality, MD 0.71% lower (0.80 lower to 0.61 lower)	14 studies (n=4495), Very low quality, MD 0.69% lower (0.77 lower to 0.62 lower)	4 studies (n=694), Very low quality, MD 0.69% lower (1.10 lower to 0.29 lower)	1 study (n=61), Low quality, MD 0.90% lower (1.78 lower to 0.02 lower)	12 studies (n=2757), Very low quality, MD 0.70% lower (0.91 lower to 0.48 lower)

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone
Weight change	4 studies (n=781), Very low quality, MD 1.19 kg lower (3.92 lower to 1.54 higher)	4 studies (n=1910), High quality, MD 0.17 kg higher (0.09 lower to 0.43 higher)	10 studies (n=4463), Moderate quality, MD 0.10 kg higher (0.08 lower to 0.28 higher)	6 studies (n=18705), Very low quality, MD 0.21 kg higher (0.15 lower to 0.57 higher)	20 studies (n=6172), Low quality, MD 0.13 kg higher (0.13 lower to 0.39 higher)	7 studies (n=1943), Very low quality, MD 0.07 kg lower (0.89 lower to 1.04 higher)	2 studies (n=291), Very low quality, MD 0.24 kg lower (8.30 lower to 7.81 higher)	No outcomes identified	9 studies (n=2379), Very low quality, MD 3.55 kg higher (2.54 higher to 4.55 higher)

Outcomes for drugs compared to placebo	Metformin	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone
BMI change	No outcomes identified	No outcomes identified	No outcomes identified	4 studies (n=17882), Low quality, MD 0.02 kg/m^2 higher (0.06 lower to 0.10 higher)	3 studies (n=466), Very low quality, MD 1.50 kg/m^2 lower (2.35 lower to 0.66 lower)	No outcomes identified	1 study (n=159), Very low quality, MD 1.09 kg/m^2 higher (0.65 higher to 1.53 higher)	No outcomes identified	4 studies (n=1216), Very low quality, MD 1.03 kg/m^2 higher (0.42 higher to 1.65 higher)

1.1.7.4.2. Adding — Insulin combination therapy compared to placebo

Table 21: A summary matrix showing the outcomes for individual drugs compared to placebo for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to placebo	Insulin degludec/liraglutide
Health-related quality of life	No outcomes identified
All-cause mortality	1 study (n=434) Low quality, 3 more per 1000 (3 fewer to 10 more)
Cardiovascular mortality	No outcomes identified
3-item MACE	No outcomes identified
4-item MACE	No outcomes identified
5-item MACE	No outcomes identified
Non-fatal stroke	No outcomes identified
Non-fatal myocardial infarction	1 study (n=434), Low quality, 3 more per 1000 (3 fewer to 10 more)
Unstable angina	No outcomes identified
Hospitalisation for heart failure	No outcomes identified
Acute kidney injury	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified
Development of end stage kidney disease	No outcomes identified

Outcomes for drugs compared to placebo	Insulin degludec/liraglutide
Death from renal cause	No outcomes identified
Cardiac arrhythmia	No outcomes identified
Diabetic ketoacidosis	No outcomes identified
Falls requiring hospitalisation	No outcomes identified
Progression of liver disease	No outcomes identified
Remission	No outcomes identified
Hypoglycaemia episodes	1 study (n=434), High quality, 245 more per 1000 (113 more to 439 more)
At night hypoglycaemic episodes	1 study (n=434), Moderate quality, 50 more per 1000 (8 fewer to 164 more)
Severe hypoglycaemic episodes	1 study (n=434), Low quality, 7 more per 1000 (3 fewer to 17 more)
HbA1c change	1 study (n=435), Moderate quality, MD 1.02% lower (1.18 lower to 0.86 lower)
Weight change	1 study (n=435), Low quality, MD 1.48 kg higher (0.90 higher to 2.06 higher)
BMI change	No outcomes identified

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1.1.7.4.3. Adding — Monotherapy compared to metformin

Table 22: A summary matrix showing the outcomes for individual drugs compared to metformin for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to metformin	Linagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone
Health-related quality of life	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
All-cause mortality	1 study (n=50), Low quality, 0 fewer per 1000 (75 fewer to 75 more)	No outcomes identified	1 study (n=3062), Low quality, 0 fewer per 1000 (3 fewer to 3 more)	No outcomes identified	No outcomes identified	2 studies (n=702), Very low quality, 6 fewer per 1000 (17 fewer to 5 more)
Cardiovascular mortality	1 study (n=50), Low quality, 0 fewer per 1000 (75 fewer to 75 more)	No outcomes identified	1 study (n=3062), Low quality, 0 fewer per 1000 (3 fewer to 3 more)	No outcomes identified	No outcomes identified	No outcomes identified
3-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
4-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to metformin	Linagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone
Non-fatal stroke	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Unstable angina	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=63), Very low quality, 31 more per 1000 (29 fewer to 92 more)
Hospitalisation for heart failure	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=78), Very low quality, 0 fewer per 1000 (49 fewer to 49 more)
Acute kidney injury	No outcomes identified	No outcomes identified	1 study (n=914), Very low quality, 2 more per 1000 (2 fewer to 6 more)	No outcomes identified	No outcomes identified	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=63) Very low quality, 131 fewer per 1000 (180 fewer to 93 more)

Outcomes for drugs compared to metformin	Linagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone
Development of end stage kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Cardiac arrhythmia	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Diabetic ketoacidosis	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Falls requiring hospitalisation	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	1 study (n=309), Very low quality, 5 more per 1000 (5 fewer to 16 more)	1 study (n=27,502), Very low quality, 27 more per 1000 (10 fewer to 63 more)	2 studies (n=3976), Very low quality, 3 fewer per 1000 (6 fewer to 4 more)	1 study (n=67), Very low quality, 134 more per 1000 (86 fewer to 485 more)	No outcomes identified	2 studies (n=721), Very low quality, 40 fewer per 1000 (77 fewer to 13 more)

Outcomes for drugs compared to metformin	Linagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=67), Very low quality, 86 more per 1000 (43 fewer to 557 more)	No outcomes identified	No outcomes identified
Severe hypoglycaemic episodes	1 study (n=309), Low quality, 0 fewer per 1000 (13 fewer to 13 more)	No outcomes identified	No outcomes identified	1 study (n=67), Very low quality, 0 fewer per 1000 (56 fewer to 56 more	No outcomes identified	1 study (n=639), Low quality 0 fewer per 1000 (6 fewer to 6 more)
HbA1c change	2 studies (n=373), Moderate quality, MD 0.10% higher (0.08 higher to 0.12 higher)	2 studies (n=207), Very low quality, MD 0.33% lower (1.25 lower to 0.60 higher)	2 studies (n=3,899), Low quality, MD 0.14% lower (0.20 lower to 0.08 lower)	1 study (n=64), Very low quality, MD 0.05% higher (0.52 lower to 0.62 higher)	1 study (n=41), Very low quality, MD 0.50% higher (0.34 lower to 1.34 higher)	7 studies (n=1,050), Low quality, MD 0.10% higher (0.02 lower to 0.22 higher)
Weight change	1 study (n=48), Moderate quality, MD 2.60 higher (1.21 higher to 3.99 higher)	2 studies (n=207), Very low quality, MD 1.47 kg higher (0.53 lower to 3.47 higher)	1 study (n=2985), Low quality, MD 0.51 kg lower (0.77 lower to 0.25 lower)	No outcomes identified	1 study (n=41), Very low quality, MD 1.30 kg higher (1.35 lower to 3.95 higher)	3 studies (n=759), Very low quality, MD 2.47 kg higher (0.96 lower to 5.89 higher)
BMI change	No outcomes identified	2 studies (n=207), Very low quality, MD 0.41 kg/m^2 higher (0.02	No outcomes identified	No outcomes identified	No outcomes identified	3 studies (n=253), Very low quality, MD 0.80 kg/m^2

Outcomes for drugs compared to metformin	Linagliptin	Sitagliptin	Vildagliptin	Glimepiride	Glipizide	Pioglitazone
		higher to 0.80 higher)				higher (1.56 lower to 3.17 higher)

1.1.7.4.4. Adding — Combination therapy compared to metformin

Table 23: A summary matrix showing the outcomes for combinations of drugs compared to metformin for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to metformin	Glimepiride + metformin	Liraglutide + metformin	Pioglitazone + metformin
Health-related quality of life	No outcomes identified	No outcomes identified	No outcomes identified
All-cause mortality	No outcomes identified	No outcomes identified	No outcomes identified
Cardiovascular mortality	No outcomes identified	No outcomes identified	No outcomes identified
3-item MACE	No outcomes identified	No outcomes identified	No outcomes identified
4-item MACE	No outcomes identified	No outcomes identified	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal stroke	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to metformin	Glimepiride + metformin	Liraglutide + metformin	Pioglitazone + metformin
Unstable angina	No outcomes identified	No outcomes identified	No outcomes identified
Hospitalisation for heart failure	No outcomes identified	No outcomes identified	No outcomes identified
Acute kidney injury	No outcomes identified	No outcomes identified	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified	No outcomes identified
Development of end stage kidney disease	No outcomes identified	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified	No outcomes identified
Cardiac arrhythmia	No outcomes identified	No outcomes identified	No outcomes identified
Diabetic ketoacidosis	No outcomes identified	No outcomes identified	No outcomes identified
Falls requiring hospitalisation	No outcomes identified	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	1 study (n=65), Very low quality, 77 more per 1000 (131 fewer to 417 more)	No outcomes identified	1 study (n=81), Very low quality, 68 more per 1000 (83 fewer to 392 more)

Outcomes for drugs compared to metformin	Glimepiride + metformin	Liraglutide + metformin	Pioglitazone + metformin
At night hypoglycaemic episodes	1 study (n=65), Very low quality, 3 more per 1000 (70 fewer to 340 more)	No outcomes identified	No outcomes identified
Severe hypoglycaemic episodes	1 study (n=65), Very low quality, 0 fewer per 1000 (58 fewer to 58 more)	No outcomes identified	No outcomes identified
HbA1c change	1 study (n=64), Low quality, MD 0.66 % lower (1.11 lower to 0.21 lower)	1 study (n=85), Very low quality, MD 0.80% lower (1.13 lower to 0.47 lower)	1 study (n=76), Low quality, MD 0.38% lower (0.70 lower to 0.06 lower)
Weight change	No outcomes identified	No outcomes identified	No outcomes identified
BMI change	No outcomes identified	1 study (n=85), Low quality, MD 4.00 kg/m2 higher (1.92 higher to 6.08 higher)	No outcomes identified

1.1.7.4.5. Adding — Monotherapy compared to alogliptin

Table 24: A summary matrix showing the outcomes for individual drugs compared to alogliptin for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to alogliptin	Glipizide
Health-related quality of life	No outcomes identified

Outcomes for drugs compared to alogliptin	Glipizide
All-cause mortality	1 study (n=2620), Very low quality, 2 more per 1000 (2 fewer to 15 more)
Cardiovascular mortality	1 study (n=2620), Very low quality, 2 more per 1000 (1 fewer to 16 more)
3-item MACE	1 study (n=2620), Very low quality, 5 more per 1000 (2 fewer to 20 more)
4-item MACE	No outcomes identified
5-item MACE	No outcomes identified
Non-fatal stroke	1 study (n=2620), Very low quality, 1 more per 1000 (2 fewer to 12 more)
Non-fatal myocardial infarction	1 study (n=2620), Very low quality, 2 more per 1000 (2 fewer to 14 more)
Unstable angina	No outcomes identified
Hospitalisation for heart failure	No outcomes identified
Acute kidney injury	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified
Development of end stage kidney disease	No outcomes identified
Death from renal cause	No outcomes identified
Cardiac arrhythmia	No outcomes identified

Outcomes for drugs compared to alogliptin	Glipizide
Diabetic ketoacidosis	No outcomes identified
Falls requiring hospitalisation	No outcomes identified
Progression of liver disease	No outcomes identified
Remission	No outcomes identified
Hypoglycaemia episodes	1 study (n=2620), Low quality, 213 more per 1000 (144 more to 312 more)
At night hypoglycaemic episodes	No outcomes identified
Severe hypoglycaemic episodes	1 study (n=2620), Very low quality, 5 more per 1000 (0 more to 49 more)
HbA1c change	1 study (n=1089), Low quality, MD 0.11% higher (0.02 higher to 0.20 higher)
Weight change	No outcomes identified
BMI change	No outcomes identified

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1.1.7.4.6. Adding — Monotherapy compared to linagliptin

Table 25: A summary matrix showing the outcomes for individual drugs compared to linagliptin for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to linagliptin	Empagliflozin	Glimepiride
Health-related quality of life	No outcomes identified	No outcomes identified
All-cause mortality	1 study (n=106), Moderate quality, 0 fewer per 1000 (36 fewer to 36 more)	2 studies (n=7584), Moderate quality, 8 more per 1000 (4 fewer to 22 more) 1 study (n=6033), Moderate quality, HR 1.10 (0.94, 1.28)
Cardiovascular mortality	1 study (n=106), Moderate quality, 0 fewer per 1000 (36 fewer to 36 more)	2 studies (n=7584), High quality, 0 fewer per 1000 (8 fewer to 10 more) 1 study (n=6033), High quality, HR 1.00 (0.81, 1.23)
3-item MACE	No outcomes identified	No outcomes identified
4-item MACE	No outcomes identified	1 study (n=6033), High quality, 2 more per 1000 (15 fewer to 20 more) 1 study (n=6033), High quality, HR 1.01 (0.88, 1.16)
5-item MACE	No outcomes identified	No outcomes identified
Non-fatal stroke	No outcomes identified	2 studies (n=7584), Very low quality, 18 more per 1000 (10 fewer to 103 more)

Outcomes for drugs compared to linagliptin	Empagliflozin	Glimepiride
		1 study (n=6033), Moderate quality, HR 1.15 (0.87, 1.52)
Non-fatal myocardial infarction	No outcomes identified	1 study (n=1551), Low quality, 5 more per 1000 (3 fewer to 28 more) 1 study (n=287), Low quality, HR 0.99 (0.78, 1.26)
Unstable angina	No outcomes identified	2 studies (n=7584), Low quality, 1 fewer per 1000 (6 fewer to 6 more) 1 study (n=116), Low quality, HR 0.93 (0.65, 1.33)
Hospitalisation for heart failure	No outcomes identified	2 studies (n=7584), Moderate quality, 5 fewer per 1000 (11 fewer to 2 more) 1 study (n=204), Moderate quality, HR 0.83 (0.63, 1.09)
Acute kidney injury	No outcomes identified	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified
Development of end stage kidney disease	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified
Cardiac arrhythmia	No outcomes identified	No outcomes identified

Outcomes for drugs compared to linagliptin	Empagliflozin	Glimepiride
Diabetic ketoacidosis	1 study (n=106), Low quality, 19 more per 1000 (18 fewer to 56 more)	No outcomes identified
Falls requiring hospitalisation	No outcomes identified	1 study (n=1551), Low quality, 1 fewer per 1000 (3 fewer to 12 more)
Progression of liver disease	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	1 study (n=106), Low quality, 0 fewer per 1000 (65 fewer to 213 more)	2 studies (n=7584), Low quality, 303 more per 1000 (199 more to 443 more) 1 study (n=6033), High quality, HR 4.35 (3.85, 4.91)
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified
Severe hypoglycaemic episodes	1 study (n=106), Moderate quality, 0 fewer per 1000 (36 fewer to 36 more)	2 studies (n=7584), High quality, 17 more per 1000 (8 more to 35 more) 1 study (n=6033), High quality, HR 5.63 (4.76, 6.67)
HbA1c change	1 study (n=104), Moderate quality, MD 0.95% lower (1.41 lower to 0.49 lower)	2 studies (n=7552), Low quality, MD 0.09% lower (0.30 lower to 0.11 higher)
Weight change	1 study (n=104), Moderate quality, MD 1.70 kg lower (2.58 lower to 0.82 lower)	2 studies (n=7584), Very low quality, MD 2.10 kg higher (0.96 higher to 3.24 higher)
BMI change	No outcomes identified	No outcomes identified

1.1.7.4.7. Adding — Monotherapy and combination therapy compared to saxagliptin

Table 26: A summary matrix showing the outcomes for individual drugs and drug combinations compared to saxagliptin for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to saxagliptin	Vildagliptin	Liraglutide	Dapagliflozin	Glimepiride	Glipizide	Dapagliflozin + saxagliptin
Health-related quality of life	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
All-cause mortality	2 studies (n=202) Very low quality, 0 fewer per 1000 (27 fewer to 27 more)	No outcomes identified	2 studies (n=943), Very low quality, 4 more per 1000 (4 fewer to 13 more)	1 study (n=718), Very low quality, 0 fewer per 1000 (3 fewer to 42 more)	1 study (n=858), Low quality, 5 fewer per 1000 (16 fewer to 6 more)	2 studies (n=943), Very low quality, 2 more per 1000 (5 fewer to 9 more)
Cardiovascular mortality	2 studies (n=202), Very low quality, 0 fewer per 1000 (27 fewer to 27 more)	No outcomes identified	2 studies (n=943), Very low quality, 4 more per 1000 (4 fewer to 13 more)	1 study (n=718), Very low quality, 3 fewer per 1000 (8 fewer to 3 more)	1 study (n=858), Low quality, 2 more per 1000 (6 fewer to 10 more)	2 studies (n=943), High quality, 0 fewer per 1000 (6 fewer to 6 more)
3-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
4-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to saxagliptin	Vildagliptin	Liraglutide	Dapagliflozin	Glimepiride	Glipizide	Dapagliflozin + saxagliptin
5-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal stroke	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=379), Low quality, 5 more per 1000 (5 fewer to 16 more)	No outcomes identified	No outcomes identified
Unstable angina	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Hospitalisation for heart failure	1 study (n=73), Very low quality, 0 fewer per 1000 (52 fewer to 52 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Acute kidney injury	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified	1 study (n=355), Moderate quality, 0 fewer per 1000 (11 fewer to 11 more)	No outcomes identified	No outcomes identified	1 study (n=355), Moderate quality, 0 fewer per 1000 (11 fewer to 11 more)

Outcomes for drugs compared to saxagliptin	Vildagliptin	Liraglutide	Dapagliflozin	Glimepiride	Glipizide	Dapagliflozin + saxagliptin
Development of end stage kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Cardiac arrhythmia	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Diabetic ketoacidosis	No outcomes identified	No outcomes identified	1 study (n=588), High quality, 0 fewer per 1000 (7 fewer to 7 more)	No outcomes identified	No outcomes identified	1 study (n=588), High quality, 0 fewer per 1000 (7 fewer to 7 more)
Falls requiring hospitalisation	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	3 studies (n=319), Very low quality, 11 fewer per 1000 (42 fewer to 92 more)	1 study (n=121), Very low quality, 16 more per 1000 (35 fewer to 231 more)	2 studies (n=943), Low quality, 6 fewer per 1000 (10 fewer to 11 more)	2 studies (n=1097), Moderate quality, 223 more per	1 study (n=858), Low quality, 91 more per 1000 (64 more to 118 more)	2 studies (n=943), Low quality, 4 more per 1000 (7 fewer to 36 more)

Outcomes for drugs compared to saxagliptin	Vildagliptin	Liraglutide	Dapagliflozin	Glimepiride	Glipizide	Dapagliflozin + saxagliptin
				1000 (135 more to 353 more)		
At night hypoglycaemic episodes	1 study (n=73), Very low quality, 0 fewer per 1000 (52 fewer to 52 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Severe hypoglycaemic episodes	2 studies (n=190), Very low quality, 0 fewer per 1000 (29 fewer to 29 more)	1 study (n=121), Very low quality, 0 fewer per 1000 (32 fewer to 32 more)	2 studies (n=943), Very low quality, 2 fewer per 1000 (9 fewer to 5 more)	1 study (n=379), Low quality, 0 more per 1000 (5 fewer to 79 more)	No outcomes identified	2 studies (n=941), Very low quality, 2 more per 1000 (5 fewer to 9 more)
HbA1c change	3 studies (n=319), Low quality, MD 0.08% lower (0.20 lower to 0.04 higher)	1 study (n=121), Low quality, MD 0.27% lower (0.47 lower to 0.07 lower)	2 studies (n=862), Low quality, MD 0.12% lower (0.50 lower to 0.25 higher)	1 study (n=373), High quality, MD 0.06% lower (0.23 lower to 0.11 higher)	1 study (n=846), Low quality, MD 0.06% higher (0.05 lower to 0.17 higher)	2 studies (n=874), Very low quality, MD 0.75% lower (1.61 lower to 0.12 higher)
Weight change	1 study (n=117), Low quality, MD 0.10 kg higher (0.63 lower to 0.83 higher)	1 study (n=121), Low quality, MD 5.10 kg lower (6.01 lower to 4.19 lower)	1 study (n=297), Low quality, MD 2.40 kg lower (3.10 lower to 1.70 lower)	2 studies (n=947), Moderate quality, MD 1.70 kg higher (1.32 higher to 2.08 higher)	1 study (n=850), Very low quality, MD 2.80 kg higher (2.25 higher to 3.35 higher)	2 studies (n=876), High quality, MD 1.79 kg lower (2.22 lower to 1.36 lower)
BMI change	2 studies (n=190), Low quality, MD	1 study (n=121), Low quality, MD	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to saxagliptin	Vildagliptin	Liraglutide	Dapagliflozin	Glimepiride	Glipizide	Dapagliflozin + saxagliptin
	0.01 kg/m^2 lower (0.25 lower to 0.24 higher)	1.8 kg/m^2 lower (2.11 lower to 1.49 lower)				

1.1.7.4.8. Adding — Monotherapy and combination therapy compared to sitagliptin

Table 27: A summary matrix showing the outcomes for individual drugs (GLP-1 receptor agonists and SGLT-2 inhibitors) compared to sitagliptin for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to sitagliptin	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Health-related quality of life	No outcomes identified	Overall (EQ-5D Index) 1 study (n=268), Very Low quality, MD 0.01 lower (0.07 lower to 0.05 higher)	Mental component (SF-36) 1 study (n=2454), Low quality, MD 0.27 lower (0.85 lower to 0.31 higher) Physical component (SF36)	No outcomes identified	Mental component (SF-36 v2) 2 studies (n=2367), High quality, MD 0.05 higher (0.52 lower to 0.63 higher) Physical component (SF36 v2)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to sitagliptin	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
		Overall (IWQOL-Lite) 1 study (n=303), Moderate quality, MD 1.30 lower (4.35 lower to 1.75 higher)	1 study (n=2454), Low quality, MD 0.66 higher (0.11 higher to 1.21 higher)		2 studies (n=2367), High quality,, MD 0.09 higher (0.33 lower to 0.52 higher)				

Outcomes for drugs compared to sitagliptin	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
		Subscale well being (DMSAT) 1 study (n=303), Moderate quality, MD 8.20 higher (1.54 higher to 14.86 higher)							

Outcomes for drugs compared to sitagliptin	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
All-cause mortality	1 study (n=921), Very low quality, 5 fewer per 1000 (6 fewer to 12 more)	1 study (n=326), Very low quality, 6 fewer per 1000 (18 fewer to 6 more)	4 studies (n=4204), Low quality, 8 fewer per 1000 (16 fewer to 0 more) 1 study (n=2529), Low quality, HR 0.66 (0.41, 1.07)	1 study (n=319), Very low quality, 0 fewer per 1000 (12 fewer to 12 more)	4 studies (n=4457), Very low quality, 1 fewer per 1000 (6 fewer to 4 more)	2 studies (n=1856), Very low quality, 1 more per 1000 (3 fewer to 5 more)	1 study (n=613), High quality, 0 fewer per 1000 (6 fewer to 6 more)	No outcomes identified	1 study (n=745), Low quality, 2 more per 1000 (2 fewer to 6 more)
Cardiovascular mortality	1 study (n=921), Very low quality, 3 fewer per 1000 (9 fewer to 3 more)	1 study (n=326), Very low quality, 6 fewer per 1000 (18 fewer to 6 more)	3 studies (n=3540), Low quality, 6 fewer per 1000 (13 fewer to 1 more) 1 study (n=2529), Low quality, HR 0.44 (0.20, 0.95)	1 study (n=319), Very low quality,, 0 fewer per 1000 (12 fewer to 12 more)	4 studies (n=4457), Very low quality,, 1 fewer per 1000 (4 fewer to 3 more)	1 study (n=755), Very low quality, 0 fewer per 1000 (0 more to 0 more)	1 study (n=613), High quality, 0 fewer per 1000 (6 fewer to 6 more)	No outcomes identified	1 study (n=745), Low quality, 2 more per 1000 (2 fewer to 6 more)"

Outcomes for drugs compared to sitagliptin	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
3-item MACE	No outcomes identified	No outcomes identified	1 study (n=2515), Low quality, 16 fewer per 1000 (28 fewer to 0 more) 1 study (n=2515), Low quality, HR 0.70 (0.48, 1.02)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
4-item MACE	No outcomes identified	No outcomes identified	1 study (n=2530), Very low quality, 19 fewer per 1000 (31 fewer to 2 fewer)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to sitagliptin	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Non-fatal stroke	No outcomes identified	No outcomes identified	1 study (n=367), Low quality, 5 fewer per 1000 (16 fewer to 5 more)	No outcomes identified	1 study (n=1861), Low quality, 4 more per 1000 (2 fewer to 10 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified	1 study (n=303), Moderate quality, 0 fewer per 1000 (14 fewer to 14 more)	1 study (n=13919), Low quality, 26 fewer per 1000 (77 fewer to 25 more)	No outcomes identified	1 study (n=1861), Low quality, 1 fewer per 1000 (8 fewer to 5 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Unstable angina	No outcomes identified	1 study (n=326), Low quality, 0 fewer per 1000 (12 fewer to 12 more)	1 study (n=2530), Very low quality, 6 fewer per 1000 (10 fewer to 2 more)	No outcomes identified	1 study (n=1861), Low quality, 2 more per 1000 (3 fewer to 8 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to sitagliptin	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Hospitalisation for heart failure	No outcomes identified	No outcomes identified	1 study (n=2515), Low quality, 13 fewer per 1000 (18 fewer to 3 fewer) 1 study (n=2515), Low quality, HR 0.47 (0.25, 0.88)	No outcomes identified	2 studies (n=2364), Very low quality, 3 fewer per 1000 (9 fewer to 4 more)	No outcomes identified	1 study (n=52, Very low quality, 0 fewer per 1000 (72 fewer to 72 more)	No outcomes identified	No outcomes identified
Acute kidney injury	No outcomes identified	1 study (n=326), Low quality, 0 fewer per 1000 (12 fewer to 12 more)	No outcomes identified	No outcomes identified	2 studies (n=2364), Very low quality, 2 more per 1000 (4 fewer to 9 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Persistent signs of worsening	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to sitagliptin	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
kidney disease									
Development of end stage kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=1861), Low quality, 1 more per 1000 (1 fewer to 2 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Cardiac arrhythmia	No outcomes identified	No outcomes identified	1 study (n=367), Low quality, 5 fewer per 1000 (16 fewer to 5 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to sitagliptin	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Diabetic ketoacidosis	No outcomes identified	No outcomes identified	1 study (n=367), Low quality, 5 more per 1000 (5 fewer to 16 more)	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=60, Very low quality, 0 fewer per 1000 (63 fewer to 63 more)	No outcomes identified	1 study (n=745), High quality, 0 fewer per 1000 (6 fewer to 6 more)
Falls requiring hospitalisation	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	No outcomes identified	2 studies (n=629), Very low quality, 15 fewer per 1000 (33	7 studies (n=4387), Very low quality, 30 fewer per 1000 (92	1 study (n=319), Very low quality, 12 fewer per 1000 (18	3 studies (n=3954), High quality, 1 fewer per 1000 (18	2 studies (n=1856), Very low quality, 51 more per 1000 (44	2 studies (n=665), Low quality, 3 fewer per 1000 (30	No outcomes identified	1 study (n=745), Very low quality, 2 more per 1000 (16

Outcomes for drugs compared to sitagliptin	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
		fewer to 3 more)	fewer to 72 more)	fewer to 42 more)	fewer to 20 more)	fewer to 196 more)	fewer to 46 more)		fewer to 45 more)
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified	1 study (n=367), High quality, 0 fewer per 1000 (11 fewer to 11 more)	No outcomes identified	2 studies (n=2364), Low quality, 2 more per 1000 (5 fewer to 18 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Severe hypoglycaemic episodes	1 study (n=921), Low quality, 0 fewer per 1000 (5 fewer to 5 more)	2 studies (n=629), Moderate quality, 0 fewer per 1000 (9 fewer to 9 more)	6 studies (n=69777), Very low quality, 2 more per 1000 (3 fewer to 6 more)	1 study (n=319), Very low quality,, 0 fewer per 1000 (12 fewer to 12 more)	3 studies (n=3589), Moderate quality, 5 fewer per 1000 (11 fewer to 0 more)	2 studies (n=1856), Very low quality, 2 more per 1000 (9 fewer to 23 more)	2 studies (n=665), Very low quality, 3 more per 1000 (10 fewer to 16 more)	No outcomes identified	1 study (n=745), Very low quality, 4 more per 1000 (2 fewer to 10 more)
HbA1c change	1 study (n=921), Low quality, MD 0.53 % lower (0.68	2 studies (n=629), Moderate quality, MD 0.44 lower (0.74 lower	8 studies (n=2419), Very low quality, MD 0.33% lower (0.56	1 study (n=319), Low quality, MD 0.00% lower (0.28 lower to	4 studies (n=4460), Very low quality, MD 0.39% lower (0.61	2 studies (n=1834), Very low quality, MD 0.22% lower (0.51	3 studies (n=723), High quality, MD 0.05% higher	1 study (n=44), Low quality, MD 1.70 mmol/mol lower (3.20	1 study (n=745), Low quality, MD 0.10% lower (0.28

Outcomes for drugs compared to sitagliptin	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
	lower to 0.38 lower)	to 0.14 lower)"	lower to 0.10 lower)	0.28 higher)	lower to 0.17 lower)	lower to 0.07 higher)	(0.21 lower to 0.31 higher)	lower to 0.20 lower)	lower to 0.08 higher)
Weight change	1 study (n=921), Low quality, MD 0.89 kg lower (1.49 lower to 0.29 lower)	2 studies (n=629), Low quality, MD 0.69 kg lower (2.26 lower to 0.88 higher)	6 studies(n=1761), Very low quality, MD 2.10 kg lower (2.65 lower to 1.55 lower)	1 study (n=312), Very low quality, MD 1.30 kg lower (2.10 lower to 0.50 lower)	4 studies (n=4460), Very low quality, MD 2.03 kg lower (2.77 lower to 1.30 lower)	2 studies (n=1835), Moderate quality, MD 2.31 kg lower (2.77 lower to 1.86 lower)	1 study (n=60, Very low quality, MD 1.59 kg lower (2.70 lower to 0.48 lower)	1 study (n=44, Very low quality, MD 0.30 higher (4.26 lower to 4.86 higher)	1 study (n=745), Very low quality, MD 2.70 kg lower (3.41 lower to 1.99 lower)
BMI change	No outcomes identified	No outcomes identified	4 studies(n=556), Very low quality, MD 0.68 kg/m2 lower (1.01 lower to 0.35 lower)	No outcomes identified	4 studies (n=4460), Very low quality, MD 0.75 kg/m^2 lower (1.02 lower to 0.49 lower)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

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Table 28: A summary matrix showing the outcomes for individual drugs (sulfonylureas and pioglitazone) and drug combinations compared to sitagliptin for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to sitagliptin	Glimepiride	Glipizide	Pioglitazone	Dapagliflozin + saxagliptin	Ertugliflozin + sitagliptin
Health-related quality of life	Mental component (SF-36) 1 study (n=2458), Low quality, MD 0.06 higher (0.52 lower to 0.64 higher) Physical component (SF-36) 1 study (n=2458), Low quality, MD 0.23 lower (0.78 lower to 0.32 higher)	No outcomes identified	Overall – EQ-5D 1 study (n=269), Very low quality, MD 0.03 lower (0.09 lower to 0.03 higher)	No outcomes identified	No outcomes identified

Outcomes for drugs compared to sitagliptin	Glimepiride	Glipizide	Pioglitazone	Dapagliflozin + saxagliptin	Ertugliflozin + sitagliptin

Outcomes for drugs compared to sitagliptin	Glimepiride	Glipizide	Pioglitazone	Dapagliflozin + saxagliptin	Ertugliflozin + sitagliptin

Outcomes for drugs compared to sitagliptin	Glimepiride	Glipizide	Pioglitazone	Dapagliflozin + saxagliptin	Ertugliflozin + sitagliptin
All-cause mortality	2 studies (n=3556), Very low quality, 2 more per 1000 (7 fewer to 15 more) 1 study (n=2521), Low quality, HR 0.86 (0.61, 1.21)	1 study (n=1172), Very low quality, 12 more per 1000 (0 more to 107 more)	1 study (n=331), Very low quality, 6 fewer per 1000 (18 fewer to 6 more)	1 study (n=461), Low quality, 0 fewer per 1000 (8 fewer to 8 more)	1 study (n=734), Low quality, 2 more per 1000 (2 fewer to 6 more)
Cardiovascular mortality	2 studies (n=3541), Very low quality, 2 fewer per 1000 (7 fewer to 6 more) 1 study (n=2509), Very low quality, HR 0.77 (0.40, 1.48)	1 study (n=1172), Very low quality, 5 more per 1000 (1 fewer to 11 more)	No outcomes identified	1 study (n=461), Low quality, 0 fewer per 1000 (8 fewer to 8 more)	1 study (n=734), High quality, 0 fewer per 1000 (6 fewer to 6 more)
3-item MACE	1 study (n=2506), Low quality, 7 fewer per 1000 (21 fewer to 12 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to sitagliptin	Glimepiride	Glipizide	Pioglitazone	Dapagliflozin + saxagliptin	Ertugliflozin + sitagliptin
	1 study (n=2511), Low quality, HR 0.86 (0.61, 1.21)				
4-item MACE	1 study (n=2522), Very low quality, 8 fewer per 1000 (23 fewer to 12 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal stroke	1 study (n=41),Very low quality, 0 fewer per 1000 (92 fewer to 92 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal myocardial infarction	1 study (n=41), Very low quality, 0 fewer per 1000 (92 fewer to 92 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Unstable angina	1 study (n=2522), Very low quality, 2 fewer per 1000 (7 fewer to 9 more)	No outcomes identified	1 study (n=331), Very low quality, 6 more per 1000 (6 fewer to 18 more)	No outcomes identified	No outcomes identified
Hospitalisation for heart failure	2 studies (n=2547), Very low quality, 0	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to sitagliptin	Glimepiride	Glipizide	Pioglitazone	Dapagliflozin + saxagliptin	Ertugliflozin + sitagliptin
	more per 1000 (12 fewer to 12 more) 1 study (n=2511), Very low quality, HR 1.01 (0.61, 1.67)				
Acute kidney injury	No outcomes identified	No outcomes identified	1 study (n=331), Very low quality, 6 more per 1000 (6 fewer to 18 more)	1 study (n=461), Very low quality, 4 more per 1000 (4 fewer to 13 more)	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Development of end stage kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Cardiac arrhythmia	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=461), Very low quality, 18 fewer per 1000 (38 fewer to 3 more)	No outcomes identified
Diabetic ketoacidosis	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=734), Low quality, 2 more per

Outcomes for drugs compared to sitagliptin	Glimepiride	Glipizide	Pioglitazone	Dapagliflozin + saxagliptin	Ertugliflozin + sitagliptin
					1000 (2 fewer to 6 more)
Falls requiring hospitalisation	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	4 studies (n=4339), Very low quality, 317 more per 1000 (125 more to 638 more) 1 study (n=2484), Low quality, HR 2.56 (2.32, 2.82)	1 study (n=1172), Low quality, 714 more per 1000 (490 more to 1031 more) 1 study (n=1172), Low quality, HR 20 (11.11, 33.33)	3 studies (n=581), Very low quality,, 17 fewer per 1000 (33 fewer to 20 more)	1 study (n=461), Very low quality, 12 more per 1000 (17 fewer to 81 more)	1 study (n=734), Very low quality, 17 more per 1000 (9 fewer to 76 more)
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Severe hypoglycaemic episodes	4 studies (n=4584), Very low quality, 10 more per 1000 (3 more to 24 more)	1 study (n=1172), Low quality, 34 more per 1000 (5 more to 156 more)	3 studies (n=581), Low quality, 0 fewer per 1000 (12 fewer to 12 more)	1 study (n=461), Low quality, 0 fewer per 1000 (8 fewer to 8 more)	1 study (n=734), Low quality, 0 fewer per 1000 (6 fewer to 6 more)

Outcomes for drugs compared to sitagliptin	Glimepiride	Glipizide	Pioglitazone	Dapagliflozin + saxagliptin	Ertugliflozin + sitagliptin
		1 study, Low quality, HR 12.5 (2.13, 100)			
HbA1c change	4 studies (n=2071), Very low quality, MD 0.18% higher (0.17 lower to 0.52 higher)	1 study (n=1135), Low quality, 0.02% lower (0.14 lower to 0.10 higher)	4 studies (n=787), Very low quality, MD 0.12% lower (0.37 lower to 0.14 higher)	1 study (n=461), Very low quality, MD 0.48% lower (0.72 lower to 0.24 lower)	1 study (n=734), Very low quality, MD 0.60% lower (0.77 lower to 0.43 lower)
Weight change	3 studies (n=1491), Very low quality, MD 1.52 kg higher (0.48 higher to 2.56 higher)	1 study (n=1135), Very low quality, MD 2.30 kg higher (1.38 higher to 3.22 higher)	4 studies (n=787), Very low quality, MD 1.62 kg higher (1.52 higher to 1.73 higher)	1 study (n=461), Low quality, MD 1.50 kg lower (2.33 lower to 0.67 lower)	1 study (n=734), Very low quality, MD 2.50 kg lower (3.23 lower to 1.77 lower)
BMI change	1 study (n=418), Low quality, MD 0.39 kg/m^2higher (0.15 higher to 0.63 higher)	No outcomes identified	1 study (n=222), Low quality, MD 3.50 kg/m^2 higher (2.62 higher to 4.38 higher)	No outcomes identified	No outcomes identified

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1.1.7.4.9. Adding — Monotherapy compared to vildagliptin

Table 29: A summary matrix showing the outcomes for individual drugs compared to vildagliptin for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to vildagliptin	Liraglutide	Empagliflozin	Gliclazide	Glimepiride	Pioglitazone
Health-related quality of life	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
All-cause mortality	No outcomes identified	No outcomes identified	2 studies (n=1045), Very low quality,1 more per 1000 (1 fewer to 22 more)	2 studies (n=5871), Very low quality, 0 more per 1000 (2 fewer to 5 more)	No outcomes identified
Cardiovascular mortality	No outcomes identified	No outcomes identified	1 study (n=42), Very low quality, 48 more per 1000 (43 fewer to 139 more)	1 study (n=2772), Very low quality, 1 fewer per 1000 (1 fewer to 7 more)	No outcomes identified
3-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
4-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to vildagliptin	Liraglutide	Empagliflozin	Gliclazide	Glimepiride	Pioglitazone
Non-fatal stroke	No outcomes identified	No outcomes identified	1 study (n=42), Very low quality, 48 fewer per 1000 (139 fewer to 43 more)	No outcomes identified	1 study (n=575), Low quality, 4 more per 1000 (3 fewer to 75 more)
Non-fatal myocardial infarction	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Unstable angina	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Hospitalisation for heart failure	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Acute kidney injury	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Development of end stage kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to vildagliptin	Liraglutide	Empagliflozin	Gliclazide	Glimepiride	Pioglitazone
Cardiac arrhythmia	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=2772), Very low quality, 1 more per 1000 (1 fewer to 13 more)	No outcomes identified
Diabetic ketoacidosis	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Falls requiring hospitalisation	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	1 study (n=118), Very low quality, 22 fewer per 1000 (69 fewer to 144 more)	No outcomes identified	1 study (n=42), Low quality, 238 more per 1000 (17 fewer to 1326 more)	2 studies (n=5871), Moderate quality, 153 more per 1000 (112 more to 205 more)	1 study (n=575), Low quality, 0 more per 1000 (3 fewer to 53 more)
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Severe hypoglycaemic episodes	1 study (n=118), Very low quality, 0 fewer	No outcomes identified	1 study (n=42), Very low quality, 0 fewer	2 studies (n=3143), Low quality, 10 more	1 study (n=575), High quality, 0 fewer per

Outcomes for drugs compared to vildagliptin	Liraglutide	Empagliflozin	Gliclazide	Glimepiride	Pioglitazone
	per 1000 (33 fewer to 33 more)		per 1000 (88 fewer to 88 more)	per 1000 (4 more to 15 more)	1000 (7 fewer to 7 more)
HbA1c change	1 study (n=118), Low quality, MD 0.25% lower (0.45 lower to 0.05 lower)	1 study (n=107), Very low quality, MD 0.15% lower (0.61 lower to 0.31 higher)	2 studies (n=821), Low quality, MD 0.07% lower (0.23 lower to 0.09 higher)	4 studies (n=5505), Low quality, MD 0.13% lower (0.21 lower to 0.05 lower)	1 study (n=576), High quality, MD 0.00% lower (0.18 lower to 0.18 higher)
Weight change	1 study (n=118), Low quality, MD 5.20kg lower (6.08 lower to 4.32 lower)	1 study (n=107), Low quality, MD 0.12 kg lower (1.44 lower to 1.20 higher)	2 studies (n=1044) Low quality, MD 1.22 kg higher (0.47 higher to 1.97 higher)	3 studies (n=3315), Low quality, MD 1.50 kg higher (1.23 higher to 1.78 higher)	1 study (n=576), Moderate quality, MD 2.40 kg higher (1.69 higher to 3.11 higher)
BMI change	1 study (n=118), Low quality, MD 1.8 kg/m^2 lower (2.09 lower to 1.51 lower)	No outcomes identified	No outcomes identified	1 study (n=153), Very low quality, MD 0.60 kg/m^2 higher (0.13 higher to 1.07 higher)	No outcomes identified

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1.1.7.4.10. Adding — Monotherapy compared to dulaglutide

Table 30: Summary table for individual drugs compared to dulaglutide for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to dulaglutide	Liraglutide	Semaglutide	Tirzepatide
Health-related quality of life	No outcomes identified	Subscale mental (SF-36 v2), 1 study (n=458). Low quality, MD 0.26 higher (0.86 lower to 1.38 higher) Subscale physical (SF-36 v2), 1 study (n=458), Low quality, MD 0.12 lower (0.88 lower to 0.64 higher)	No outcomes identified
All-cause mortality	1 study (n=599), High quality, 0 fewer per 1000 (7 fewer to 7 more)	2 studies (n=1657), Very low quality, 3 fewer per 1000 (10 fewer to 5 more)	1 study (n=265), Moderate quality, 0 fewer per 1000 (26 fewer to 26 more)
Cardiovascular mortality	1 study (n=599), High quality, 0 fewer per 1000 (7 fewer to 7 more)	2 studies (n=1657) Very low quality, 1 fewer per 1000 (7 fewer to 4 more)	No outcomes identified
3-item MACE	No outcomes identified	No outcomes identified	No outcomes identified
4-item MACE	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to dulaglutide	Liraglutide	Semaglutide	Tirzepatide
5-item MACE	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal stroke	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified	No outcomes identified	No outcomes identified
Unstable angina	No outcomes identified	No outcomes identified	No outcomes identified
Hospitalisation for heart failure	No outcomes identified	No outcomes identified	No outcomes identified
Acute kidney injury	No outcomes identified	1 study (n=458), High quality, 0 fewer per 1000 (21 fewer to 21 more)	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified	No outcomes identified
Development of end stage kidney disease	No outcomes identified	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	1 study (n=458), High quality, 0 fewer per 1000 (21 fewer to 21 more)	No outcomes identified
Cardiac arrhythmia	No outcomes identified	No outcomes identified	No outcomes identified
Diabetic ketoacidosis	No outcomes identified	No outcomes identified	No outcomes identified
Falls requiring hospitalisation	1 study (n=599), Low quality, 3 more per 1000 (3 fewer to 10 more)	No outcomes identified	No outcomes identified

Outcomes for drugs compared to dulaglutide	Liraglutide	Semaglutide	Tirzepatide
Progression of liver disease	No outcomes identified	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	1 study (n=599), Moderate quality, 30 more per 1000 (8 fewer to 100 more)	2 studies (n=490), Very low quality, 26 fewer per 1000 (118 fewer to 67 more)	1 study (n=265), Low quality, 29 more per 1000 (21 fewer to 246 more)
At night hypoglycaemic episodes	1 study (n=599), Low quality, 7 fewer per 1000 (16 fewer to 27 more)	No outcomes identified	No outcomes identified
Severe hypoglycaemic episodes	1 study (n=599), High quality, 0 fewer per 1000 (7 fewer to 7 more)	2 studies (n=1657), Very low quality, 5 fewer per 1000 (15 fewer to 5 more)	No outcomes identified
HbA1c change	1 study (n=599), High quality, MD 0.06% lower (0.20 lower to 0.08 higher)	3 studies (n=1689), Very low quality, MD 0.25% lower (0.56 lower to 0.06 higher)	1 study (n=265), Moderate quality, MD 0.68% lower (0.86 lower to 0.50 lower)
Weight change	1 study (n=599), High quality, MD 0.71 kg higher (0.16 higher to 1.26 higher)	3 studies (n=1689), Low quality, MD 2.45 kg lower (3.26 lower to 1.64 lower)	1 study (n=265), Moderate quality, MD 2.07 kg lower (3.96 lower to 0.18 lower)
BMI change	No outcomes identified	2 studies (n=1657), Very low quality, MD 0.74 kg/m^2 lower (1.05 lower to 0.43 lower)	1 study (n=265), Moderate quality, MD 1.30 kg/m^2 lower (1.93 lower to 0.67 lower)

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1.1.7.4.11. Adding — Monotherapy and combination therapy compared to exenatide

Table 31: Summary table for individual drugs and drug combinations compared to exenatide for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to exenatide	Dulaglutide	Lixisenatide	Semaglutide	Dapagliflozin	Glimepiride	Pioglitazone	Dapagliflozin + exenatide
Health-related quality of life	No outcomes identified	No outcomes identified	Subscale mental component (SF-36) 1 study (n=809), Low quality, MD 0.16 higher (1.14 lower to 1.46 higher) Subscale physical component (SF-36) 1 study (n=809), Low quality, MD 0.46 higher (0.64 lower to 1.56 higher)	No outcomes identified	No outcomes identified	Overall EQ-5D 1 study (n=259), Very low quality, MD 0.02 lower (0.08 lower to 0.04 higher)	No outcomes identified

Outcomes for drugs compared to exenatide	Dulaglutide	Lixisenatide	Semaglutide	Dapagliflozin	Glimepiride	Pioglitazone	Dapagliflozin + exenatide
All-cause mortality	1 study (n=835), Very low quality, 0 fewer per 1000 (0 more to 0 more)	1 study (n=634), Low quality, 0 fewer per 1,000 (9 fewer to 9 more)	1 study (n=809) Very low quality, 5 fewer per 1000 (12 fewer to 2 more)	1 study (n=463), Very low quality, 4 more per 1000 (10 fewer to 19 more)	1 study (n=1019), Low quality, 0 more per 1000 (7 fewer to 24 more)	1 study (n=325), Very low quality, 0 fewer per 1000 (12 fewer to 12 more)	1 study (n=461), Very low quality, 9 more per 1000 (8 fewer to 26 more)
Cardiovascular mortality	1 study (n=835), Very low quality, 4 more per 1000 (1 fewer to 9 more)	No outcomes identified	No outcomes identified	1 study (n=463), Very low quality, 0 fewer per 1000 (12 fewer to 12 more)	No outcomes identified	1 study (n=325) Very low quality, 0 fewer per 1000 (12 fewer to 12 more)	1 study (n=461), Very low quality, 0 fewer per 1000 (12 fewer to 12 more)
3-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
4-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal stroke	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to exenatide	Dulaglutide	Lixisenatide	Semaglutide	Dapagliflozin	Glimepiride	Pioglitazone	Dapagliflozin + exenatide
Non-fatal myocardial infarction	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Unstable angina	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=325), Very low quality, 6 more per 1000 (6 fewer to 18 more)	No outcomes identified
Hospitalisation for heart failure	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Acute kidney injury	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=463), Very low quality, 4 more per 1000 (15 fewer to 23 more)	No outcomes identified	1 study (n=325), Very low quality, 6 more per 1000 (6 fewer to 18 more)	1 study (n=461), Very low quality, 9 fewer per 1000 (21 fewer to 3 more)
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to exenatide	Dulaglutide	Lixisenatide	Semaglutide	Dapagliflozin	Glimepiride	Pioglitazone	Dapagliflozin + exenatide
Development of end stage kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Cardiac arrhythmia	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Diabetic ketoacidosis	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Falls requiring hospitalisation	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	1 study (n=835), Low quality, 54 fewer per 1000 (86 fewer to 8 fewer)	1 study (n=634), High quality, 0 fewer per 1000 (0 more to 0 more)	No outcomes identified	1 study (n=463), Very low quality, 4 more per 1000 (4 fewer to 13 more)	2 studies (n=1130), High quality, 276 more per 1000 (202 more to 360 more)	1 study (n=325), Very low quality, 6 fewer per 1000 (27 fewer to 14 more)	1 study (n=461), Very low quality, 17 more per 1000 (1 more to 34 more)

Outcomes for drugs compared to exenatide	Dulaglutide	Lixisenatide	Semaglutide	Dapagliflozin	Glimepiride	Pioglitazone	Dapagliflozin + exenatide
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=1019), Moderate quality, 58 more per 1000 (13 more to 119 more)	No outcomes identified	No outcomes identified
Severe hypoglycaemic episodes	1 study (n=835), Low quality, 7 fewer per 1000 (17 fewer to 3 more)	1 study (n=634), High quality, 0 fewer per 1000 (6 fewer to 6 more)	1 study (n=809), Very low quality, 0 more per 1000 (30 fewer to 48 more)	1 study (n=463), Low quality, 0 fewer per 1000 (8 fewer to 8 more)	1 study (n=1019), Low quality, 2 fewer per 1000 (6 fewer to 2 more)	1 study (n=325), Very low quality, 0 fewer per 1000 (12 fewer to 12 more)	1 study (n=461), Low quality, 0 fewer per 1000 (8 fewer to 8 more)
HbA1c change	1 study (n=835), Moderate quality, MD 0.13% lower (0.32 lower to 0.06 higher)	1 study (n=630), High quality, MD 0.17% higher (0.03 higher to 0.31 higher)	1 study (n=809), Very low quality, MD 0.60% lower (0.77 lower to 0.43 lower)	1 study (n=457), Very low quality, MD 0.23% higher (0.10 lower to 0.56 higher)	2 studies (n=480), Low quality, MD 0.03% higher (0.04 lower to 0.10 higher)	1 study (n=325), Low quality, MD 0.30% higher (0.05 higher to 0.55 higher)	1 study (n=455), Very low quality, MD 0.41% lower (0.73 lower to 0.09 lower)
Weight change	1 study (n=835), Moderate quality, MD	1 study (n=630), High quality, MD 1.02 kg higher	1 study (n=809), Low quality, MD 3.70 kg lower	1 study (n=457), Very low quality, MD 2.22 kg lower	2 studies (n=1120), Low quality, MD 4.03 kg lower	1 study (n=325) Moderate quality, MD 5.10 kg higher	1 study (n=455), Very low quality, MD 1.71 kg lower

Outcomes for drugs compared to exenatide	Dulaglutide	Lixisenatide	Semaglutide	Dapagliflozin	Glimepiride	Pioglitazone	Dapagliflozin + exenatide
	0.52 kg higher (0.18 lower to 1.22 higher)	(0.46 higher to 1.58 higher)	(4.50 lower to 2.90 lower)	(3.55 lower to 0.89 lower)	(4.61 lower to 3.45 lower)	(4.26 higher to 5.94 higher)	(2.96 lower to 0.46 lower)
BMI change	No outcomes identified	No outcomes identified	1 study (n=809), Low quality, MD 1.40 kg/m^2 lower (1.68 lower to 1.12 lower)	No outcomes identified	2 studies (n=1120), High quality, MD 1.79 kg/m^2 higher (1.53 higher to 2.04 higher)	No outcomes identified	No outcomes identified

1.1.7.4.12. Adding — Monotherapy and non-insulin combination therapy compared to liraglutide

Table 32: Summary table for individual drugs and insulin drug combinations compared to liraglutide for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to liraglutide	Exenatide	Lixisenatide	Semaglutide	Dapagliflozin	Empagliflozin	Glimepiride	Empagliflozin + liraglutide
Health-related quality of life	No outcomes identified	No outcomes identified	Subscale mental component (SF-36 v2)	No outcomes identified	No outcomes identified	Subscale mental component (SF-36)	No outcomes identified

Outcomes for drugs compared to liraglutide	Exenatide	Lixisenatide	Semaglutide	Dapagliflozin	Empagliflozin	Glimepiride	Empagliflozin + liraglutide
			1 study (n=577), Low quality, MD 1.00 higher (0.11 lower to 2.11 higher) Subscale physical component (SF-36 v2) 1 study (n=577), Low quality, MD 0.70 higher (0.41 lower to 1.81 higher)			1 study (n=2440), Low quality, MD 0.33 higher (0.25 lower to 0.91 higher) Subscale physical component (SF-36) 1 study (n=2440), Low quality, MD 0.89 lower (1.44 lower to 0.34 lower)	
All-cause mortality	1 study (n=911), Very low quality, 0 fewer per 1000 (9 fewer to 8 more)	No outcomes identified	2 studies (n=1146), Very low quality, 2 fewer per 1000 (11 fewer to 8 more)	1 study (n=156), Very low quality, 0 fewer per 1000 (25 fewer to 25 more)	No outcomes identified	1 study (n=2516), Low quality, 13 more per 1000 (0 more to 34 more) 1 study (n=2516), Low	No outcomes identified

Outcomes for drugs compared to liraglutide	Exenatide	Lixisenatide	Semaglutide	Dapagliflozin	Empagliflozin	Glimepiride	Empagliflozin + liraglutide
						quality, HR 1.61 (1.00, 2.59)	
Cardiovascular mortality	No outcomes identified	No outcomes identified	2 studies (n=1146), Very low quality, 2 fewer per 1000 (9 fewer to 5 more)	1 study (n=156), Very low quality, 0 fewer per 1000 (25 fewer to 25 more)	No outcomes identified	1 study (n=2498), Very low quality, 6 more per 1000 (2 fewer to 22 more) 1 study (n=2498), Very low quality, HR 1.78 (0.79, 4.01)	No outcomes identified
3-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=2498), Low quality, 9 more per 1000 (6 fewer to 30 more) 1 study (n=2498), Low quality, HR	No outcomes identified

Outcomes for drugs compared to liraglutide	Exenatide	Lixisenatide	Semaglutide	Dapagliflozin	Empagliflozin	Glimepiride	Empagliflozin + liraglutide
						1.24 (0.85, 1.81)	
4-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=2516), Very low quality, 11 more per 1000 (5 fewer to 33 more)	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal stroke	No outcomes identified	No outcomes identified	1 study (n=569), Low quality, 7 more per 1000 (3 fewer to 17 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified	No outcomes identified	1 study (n=569), Low quality, 4 fewer per 1000 (10 fewer to 3 more)	1 study (n=309), Very low quality, 0 fewer per 1000 (13 fewer to 13 more)	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to liraglutide	Exenatide	Lixisenatide	Semaglutide	Dapagliflozin	Empagliflozin	Glimepiride	Empagliflozin + liraglutide
Unstable angina	No outcomes identified	No outcomes identified	1 study (n=569), Low quality, 4 more per 1000 (3 fewer to 10 more)	1 study (n=309), Very low quality, 2 fewer per 1000 (12 fewer to 70 more)	No outcomes identified	1 study (n=2516), Very low quality, 4 more per 1000 (2 fewer to 19 more)	No outcomes identified
Hospitalisation for heart failure	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=309), Very low quality, 0 fewer per 1000 (13 fewer to 13 more)	No outcomes identified	1 study (n=2493), Low quality, 13 more per 1000 (2 more to 34 more) 1 study (n=2516), Low quality, HR 2.16 (1.14, 4.09)	No outcomes identified
Acute kidney injury	No outcomes identified	No outcomes identified	1 study (n=569), Low quality, 4 fewer per 1000 (10 fewer to 3 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to liraglutide	Exenatide	Lixisenatide	Semaglutide	Dapagliflozin	Empagliflozin	Glimepiride	Empagliflozin + liraglutide
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Development of end stage kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=966), Very low quality, 1 fewer per 1000 (4 fewer to 1 more)	No outcomes identified
Cardiac arrhythmia	No outcomes identified	1 study (n=404), Very low quality, 5 more per 1000 (5 fewer to 15 more)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Diabetic ketoacidosis	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=156), Very low quality, 0 fewer per 1000 (25 fewer to 25 more)	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to liraglutide	Exenatide	Lixisenatide	Semaglutide	Dapagliflozin	Empagliflozin	Glimepiride	Empagliflozin + liraglutide
Falls requiring hospitalisation	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	2 studies (n=1378), Moderate quality, 42 more per 1000 (3 more to 91 more)	1 study (n=404), Low quality, 10 more per 1000 (9 fewer to 87 more)	2 studies (n=1146), Very low quality, 12 fewer per 1000 (20 fewer to 5 more)	1 study (n=309), Very low quality, 28 more per 1000 (42 fewer to 146 more)	No outcomes identified	2 studies (n=3430), Very low quality, 29 more per 1000 (119 fewer to 569 more) 1 study (n=2464), Low quality, HR 2.64 (2.32, 3.00)	No outcomes identified
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to liraglutide	Exenatide	Lixisenatide	Semaglutide	Dapagliflozin	Empagliflozin	Glimepiride	Empagliflozin + liraglutide
Severe hypoglycaemic episodes	2 studies (n=1378), Very low quality, 1 more per 1000 (3 fewer to 6 more)	1 study (n=404), Low quality, 0 fewer per 1000 (10 fewer to 10 more)	1 study (n=577), Low quality, 0 fewer per 1000 (7 fewer to 7 more)	2 studies (n=465), Low quality, 0 fewer per 1000 (12 fewer to 12 more)	1 study (n=61), Low quality, 0 fewer per 1000 (62 fewer to 62 more)	2 studies (n=3482), Very low quality, 8 more per 1000 (1 more to 22 more)	No outcomes identified
HbA1c change	2 studies (n=1242), Moderate quality, MD 0.26% higher (0.16 higher to 0.35 higher)	1 study (n=404), Moderate quality, MD 0.60% higher (0.40 higher to 0.80 higher)	2 studies (n=1127), Very low quality, MD 0.41% lower (0.99 lower to 0.17 higher)	1 study (n=309), Very low quality, MD 0.36% higher (0.01 lower to 0.73 higher)	2 studies (n=141), Very low quality, MD 0.46 higher (0.41 lower to 1.33 higher)	2 studies (n=1613), Low quality, MD 0.00% higher (0.23 lower to 0.23 higher)	1 study (n=80), Low quality, MD 0.70% lower (1.12 lower to 0.28 lower)
Weight change	2 studies (n=1268), Moderate quality, MD 0.69 kg higher (0.30 higher to 1.07 higher)”	1 study, High quality, MD 0.60 kg higher (0.18 lower to 1.38 higher)	2 studies (n=1126), Very low quality, MD 2.55 kg lower (5.03 lower to 0.07 lower)	2 studies (n=465), Low quality, MD 0.24 kg lower (1.92 lower to 1.43 higher)	2 studies (n=141), High quality, MD 0.34 lower (1.30 lower to 0.61 higher)	No outcomes identified	1 study (n=80), Very low quality, MD 1.10 kg higher (3.07 lower to 5.27 higher)

Outcomes for drugs compared to liraglutide	Exenatide	Lixisenatide	Semaglutide	Dapagliflozin	Empagliflozin	Glimepiride	Empagliflozin + liraglutide
BMI change	No outcomes identified	No outcomes identified	2 studies (n=1121), Very low quality, MD 0.90 kg/m^2 lower (1.68 lower to 0.12 lower)	No outcomes identified	2 studies (n=141), Low quality, MD 0.51 kg/m^2 lower (1.55 lower to 0.53 higher)	No outcomes identified	1 study (n=80), Low quality, MD 1.10 kg/m^2 lower (2.49 lower to 0.29 higher)

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2 ***1.1.7.4.13. Adding — Insulin combination therapy compared to liraglutide***

Outcomes for drugs compared to liraglutide	Insulin degludec/liraglutide
Health-related quality of life	No outcomes identified
All-cause mortality	2 studies (n=1788), Very low quality, 2 more per 1000 (3 fewer to 6 more)
Cardiovascular mortality	1 study (n=1247), Low quality, 2 more per 1000 (1 fewer to 6 more)
3-item MACE	1 study (n=1247), Low quality, 2 more per 1000 (2 fewer to 40 more)
4-item MACE	No outcomes identified
5-item MACE	No outcomes identified
Non-fatal stroke	1 study (n=541), Low quality, 17 fewer per 1000 (21 fewer to 8 more)
Non-fatal myocardial infarction	1 study (n=1247), Low quality, 0 fewer per 1000 (2 fewer to 24 more)
Unstable angina	1 study (n=541), High quality, 0 fewer per 1000 (9 fewer to 9 more)

Outcomes for drugs compared to liraglutide	Insulin degludec/liraglutide
Hospitalisation for heart failure	No outcomes identified
Acute kidney injury	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified
Development of end stage kidney disease	No outcomes identified
Death from renal cause	No outcomes identified
Cardiac arrhythmia	No outcomes identified
Diabetic ketoacidosis	No outcomes identified
Falls requiring hospitalisation	No outcomes identified
Progression of liver disease	No outcomes identified
Remission	No outcomes identified
Hypoglycaemia episodes	3 studies (n=2326), Low quality, 315 more per 1000 (82 more to 988 more)
At night hypoglycaemic episodes	No outcomes identified
Severe hypoglycaemic episodes	1 study (n=1239), Low quality, 4 more per 1000 (0 more to 8 more)
HbA1c change	2 studies (n=1883), Moderate quality, MD 0.54% lower (0.62 lower to 0.45 lower) 1 study (n=541), Moderate quality, MD 6.87 mmol/mol lower (8.32 lower to 5.42 lower)

Outcomes for drugs compared to liraglutide	Insulin degludec/liraglutide
Weight change	3 studies (n=2337), Very low quality, MD 2.96 higher (2.17 higher to 3.75 higher)
BMI change	No outcomes identified

1.1.7.4.14. Adding — Insulin combination therapy compared to lixisenatide

Table 33: Summary table for insulin drug combinations compared to lixisenatide for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to lixisenatide	Insulin glargine/lixisenatide
Health-related quality of life	No outcomes identified
All-cause mortality	2 studies (n=1226), Very low quality, 0 fewer per 1000 (7 fewer to 7 more)
Cardiovascular mortality	2 studies (n=1226), Very low quality, 1 fewer per 1000 (7 fewer to 4 more)
3-item MACE	No outcomes identified
4-item MACE	No outcomes identified
5-item MACE	No outcomes identified
Non-fatal stroke	1 study (n=702), Very low quality, 4 fewer per 1000 (13 fewer to 4 more)

Outcomes for drugs compared to lixisenatide	Insulin glargine/lixisenatide
Non-fatal myocardial infarction	1 study (n=702), Moderate quality, 0 fewer per 1000 (7 fewer to 7 more)
Unstable angina	1 study (n=702), Very low quality, 2 more per 1000 (2 fewer to 6 more)
Hospitalisation for heart failure	1 study (n=702), Moderate quality, 0 fewer per 1000 (7 fewer to 7 more)
Acute kidney injury	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified
Development of end stage kidney disease	No outcomes identified
Death from renal cause	No outcomes identified
Cardiac arrhythmia	No outcomes identified
Diabetic ketoacidosis	No outcomes identified
Falls requiring hospitalisation	No outcomes identified
Progression of liver disease	No outcomes identified
Remission	No outcomes identified
Hypoglycaemia episodes	2 studies (n=1226), Low quality, 291 more per 1000 (179 more to 454 more)
At night hypoglycaemic episodes	No outcomes identified

Outcomes for drugs compared to lixisenatide	Insulin glargine/lixisenatide
Severe hypoglycaemic episodes	2 studies (n=1226), Very low quality, 1 fewer per 1000 (8 fewer to 5 more)
HbA1c change	2 studies (n=1224), Low quality, MD 0.83% lower (0.93 lower to 0.74 lower)
Weight change	2 studies (n=1224), Moderate quality, MD 1.83 kg higher (1.40 higher to 2.25 higher)
BMI change	No outcomes identified

1.1.7.4.15. Adding — Monotherapy therapy compared to semaglutide

Table 34: Summary table for individual drugs compared to semaglutide for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to semaglutide	Tirzepatide	Canagliflozin	Empagliflozin
Health-related quality of life	No outcomes identified	No outcomes identified	Subscale mental component (SF-36) 1 study (n=818), Moderate quality, MD 0.20 lower (1.33 lower to 0.93 higher) Subscale physical component (SF-36)

Outcomes for drugs compared to semaglutide	Tirzepatide	Canagliflozin	Empagliflozin
			1 study (n=819), Moderate quality, MD 1.00 higher (0.12 higher to 1.88 higher)
All-cause mortality	2 studies (n=1967), Very low quality, 6 more per 1000 (1 fewer to 13 more)	1 study (n=786), Moderate quality, 10 fewer per 1000 (20 fewer to 0 more)	1 study (n=819), Low quality, 2 more per 1000 (2 fewer to 7 more)
Cardiovascular mortality	2 studies (n=1968), Very low quality, 3 more per 1000 (2 fewer to 8 more)	1 study (n=786), Low quality, 3 fewer per 1000 (8 fewer to 2 more)	1 study (n=819), Low quality, 2 more per 1000 (2 fewer to 7 more)
3-item MACE	No outcomes identified	No outcomes identified	No outcomes identified
4-item MACE	No outcomes identified	No outcomes identified	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal stroke	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal myocardial infarction	1 study (n=1878), Very low quality, 2 more per 1000 (0 more to 5 more)	No outcomes identified	No outcomes identified
Unstable angina	No outcomes identified	No outcomes identified	No outcomes identified
Hospitalisation for heart failure	No outcomes identified	No outcomes identified	1 study (n=819), Low quality, 2 fewer per 1000 (11 fewer to 6 more)

Outcomes for drugs compared to semaglutide	Tirzepatide	Canagliflozin	Empagliflozin
Acute kidney injury	No outcomes identified	1 study (n=786), Moderate quality, 10 fewer per 1000 (20 fewer to 0 more)	1 study (n=819), Low quality, 2 more per 1000 (2 fewer to 6 more)
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified	No outcomes identified
Development of end stage kidney disease	No outcomes identified	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified	No outcomes identified
Cardiac arrhythmia	1 study (n=1878), Very low quality, 1 more per 1000 (1 fewer to 3 more)	No outcomes identified	No outcomes identified
Diabetic ketoacidosis	No outcomes identified	No outcomes identified	No outcomes identified
Falls requiring hospitalisation	No outcomes identified	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	2 studies (n=1967), Very low quality, 4 more per 1000 (4 fewer to 13 more)	1 study (n=786), Moderate quality, 54 fewer per 1000 (82 fewer to 12 fewer)	1 study (n=819), Low quality, 14 fewer per 1000 (46 fewer to 33 more)

Outcomes for drugs compared to semaglutide	Tirzepatide	Canagliflozin	Empagliflozin
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified	No outcomes identified
Severe hypoglycaemic episodes	2 studies (n=1967), Very low quality, 1 more per 1000 (3 fewer to 6 more)	1 study (n=786), Low quality, 3 fewer per 1000 (8 fewer to 2 more)	1 study (n=819), Low quality, 0 more per 1000 (7 fewer to 7 more)
HbA1c change	1 study (n=1876), Low quality, MD 0.33% lower (0.51 lower to 0.16 lower) 1 study (n=84), Low quality, MD 4.50 mmol/mol lower (6.99 lower to 2.01 lower)	No outcomes identified	1 study (n=821) High quality, MD 0.40 mmol/mol higher (0.30 higher to 0.50 higher)
Weight change	2 studies (n=1960), Very low quality, MD 3.82 kg lower (5.24 lower to 2.41 lower)	1 study (n=788), High quality, MD 1.10 higher (0.41 higher to 1.79 higher)	1 study (n=821), High quality, MD 0.20 kg higher (0.50 lower to 0.90 higher)
BMI change	No outcomes identified	No outcomes identified	1 study (n=821), High quality, MD 0.10 higher (0.15 lower to 0.35 higher)

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1.1.7.4.16. Adding — Subcutaneous semaglutide compared to oral semaglutide

Table 35: Summary table for subcutaneous semaglutide compared to oral semaglutide for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to oral semaglutide	Subcutaneous Semaglutide
Health-related quality of life	Subscale mental component (SF-36) 1 study (n=559), Low quality, MD 0.22 higher (1.30 lower to 1.74 higher) Subscale physical component (SF-36) 1 study (n=559), Low quality, MD 0.43 lower (2.63 lower to 1.77 higher)
All-cause mortality	1 study (n=559), Low quality, 0 fewer per 1000 (20 fewer to 20 more)
Cardiovascular mortality	1 study (n=559), Low quality, 0 fewer per 1000 (20 fewer to 20 more)
3-item MACE	No outcomes identified
4-item MACE	No outcomes identified
5-item MACE	No outcomes identified
Non-fatal stroke	1 study (n=559), Low quality, 0 fewer per 1000 (20 fewer to 20 more)
Non-fatal myocardial infarction	1 study (n=559), Very low quality, 4 fewer per 1000 (10 fewer to 2 more)
Unstable angina	No outcomes identified

Outcomes for drugs compared to oral semaglutide	Subcutaneous Semaglutide
Hospitalisation for heart failure	No outcomes identified
Acute kidney injury	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified
Development of end stage kidney disease	No outcomes identified
Death from renal cause	No outcomes identified
Cardiac arrhythmia	No outcomes identified
Diabetic ketoacidosis	No outcomes identified
Falls requiring hospitalisation	No outcomes identified
Progression of liver disease	No outcomes identified
Remission	No outcomes identified
Hypoglycaemia episodes	1 study (n=559), Very low quality, 45 more per 1000 (30 fewer to 177 more)
At night hypoglycaemic episodes	No outcomes identified
Severe hypoglycaemic episodes	1 study (n=559), Very low quality, 12 more per 1000 (16 fewer to 41 more)
HbA1c change	1 study (n=559), Very low quality, MD 0.41% lower (0.62 lower to 0.20 lower)

Outcomes for drugs compared to oral semaglutide	Subcutaneous Semaglutide
Weight change	1 study (n=559), Very low quality, MD 1.12 kg lower (2.29 lower to 0.05 higher)
BMI change	No outcomes identified

1.1.7.4.17. Adding — Monotherapy compared to canagliflozin

Table 36: Summary table for individual drugs and drug combinations compared to canagliflozin for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to canagliflozin	Glimepiride
Health-related quality of life	No outcomes identified
All-cause mortality	1 study (n=1450), Low quality, 2 more per 1000 (1 fewer to 27 more)
Cardiovascular mortality	1 study (n=1450), Moderate quality, 4 more per 1000 (2 fewer to 10 more)
3-item MACE	No outcomes identified
4-item MACE	No outcomes identified
5-item MACE	No outcomes identified
Non-fatal stroke	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified
Unstable angina	No outcomes identified

Outcomes for drugs compared to canagliflozin	Glimepiride
Hospitalisation for heart failure	No outcomes identified
Acute kidney injury	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified
Development of end stage kidney disease	No outcomes identified
Death from renal cause	1 study (n=1450), Low quality, 1 fewer per 1000 (3 fewer to 1 more)
Cardiac arrhythmia	No outcomes identified
Diabetic ketoacidosis	No outcomes identified
Falls requiring hospitalisation	No outcomes identified
Progression of liver disease	No outcomes identified
Remission	No outcomes identified
Hypoglycaemia episodes	1 study (n=1450), High quality, 335 more per 1000 (245 more to 451 more)
At night hypoglycaemic episodes	No outcomes identified
Severe hypoglycaemic episodes	1 study (n=1450), High quality, 29 more per 1000 (7 more to 95 more)
HbA1c change	1 study (n=1450), Low quality, MD 0.14% higher (0.05 higher to 0.22 higher)
Weight change	1 study (n=1450), Low quality, MD 5.15 kg higher (4.76 higher to 5.54 higher)

Outcomes for drugs compared to canagliflozin	Glimepiride
BMI change	No outcomes identified

1.1.7.4.18. Adding — Monotherapy and combination therapy compared to dapagliflozin

Table 37: Summary table for individual drugs and drug combinations compared to dapagliflozin for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to dapagliflozin	Glimepiride	Glipizide	Pioglitazone	Dapagliflozin + exenatide	Dapagliflozin + saxagliptin
Health-related quality of life	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
All-cause mortality	1 study (n=121), Moderate quality, 0 fewer per 1000 (32 fewer to 32 more)	1 study (n=814), Very low quality, 7 more per 1000 (3 fewer to 58 more)	No outcomes identified	1 study (n=464), Very low quality, 4 more per 1000 (14 fewer to 23 more)	2 studies (n=944), Very low quality, 2 fewer per 1000 (10 fewer to 6 more)
Cardiovascular mortality	1 study (n=121), Moderate quality, 0 fewer per 1000 (32 fewer to 32 more)	No outcomes identified	No outcomes identified	1 study (n=464), Very low quality, 0 more per 1000 (12 fewer to 12 more)	2 studies (n=944), Very low quality, 4 fewer per 1000 (13 fewer to 4 more)
3-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
4-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to dapagliflozin	Glimepiride	Glipizide	Pioglitazone	Dapagliflozin + exenatide	Dapagliflozin + saxagliptin
5-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal stroke	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Unstable angina	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Hospitalisation for heart failure	1 study (n=625), Low quality, 3 more per 1000 (3 fewer to 9 more)	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=625), High quality, 0 fewer per 1000 (6 fewer to 6 more)
Acute kidney injury	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=464), Very low quality, 13 fewer per 1000 (27 fewer to 2 more)	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=358), Moderate quality, 0 fewer per 1000 (11 fewer to 11 more)

Outcomes for drugs compared to dapagliflozin	Glimepiride	Glipizide	Pioglitazone	Dapagliflozin + exenatide	Dapagliflozin + saxagliptin
Development of end stage kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Cardiac arrhythmia	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Diabetic ketoacidosis	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=586), High quality, 0 fewer per 1000 (7 fewer to 7 more)
Falls requiring hospitalisation	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	3 studies (n=807), Moderate quality, 47 more per 1000 (24 more to 71 more)	1 study (n=814), Low quality, 343 more per 1000 (154 more to 742 more)	1 study (n=66), Low quality, 0 fewer per 1000 (57 fewer to 57 more)	1 study (n=464), Very low quality, 13 more per 1000 (6 fewer to 32 more)	3 studies (n=1567), Low quality, 8 more per 1000 (1 fewer to 16 more)

Outcomes for drugs compared to dapagliflozin	Glimepiride	Glipizide	Pioglitazone	Dapagliflozin + exenatide	Dapagliflozin + saxagliptin
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Severe hypoglycaemic episodes	1 study (n=625), High quality, 0 fewer per 1000 (6 fewer to 6 more)	1 study (n=814), Very low quality, 7 more per 1000 (1 fewer to 16 more)	No outcomes identified	1 study (n=464), Low quality, 0 fewer per 1000 (8 fewer to 8 more)	3 studies (n=1567), Very low quality, 0 fewer per 1000 (5 fewer to 5 more)
HbA1c change	3 studies (n=791), Very low quality, MD 0.14% higher (0.29 lower to 0.57 higher)	1 study (n=801), Very low quality, MD 0.30% higher (0.08 higher to 0.52 higher)	1 study (n=65), High quality, MD 0.04% higher (0.38 lower to 0.46 higher)	1 study (n=458), Very low quality, MD 0.64% lower (0.96 lower to 0.32 lower)	3 studies (n=1493), High quality, MD 0.37% lower (0.46 lower to 0.27 lower)
Weight change	3 studies (n=796), Very low quality, MD 1.59 kg higher (4.00 lower to 7.18 higher)	1 study (n=801), Low quality, MD 4.38 kg higher (3.45 higher to 5.31 higher)	1 study (n=65), High quality, MD 5.30 kg higher (4.32 higher to 6.28 higher)	1 study (n=458), Low quality, MD 0.51 kg higher (0.77 lower to 1.79 higher)	2 studies (n=934), High quality, MD 0.31 kg higher (0.12 lower to 0.74 higher)
BMI change	1 study (n=112), High quality, MD 1.37 kg/m^2 higher (1.00 higher to 1.74 higher)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

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1.1.7.4.19. Adding — Monotherapy and combination therapy compared to empagliflozin

Table 38: Summary table for individual drugs and drug combinations compared to empagliflozin for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to Empagliflozin	Glimepiride	Pioglitazone	Empagliflozin + liraglutide
Health-related quality of life	No outcomes identified	No outcomes identified	No outcomes identified
All-cause mortality	1 study (n=1545), Low quality, 0 fewer per 1000 (5 fewer to 16 more)	No outcomes identified	No outcomes identified
Cardiovascular mortality	No outcomes identified	No outcomes identified	No outcomes identified
3-item MACE	No outcomes identified	No outcomes identified	No outcomes identified
4-item MACE	No outcomes identified	No outcomes identified	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal stroke	No outcomes identified	1 study (n=73), Very low quality, 27 fewer per 1000 (79 fewer to 25 more)	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified	No outcomes identified	No outcomes identified
Unstable angina	No outcomes identified	No outcomes identified	No outcomes identified
Hospitalisation for heart failure	No outcomes identified	No outcomes identified	No outcomes identified
Acute kidney injury	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to Empagliflozin	Glimepiride	Pioglitazone	Empagliflozin + liraglutide
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified	No outcomes identified
Development of end stage kidney disease	No outcomes identified	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified	No outcomes identified
Cardiac arrhythmia	No outcomes identified	No outcomes identified	No outcomes identified
Diabetic ketoacidosis	No outcomes identified	No outcomes identified	No outcomes identified
Falls requiring hospitalisation	No outcomes identified	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	1 study (n=1545), High quality, 217 more per 1000 (128 more to 359 more)	2 studies (n=186), Very low quality, 18 more per 1000 (47 fewer to 83 more)	No outcomes identified
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified	No outcomes identified
Severe hypoglycaemic episodes	No outcomes identified	2 studies (n=186), Low quality, 0 fewer per 1000 (30 fewer to 30 more)	No outcomes identified

Outcomes for drugs compared to Empagliflozin	Glimepiride	Pioglitazone	Empagliflozin + liraglutide
HbA1c change	1 study (n=1545), High quality, MD 0.11% higher (0.03 higher to 0.19 higher)	2 studies (n=186), Moderate quality, MD 0.07% higher (0.20 lower to 0.35 higher)	1 study (n=80), Low quality, MD 0.70% lower (1.12 lower to 0.28 lower)
Weight change	1 study (n=1545), High quality, MD 4.61 kg higher (4.18 higher to 5.04 higher)	No outcomes identified	1 study (n=80), Very low quality, MD 1.10 kg higher (3.07 lower to 5.27 higher)
BMI change	No outcomes identified	2 studies (n=186), Moderate quality, MD 1.73 kg/m^2 higher (1.32 higher to 2.14 higher)	1 study (n=80), Low quality, MD 1.10 lower kg/m^2 (2.49 lower to 0.29 higher)

1.1.7.4.20. Adding — Monotherapy and combination therapy compared to ertugliflozin

Table 39: A summary matrix showing the outcomes for individual drugs and drug combinations compared to ertugliflozin in people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to ertugliflozin	Glimepiride	Ertugliflozin + sitagliptin
Health-related quality of life	No outcomes identified	No outcomes identified
All-cause mortality	1 study (n=1325), Very low quality, 7 fewer per 1000 (12 fewer to 1 fewer)	1 study (n=985), Low quality, 0 more per 1000 (6 fewer to 6 more)
Cardiovascular mortality	1 study (n=1315), Very low quality, 1 fewer per 1000 (3 fewer to 1 more)	1 study (n=985), Low quality, 2 fewer per 1000 (6 fewer to 2 more)

Outcomes for drugs compared to ertugliflozin	Glimepiride	Ertugliflozin + sitagliptin
3-item MACE	No outcomes identified	No outcomes identified
4-item MACE	No outcomes identified	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified
Non-fatal stroke	No outcomes identified	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified	No outcomes identified
Unstable angina	No outcomes identified	No outcomes identified
Hospitalisation for heart failure	No outcomes identified	No outcomes identified
Acute kidney injury	1 study (n=1325), Very low quality, 0 fewer per 1000 (1 fewer to 18 more)	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified
Development of end stage kidney disease	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified
Cardiac arrhythmia	No outcomes identified	No outcomes identified
Diabetic ketoacidosis	1 study (n=1325), Very low quality, 1 fewer per 1000 (3 fewer to 1 more)	1 study (n=985), Low quality, 2 more per 1000 (2 fewer to 6 more)
Falls requiring hospitalisation	No outcomes identified	No outcomes identified

Outcomes for drugs compared to ertugliflozin	Glimepiride	Ertugliflozin + sitagliptin
Progression of liver disease	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	1 study (n=1325), Low quality, 151 more per 1000 (91 more to 236 more)	1 study (n=985), Very low quality, 15 more per 1000 (6 fewer to 56 more)
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified
Severe hypoglycaemic episodes	1 study (n=1325), Low quality, 21 more per 1000 (3 more to 102 more)	1 study (n=985), Very low quality, 4 fewer per 1000 (10 fewer to 2 more)
HbA1c change	1 study (n=1325), Low quality, MD 0.10% lower (0.17 lower to 0.03 lower)	1 study (n=985), Very low quality, MD 0.50% lower (0.64 lower to 0.36 lower)
Weight change	1 study (n=1325), Low quality, MD 4.10 kg higher (3.67 higher to 4.53 higher)	1 study (n=985), Low quality, MD 0.20 kg higher (0.37 lower to 0.77 higher)
BMI change	No outcomes identified	No outcomes identified

1.1.7.4.21. Adding – Monotherapy compared to gliclazide

Table 40: A summary matrix showing the outcomes for individual drugs and drug combinations compared to gliclazide for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to gliclazide	Glimepiride	Pioglitazone
Health-related quality of life	No outcomes identified	No outcomes identified

Outcomes for drugs compared to gliclazide	Glimepiride	Pioglitazone
All-cause mortality	1 study (n=1099), Low quality, 0 fewer per 1000 (4 fewer to 4 more)	1 study (n=630), Very low quality, 6 fewer per 1000 (15 fewer to 2 more)
Cardiovascular mortality	1 study (n=1099), Low quality, 0 fewer per 1000 (4 fewer to 4 more)	No outcomes identified
3-item MACE	No outcomes identified	No outcomes identified
4-item MACE	No outcomes identified	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified
Non-fatal stroke	1 study (n=1099), Low quality, 0 fewer per 1000 (4 fewer to 4 more)	No outcomes identified
Non-fatal myocardial infarction	1 study (n=1099), Very low quality, 4 fewer per 1000 (9 fewer to 1 more)	1 study (n=630), Very low quality, 3 more per 1000 (3 fewer to 9 more)
Unstable angina	No outcomes identified	No outcomes identified
Hospitalisation for heart failure	No outcomes identified	No outcomes identified
Acute kidney injury	No outcomes identified	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified
Development of end stage kidney disease	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified
Cardiac arrhythmia	No outcomes identified	No outcomes identified

Outcomes for drugs compared to gliclazide	Glimepiride	Pioglitazone
Diabetic ketoacidosis	1 study (n=1099), Very low quality, 2 fewer per 1000 (5 fewer to 2 more)	No outcomes identified
Falls requiring hospitalisation	1 study (n=1099), Low quality, 0 fewer per 1000 (4 fewer to 4 more)	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	1 study (n=1099), Low quality, 53 more per 1000 (17 more to 112 more)	1 study (n=630), Low quality, 93 fewer per 1000 (105 fewer to 66 fewer)
At night hypoglycaemic episodes	No outcome identified	No outcomes identified
Severe hypoglycaemic episodes	1 study (n=1099), Very low quality, 0 fewer per 1000 (0 more to 0 more)	1 study (n=630), Low quality, 0 fewer per 1000 (6 fewer to 6 more)
HbA1c change	1 study (n=832), Low quality, MD 0.05% higher (0.11 lower to 0.21 higher)	1 study (n=630), Low quality, MD 0.12% lower (0.31 lower to 0.07 higher)
Weight change	1 study (n=1099), High quality, MD 0.24kg higher (0.05 higher to 0.43 higher)	No outcomes identified
BMI change	No outcomes identified	No outcomes identified

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1.1.7.4.22. Adding — Monotherapy and combination therapy compared to glimepiride

Table 41: A summary matrix showing the outcomes for individual drugs and drug combinations compared to glimepiride for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to glimepiride	Pioglitazone	Dapagliflozin + saxagliptin	Glimepiride + metformin
Health-related quality of life	No outcomes identified	No outcomes identified	No outcomes identified
All-cause mortality	1 study (n=458), Very low quality, 4 more per 1000 (4 fewer to 13 more)	1 study (n=443), Very low quality, 9 fewer per 1000 (27 fewer to 8 more)	No outcomes identified
Cardiovascular mortality	1 study (n=458), Very low quality, 0 fewer per 1000 (9 fewer to 9 more)	No outcomes identified	No outcomes identified
3-item MACE	1 study (n=458), Very low quality, 9 fewer per 1000 (21 fewer to 3 more)	No outcomes identified	No outcomes identified
4-item MACE	No outcomes identified	No outcomes identified	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal stroke	2 studies (n=521), Very low quality, 0 fewer per 1000 (11 fewer to 11 more)	No outcomes identified	No outcomes identified
Non-fatal myocardial infarction	2 studies (n=521), Very low quality, 8 fewer per 1000 (18 fewer to 3 more)	No outcomes identified	No outcomes identified

Outcomes for drugs compared to glimepiride	Pioglitazone	Dapagliflozin + saxagliptin	Glimepiride + metformin
Unstable angina	1 study (n=458), Very low quality, 0 fewer per 1000 (9 fewer to 9 more)	No outcomes identified	No outcomes identified
Hospitalisation for heart failure	5 studies (n=1295), Very low quality, 4 more per 1000 (6 fewer to 15 more)	2 studies (n=1067), Very low quality, 2 fewer per 1000 (8 fewer to 4 more)	No outcomes identified
Acute kidney injury	1 study (n=288), Very low quality, 7 fewer per 1000 (20 fewer to 7 more)	No outcomes identified	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified	No outcomes identified
Development of end stage kidney disease	No outcomes identified	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified	No outcomes identified
Cardiac arrhythmia	No outcomes identified	No outcomes identified	No outcomes identified
Diabetic ketoacidosis	No outcomes identified	1 study (n=443), Low quality, 0 fewer per 1000 (9 fewer to 9 more)	No outcomes identified
Falls requiring hospitalisation	1 study (n=135), Very low quality, 29 more per 1000 (11 fewer to 69 more)	No outcomes identified	No outcomes identified

Outcomes for drugs compared to glimepiride	Pioglitazone	Dapagliflozin + saxagliptin	Glimepiride + metformin
Progression of liver disease	No outcomes identified	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	7 studies (n=1491), Very low quality, 98 fewer per 1000 (145 fewer to 2 fewer)	2 studies (n=1064), Very low quality, 98 fewer per 1000 (119 fewer to 16 fewer)	1 study (n=66), Very low quality, 57 fewer per 1000 (243 fewer to 229 more)
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified	1 study (n=66), Very low quality, 83 fewer per 1000 (151 fewer to 167 more)
Severe hypoglycaemic episodes	3 studies (n=549), Low quality, 0 fewer per 1000 (12 fewer to 12 more)	2 studies (n=1064), Very low quality, 6 fewer per 1000 (24 fewer to 13 more)	1 study (n=66), Very low quality, 0 fewer per 1000 (57 fewer to 57 more)
HbA1c change	12 studies (n=1579), Very low quality, MD 0.07% lower (0.19 lower to 0.05 higher)	2 studies (n=1046), Low quality, MD 0.34% lower (0.65 lower to 0.02 lower)	1 study (n=64), Very low quality, MD 0.71% lower (1.20 lower to 0.22 lower)
Weight change	8 studies (n=1319), Very low quality, MD 0.88 kg higher (0.02 higher to 1.74 higher)	2 studies (n=1058), Very low quality, MD 4.12 kg lower (6.12 lower to 2.12 lower)	1 study (n=64) Low quality, MD 0.12 kg higher (1.25 lower to 1.49 higher)
BMI change	7 studies (n=860), Low quality, MD 0.32 kg/m^2 higher (0.14 lower to 0.79 higher)	No outcomes identified	No outcomes identified

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1.1.7.4.23. Adding — Monotherapy compared to glipizide

Table 42: A summary matrix showing the outcomes for monotherapy compared to glipizide for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to glipizide	Pioglitazone
Health-related quality of life	No outcomes identified
All-cause mortality	No outcomes identified
Cardiovascular mortality	No outcomes identified
3-item MACE	No outcomes identified
4-item MACE	No outcomes identified
5-item MACE	No outcomes identified
Non-fatal stroke	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified
Unstable angina	No outcomes identified
Hospitalisation for heart failure	No outcomes identified
Acute kidney injury	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified
Development of end stage kidney disease	No outcomes identified

Outcomes for drugs compared to glipizide	Pioglitazone
Death from renal cause	No outcomes identified
Cardiac arrhythmia	No outcomes identified
Diabetic ketoacidosis	No outcomes identified
Falls requiring hospitalisation	No outcomes identified
Progression of liver disease	No outcomes identified
Remission	No outcomes identified
Hypoglycaemia episodes	No outcomes identified
At night hypoglycaemic episodes	No outcomes identified
Severe hypoglycaemic episodes	No outcomes identified
HbA1c change	1 study (n=70), Very low quality, MD 0.58 higher (0.34 higher to 0.82 higher)
Weight change	No outcomes identified
BMI change	No outcomes identified

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1.1.7.4.24. Adding — Combination therapy compared to pioglitazone

Table 43: A summary matrix showing the outcomes for drug combinations compared to pioglitazone for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to pioglitazone	Pioglitazone + alogliptin	Pioglitazone + exenatide	Pioglitazone + metformin
Health-related quality of life	No outcomes identified	No outcomes identified	No outcomes identified
All-cause mortality	1 study (n=1167), Very low quality, 3 fewer per 1000 (8 fewer to 2 more)	No outcomes identified	No outcomes identified
Cardiovascular mortality	1 study (n=1167), Very low quality, 3 fewer per 1000 (8 fewer to 2 more)	No outcomes identified	No outcomes identified
3-item MACE	No outcomes identified	No outcomes identified	No outcomes identified
4-item MACE	No outcomes identified	No outcomes identified	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal stroke	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified	No outcomes identified	No outcomes identified
Unstable angina	No outcomes identified	No outcomes identified	No outcomes identified
Hospitalisation for heart failure	No outcomes identified	No outcomes identified	No outcomes identified
Acute kidney injury	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to pioglitazone	Pioglitazone + alogliptin	Pioglitazone + exenatide	Pioglitazone + metformin
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified	No outcomes identified
Development of end stage kidney disease	No outcomes identified	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified	No outcomes identified
Cardiac arrhythmia	No outcomes identified	No outcomes identified	No outcomes identified
Diabetic ketoacidosis	No outcomes identified	No outcomes identified	No outcomes identified
Falls requiring hospitalisation	No outcomes identified	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	1 study (n=1167), Very low quality, 8 fewer per 1000 (16 fewer to 12 more)	No outcomes identified	1 study (n=79), Very low quality, 82 more per 1000 (73 fewer to 426 more)
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified	No outcomes identified
Severe hypoglycaemic episodes	1 study (n=1167), Very low quality, 4 fewer per 1000 (11 fewer to 4 more)	No outcomes identified	No outcomes identified

Outcomes for drugs compared to pioglitazone	Pioglitazone + alogliptin	Pioglitazone + exenatide	Pioglitazone + metformin
HbA1c change	1 study (n=933), Very low quality, MD 0.50% lower (0.62 lower to 0.38 lower)	1 study (n=21), Very low quality, MD 0.50% lower (0.80 lower to 0.20 lower)	1 study (n=74), Low quality, MD 0.34% lower (0.68 lower to 0.00 lower)
Weight change	No outcomes identified	1 study (n=21), Very low quality, MD 1.10 kg lower (6.54 lower to 4.34 higher)	No outcomes identified
BMI change	No outcomes identified	1 study (n=21), Very low quality, MD 3.40 kg/m^2 higher (1.83 higher to 4.97 higher)	No outcomes identified

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1.1.7.4.25. Adding — Monotherapy compared to insulin

Table 44: A summary matrix showing the outcomes for individual drugs (GLP-1 receptor agonists, dual GIP/GLP-1 receptor co-agonists, SGLT-2 inhibitors) compared to insulin for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to insulin	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Empagliflozin
Health-related quality of life	No outcomes identified	Overall (EQ-5D) 2 studies (n=888), Low quality, MD 0.00 lower (0.03 lower to 0.02 higher)	Subscale mental component (SF-36) 2 studies (n=2547), Low quality, MD 0.04 higher (0.10 lower to 0.18 higher) Subscale physical component (SF-36) 2 studies (n=2547), Very low quality, MD 0.48 higher (0.29 lower to 1.24 higher)	No outcomes identified	Subscale mental component (SF-36 v2) 1 study (n=1748), Low quality MD 0.59 higher (0.14 lower to 1.32 higher) Subscale physical component (SF-36 v2) 1 study (n=1748), Low quality, MD 0.95 higher (0.37	No outcomes identified	No outcomes identified

Outcomes for drugs compared to insulin	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Empagliflozin
		Overall (IWQoL) 2 studies (n=726), Moderate quality, MD 3.71 higher (1.95 higher to 5.46 higher)			higher to 1.53 higher)		

Outcomes for drugs compared to insulin	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Empagliflozin
All-cause mortality	3 studies (n=2459), Very low quality, 4 fewer per 1000 (10 fewer to 2 more)	6 studies (n=2475), Very low quality, 2 more per 1000 (3 fewer to 8 more)	5 studies (n=4045), Very low quality, 2 fewer per 1000 (12 fewer to 8 more) 1 study (n=2525), Low quality, HR 0.65 (0.40, 1.05)	3 studies (n=2118), Very low quality, 1 fewer per 1000 (6 fewer to 5 more)	2 studies (n=2820), Low quality, 8 more per 1000 (2 more to 13 more)	3 studies (n=3769), Low quality, 5 fewer per 1000 (9 fewer to 2 more)	No outcomes identified

Outcomes for drugs compared to insulin	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Empagliflozin
Cardiovascular mortality	1 study (n=807), Low quality, 2 more	4 studies (n=1518), Very low	4 studies (n=3755), Very low	3 studies (n=2118),	1 study (n=1082), Very low	2 studies (n=2344), Very low quality, 2	No outcomes identified

Outcomes for drugs compared to insulin	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Empagliflozin
	per 1000 (2 fewer to 5 more)	quality, 3 more per 1000 (4 fewer to 9 more)	quality, 3 fewer per 1000 (12 fewer to 6 more) 1 study (n=2508), Low quality, HR 0.43 (0.20, 0.95)	Very low quality, 1 fewer per 1000 (6 fewer to 4 more)	quality, 1 fewer per 1000 (10 fewer to 8 more)	fewer per 1000 (7 fewer to 3 more)	
3-item MACE	No outcomes identified	No outcomes identified	2 studies (n=3335), Low quality, 10 fewer per 1000 (19 fewer to 3 more) 1 study (n=2508), Low quality, HR 0.74 (0.51, 1.07)	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to insulin	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Empagliflozin
4-item MACE	No outcomes identified	No outcomes identified	1 study (n=2525), Very low quality, 13 fewer per 1000 (26 fewer to 4 more)	No outcomes identified	No outcomes identified	2 studies (n=2344), Low quality, 1 more per 1000 (4 fewer to 17 more)	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal stroke	1 study (n=361), Low quality, 11 more per 1000 (4 fewer to 26 more)	1 study (n=427, Low quality, 5 more per 1000 (4 fewer to 14 more)	2 studies (n=1324), Very low quality, 5 more per 1000 (2 fewer to 11 more)	1 study (n=700), Very low quality, 2 more per 1000 (2 fewer to 66 more)	No outcomes identified	1 study (n=907), Very low quality, 5 more per 1000 (6 fewer to 57 more)	No outcomes identified
Non-fatal myocardial infarction	1 study (n=361), Low quality, 6 more per 1000 (5 fewer to 16 more)	1 study (n=627), Very low quality, 6 fewer per 1000 (15 fewer to 2 more)	1 study (n=827), Low quality, 0 fewer per 1000 (7 fewer to 7 more)	No outcomes identified	No outcomes identified	1 study (n=907), Very low quality,1 more per 1000 (1 fewer to 4 more)	No outcomes identified

Outcomes for drugs compared to insulin	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Empagliflozin
Unstable angina	No outcomes identified	No outcomes identified	2 studies (n=2884), Very low quality, 2 fewer per 1000 (8 fewer to 4 more)	1 study (n=700), Very low quality, 2 fewer per 1000 (6 fewer to 2 more)	1 study (n=1738), Very low quality, 0 fewer per 1000 (3 fewer to 3 more)	No outcomes identified	No outcomes identified
Hospitalisation for heart failure	No outcomes identified	No outcomes identified	1 study (n=2508), Low quality, 9 fewer per 1000 (15 fewer to 1 more) 1 study (n=2508), Low quality, HR 0.54 (0.28, 1.04)	1 study (n=700), Very low quality, 4 fewer per 1000 (10 fewer to 2 more)	No outcomes identified	1 study (n=907), Very low quality, 1 more per 1000 (1 fewer to 4 more)	No outcomes identified
Acute kidney injury	No outcomes identified	1 study (n=627), Very low quality, 3	1 study (n=273), Very low quality, 15	No outcomes identified	No outcomes identified	1 study (n=1425), Very low quality, 1	No outcomes identified

Outcomes for drugs compared to insulin	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Empagliflozin
		more per 1000 (3 fewer to 9 more)	fewer per 1000 (21 fewer to 48 more)			more per 1000 (1 fewer to 4 more)	
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Development of end stage kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Cardiac arrhythmia	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	1 study (n=907), Very low quality, 5 fewer per 1000 (13 fewer to 4 more)	No outcomes identified
Diabetic ketoacidosis	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Falls requiring hospitalisation	1 study (n=361), Low	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to insulin	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Empagliflozin
	quality, 6 more per 1000 (5 fewer to 16 more)						
Progression of liver disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	3 studies (n=1936), Low quality, 147 fewer per 1000 (208 fewer to 70 fewer)	8 studies (n=2152), Moderate quality, 86 fewer per 1000 (111 fewer to 58 fewer)	9 studies (n=5580), Low quality, 193 fewer per 1000 (246 fewer to 115 fewer) 1 study (n=2478), Low quality, HR 0.61 (0.53, 0.70)	3 studies (n=2118), Very low quality, 310 fewer per 1000 (386 fewer to 126 fewer)	1 study (n=1738), Moderate quality, 235 fewer per 1000 (271 fewer to 195 fewer)	3 studies (n=3769), Very low quality, 312 fewer per 1000 (394 fewer to 141 fewer)	No outcomes identified
At night hypoglycaemic episodes	3 studies (n=1936), High quality, 138 fewer per	6 studies (n=2277), Low quality, 105 fewer per	3 studies (n=1786), Moderate quality, 57	No outcomes identified	1 study (n=1082), Very low quality, 13	No outcomes identified	No outcomes identified

Outcomes for drugs compared to insulin	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Empagliflozin
	1000 (159 fewer to 112 fewer)	1000 (141 fewer to 55 fewer)	fewer per 1000 (234 fewer to 121 more)		fewer per 1000 (19 fewer to 4 more)		
Severe hypoglycaemic episodes	4 studies (n=2820), Very low quality, 4 fewer per 1000 (15 fewer to 7 more)	10 studies (n=3442), Very low quality, 6 fewer per 1000 (13 fewer to 1 more)	7 studies (n=5223), Very low quality 0 fewer per 1000 (6 fewer to 5 more)	3 studies (n=2118), Very low quality, 1 fewer per 1000 (5 fewer to 2 more)	2 studies (n=2820), Low quality, 19 fewer per 1000 (25 fewer to 10 fewer)	3 studies (n=3769), Low quality, 17 fewer per 1000 (24 fewer to 10 fewer)	No outcomes identified
HbA1c change	4 studies (n=2807), Very low quality, MD 0.33% lower (0.51 lower to 0.15 lower)	15 studies (n=4069), Very low quality, MD 0.09% lower (0.24 lower to 0.06 higher)	9 studies (n=3501), Moderate quality, MD 0.10% lower (0.29 lower to 0.09 higher)	3 studies (n=2102), Low quality, MD 0.36% higher (0.17 higher to 0.54 higher)	2 studies (n=2830), Very low quality, MD 0.49% lower (0.79 lower to 0.19 lower)	3 studies (n=3766), Very low quality, MD 1.08% lower (1.46 lower to 0.70 lower)	1 study (n=80), Very low quality, MD 0.00% lower (0.50 lower to 0.50 higher)
Weight change	3 studies (n=2446), Low quality, MD 2.60 kg lower	15 studies (n=3991, Very low quality, MD 4.26 kg lower	8 studies (n=2728), Moderate quality, MD 4.13 kg lower	3 studies (n=2105), Very low quality, MD 2.73 kg lower (3.59 lower to 1.87 lower)	2 studies (n=2830), Very low quality, MD 6.69 kg	3 studies (n=3766), Very low quality, MD 10.90 kg lower (14.29	1 study (n=80), Low quality, MD 2.90 kg lower (7.07 lower to 1.27 higher)

Outcomes for drugs compared to insulin	Dulaglutide	Exenatide	Liraglutide	Lixisenatide	Semaglutide	Tirzepatide	Empagliflozin
	(3.15 lower to 2.05 lower)	(5.05 lower to 3.48 lower)	(4.81 lower to 3.45 lower)		lower (8.73 lower to 4.65 lower)	lower to 7.52 lower)	
BMI change	No outcomes identified	6 studies (n=1198), Very low quality, MD 1.34 kg/m^2 lower (1.88 lower to 0.79 lower)	3 studies (n=189), Low quality, MD 1.18 kg/m2 lower (1.73 lower to 0.63 lower)	No outcomes identified	1 study (n=1748), Low quality, MD 2.54 kg/m^2 lower (2.69 lower to 2.39 lower)	No outcomes identified	1 study (n=80), Low quality, MD 1.20 kg/m^2 lower (2.32 lower to 0.08 lower

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Table 45: A summary matrix showing the outcomes for individual drugs (biguanides, DPP-4 inhibitors, sulfonylureas, thiazolidinediones) compared to insulin for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to insulin	Metformin	Sitagliptin	Vildagliptin	Glimepiride	Pioglitazone
Health-related quality of life	No outcomes identified	Subscale mental component (SF-36) 1 study (n=2445), Low quality, MD 0.12 higher (0.48 lower to 0.72 higher) Subscale physical component (SF-36) 1 study (n=2445), Low quality, MD 0.23 higher (0.32 lower to 0.78 higher)	No outcomes identified	Subscale mental component (SF-36) 1 study (n=2431), Low quality, MD 0.18 higher (0.42 lower to 0.78 higher) Subscale physical component (SF-36) 1 study (n=2431), Low quality, MD 0.00 lower (0.55 lower to 0.55 higher)	No outcomes identified

Outcomes for drugs compared to insulin	Metformin	Sitagliptin	Vildagliptin	Glimepiride	Pioglitazone

Outcomes for drugs compared to insulin	Metformin	Sitagliptin	Vildagliptin	Glimepiride	Pioglitazone
All-cause mortality	1 study (n=25), Very low quality, 77 fewer per 1000 (222 fewer to 68 more)	2 studies (n=2984), Very low quality, 1 fewer per 1000 (13 fewer to 10 more)	1 study (n=28938), Very low quality, 13 fewer per 1000 (37 fewer to 12 more)	1 study (n=2512), Moderate quality, 2 more per 1000 (10 fewer to 20 more) 1 study (n=2504),Very low quality, HR 1.04 (0.68, 1.58)	No outcomes identified

Outcomes for drugs compared to insulin	Metformin	Sitagliptin	Vildagliptin	Glimepiride	Pioglitazone
		1 study (n=2530), Very low quality, HR 0.98 (0.68, 1.41)			
Cardiovascular mortality	1 study (n=25), Very low quality, 77 fewer per 1000	1 study (n=2521), Very low quality, 0 fewer per 1000 (8 fewer to 14 more)	No outcomes identified	1 study (n=2499, Very low quality, 4 fewer per 1000 (10 fewer to 8	No outcomes identified

Outcomes for drugs compared to insulin	Metformin	Sitagliptin	Vildagliptin	Glimepiride	Pioglitazone
	(222 fewer to 68 more)	1 study (n=2521), Very low quality, HR 1.00 (0.55, 1.82)		more) 1 study (n=2499, Very low quality, HR 0.78 (0.40, 1.48)	
3-item MACE	No outcomes identified	1 study (n=2521), Very low quality, 3 more per 1000 (12 fewer to 24 more) 1 study (n=2521) Very low quality, HR 1.06 (0.76, 1.48)	No outcomes identified	1 study (n=2499), Very low quality, 4 fewer per 1000 (18 fewer to 15 more) 1 study (n=2504, Very low quality, HR 0.92 (0.65, 1.30)	No outcomes identified
4-item MACE	No outcomes identified	1 study (n=2531), Very low quality, 5 more per 1000 (11 fewer to 28 more)	No outcomes identified	1 study (n=2517), Very low quality, 3 fewer per 1000 (18 fewer to 18 more)	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal stroke	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified	1 study (n=501), Very low quality, 4	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to insulin	Metformin	Sitagliptin	Vildagliptin	Glimepiride	Pioglitazone
		more per 1000 (4 fewer to 11 more)			
Unstable angina	No outcomes identified	2 studies (n=3032), Very low quality, 2 more per 1000 (4 fewer to 9 more)	No outcomes identified	1 study (n=2522), Very low quality, 2 fewer per 1000 (7 fewer to 9 more)	No outcomes identified
Hospitalisation for heart failure	No outcomes identified	1 study (n=2521), Very low quality, 3 more per 1000 (7 fewer to 19 more) 1 study (n=2521), Very low quality, HR 1.15 (0.67, 1.96)	No outcomes identified	1 study (n=2499), Very low quality, 3 more per 1000 (6 fewer to 20 more) 1 study (n=2511), Very low quality, HR 1.16 (0.69, 1.96)	No outcomes identified
Acute kidney injury	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Development of end stage kidney disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to insulin	Metformin	Sitagliptin	Vildagliptin	Glimepiride	Pioglitazone
Cardiac arrhythmia	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Diabetic ketoacidosis	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Falls requiring hospitalisation	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	No outcomes identified	5 studies (n=3628), Very low quality, 227 fewer per 1000 (295 fewer to 107 fewer) 1 study (n=2498), Low quality, HR 0.63 (0.59, 0.67)	1 study (n=30365), Very low quality,145 fewer per 1000 (213 fewer to 18 fewer)	2 studies (n=2548), Low quality, 155 more per 1000 (110 more to 203 more) 1 study (n=2476), Low quality, HR 1.61 (1.43, 1.81)	2 studies (n=274) Very low quality, 56 fewer per 1000 (80 fewer to 7 fewer)
At night hypoglycaemic episodes	No outcomes identified	2 studies (n=955), Low quality,108 fewer per 1000 (134 fewer to 43 fewer	No outcomes identified	No outcomes identified	No outcomes identified

Outcomes for drugs compared to insulin	Metformin	Sitagliptin	Vildagliptin	Glimepiride	Pioglitazone
Severe hypoglycaemic episodes	No outcomes identified	4 studies (n=3610), Very low quality,7 fewer per 1000 (14 fewer to 1 fewer)	1 study (n=161), Very low quality, 0 fewer per 1000 (24 fewer to 24 more)	2 studies (n=2589), Very low quality, 9 more per 1000 (1 fewer to 19 more)	2 studies (n=274), Very low quality, 23 fewer per 1000 (58 fewer to 12 more)
HbA1c change	1 study (n=25), Low quality, MD 0.70% higher (0.40 lower to 1.80 higher)	7 studies (n=1878), Very low quality, MD 0.18% higher (0.09 lower to 0.46 higher)	1 study (n=161), Very low quality, MD 0.30% higher (0.05 higher to 0.55 higher)	2 studies (n=808), Very low quality, MD 0.00% higher (0.56 lower to 0.57 higher)	3 studies (n=304), Very low quality, MD 0.57% higher (0.32 higher to 0.81 higher)
Weight change	1 study (n=25), Low quality, MD 1.30 kg lower (3.42 lower to 0.82 higher)	6 studies (n=1179), Very low quality, MD 1.89 kg lower (2.62 lower to 1.16 lower)	No outcomes identified	1 study (n=72), Very low quality, MD 1.70 kg lower (3.05 lower to 0.35 lower)	1 study (n=27), Very low quality, MD 1.30 kg higher (0.75 lower to 3.35 higher)
BMI change	No outcomes identified	3 studies (n=117), Moderate quality, MD 0.39 kg/m^2 lower (1.00 lower to 0.23 higher)	No outcomes identified	No outcomes identified	1 study (n=30) Very low quality, MD 0.60 kg/m^2 lower (4.93 lower to 3.73 higher)

1.1.7.4.26. Adding — Non-insulin combination therapy compared to insulin

Table 46: A summary matrix showing the outcomes for drug combinations compared to insulin for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to insulin	Dapagliflozin + saxagliptin	Empagliflozin + liraglutide	Pioglitazone + exenatide
Health-related quality of life	Subscale net benefit (Phase V Health Outcomes Information Systems Diabetes Module) 1 study (n=643), High quality, MD 1.10 higher (0.84 lower to 3.04 higher) Subscale regimen acceptance (Phase V Health Outcomes Information Systems Diabetes Module) 1 study (n=643), High quality, MD 4.20 higher (1.98 higher to 6.42 higher) Subscale satisfaction (Phase V Health Outcomes Information Systems Diabetes Module) 1 study (n=643), High quality, MD 3.40 higher (1.46 higher to 5.34 higher)	No outcomes identified	No outcomes identified

Outcomes for drugs compared to insulin	Dapagliflozin + saxagliptin	Empagliflozin + liraglutide	Pioglitazone + exenatide
All-cause mortality	1 study (n=643), Low quality, 6 more per 1000 (2 fewer to 15 more)	No outcomes identified	1 study (n=286), Very low quality, 7 fewer per 1000 (31 fewer to 16 more)
Cardiovascular mortality	1 study (n=643), High quality, 0 fewer per 1000 (6 fewer to 6 more)	No outcomes identified	No outcomes identified
3-item MACE	No outcomes identified	No outcomes identified	No outcomes identified
4-item MACE	No outcomes identified	No outcomes identified	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified	No outcomes identified
Non-fatal stroke	No outcomes identified	No outcomes identified	1 study (n=286), Very low quality, 14 fewer per 1000 (34 fewer to 5 more)
Non-fatal myocardial infarction	No outcomes identified	No outcomes identified	No outcomes identified
Unstable angina	No outcomes identified	No outcomes identified	No outcomes identified
Hospitalisation for heart failure	No outcomes identified	No outcomes identified	1 study (n=286), Moderate quality, 0 fewer per 1000 (14 more to 14 more)
Acute kidney injury	1 study (n=643), High quality, 0 fewer per 1000 (0 more to 0 more)	No outcomes identified	No outcomes identified

Outcomes for drugs compared to insulin	Dapagliflozin + saxagliptin	Empagliflozin + liraglutide	Pioglitazone + exenatide
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified	No outcomes identified
Development of end stage kidney disease	No outcomes identified	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified	No outcomes identified
Cardiac arrhythmia	No outcomes identified	No outcomes identified	No outcomes identified
Diabetic ketoacidosis	1 study (n=643), Low quality, 3 fewer per 1000 (9 fewer to 3 more)	No outcomes identified	No outcomes identified
Falls requiring hospitalisation	No outcomes identified	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	1 study (n=643), High quality, 174 fewer per 1000 (228 fewer to 107 fewer)	No outcomes identified	1 study (n=286), Low quality, 215 fewer per 1000 (295 fewer to 124 fewer)
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified	No outcomes identified
Severe hypoglycaemic episodes	1 study (n=643), Low quality, 9 fewer per 1000 (20 fewer to 1 more)	No outcomes identified	1 study (n=286), Very low quality, 7 fewer per 1000 (21 fewer to 7 more)

Outcomes for drugs compared to insulin	Dapagliflozin + saxagliptin	Empagliflozin + liraglutide	Pioglitazone + exenatide
HbA1c change	1 study (n=389), Low quality, MD 0.25% lower (0.40 lower to 0.10 lower)	1 study (n=80), Low quality, MD 0.70% lower (1.15 lower to 0.25 lower)	No outcomes identified
Weight change	1 study (n=390), Low quality, MD 4.60 kg lower (5.37 lower to 3.83 lower)	1 study (n=80), Low quality, MD 1.80 kg lower (5.74 lower to 2.14 higher)	1 study (n=286) Moderate quality, MD 4.40 kg lower (4.73 lower to 4.07 lower)
BMI change	No outcomes identified	1 study (n=80), Low quality, MD 2.30 kg/m^2 lower (3.85 lower to 0.75 lower)	No outcomes identified

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1.1.7.4.27. Adding — Insulin combination therapy compared to insulin

Table 47: A summary matrix showing the outcomes for insulin drug combinations compared to insulin for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to insulin	Insulin degludec/liraglutide	Insulin glargine/lixisenatide
Health-related quality of life	EQ-5D-5L 1 study (n=210), Low quality, MD 0.03 higher (0.00 lower to 0.06 higher) SF-36 – subscale mental component 2 studies (n=1028), Very low quality, MD 0.57 higher (1.91 lower to 3.05 higher) SF-36 – subscale physical component 2 studies (n=1027), Very low quality, MD 0.55 higher (1.81 lower to 2.92 higher)	No outcomes identified
All-cause mortality	9 studies (n=5112), Very low quality, 2 fewer per 1000 (5 fewer to 2 more)	7 studies (n=4143), Very low quality, 0 fewer per 1000 (4 fewer to 3 more)
Cardiovascular mortality	9 studies (n=5112), Very low quality, 2 fewer per 1000 (5 fewer to 2 more)	7 studies (n=4143), Very low quality, 2 more per 1000 (7 fewer to 11 more)
3-item MACE	3 studies (n=2117), Low quality, 0 more per 1000 (7 fewer to 7 more)	No outcomes identified
4-item MACE	No outcomes identified.	No outcomes identified
5-item MACE	No outcomes identified.	No outcomes identified

Outcomes for drugs compared to insulin	Insulin degludec/liraglutide	Insulin glargine/lixisenatide
Non-fatal stroke	6 studies (n=3130), Very low quality, 1 more per 1000 (3 fewer to 5 more)	1 study (n=936), Very low quality, 2 fewer per 1000 (6 fewer to 2 more)
Non-fatal myocardial infarction	7 studies (n=4240), Very low quality, 1 more per 1000 (2 fewer to 4 more)	1 study (n=936), Moderate quality, 0 fewer per 1000 (4 fewer to 4 more)
Unstable angina	3 studies (n=2055), Very low quality, 3 more per 1000 (1 fewer to 8 more)	1 study (n=936), Very low quality, 0 fewer per 1000 (6 fewer to 6 more)
Hospitalisation for heart failure	2 studies (n=1515), Very low quality, 1 fewer per 1000 (6 fewer to 3 more)	1 study (n=936), Very low quality, 4 fewer per 1000 (10 fewer to 2 more)
Acute kidney injury	1 study (n=419), Low quality, 5 fewer per 1000 (14 fewer to 5 more)	No outcomes identified
Persistent signs of worsening kidney disease	1 study (n=419), Low quality, 5 fewer per 1000 (14 fewer to 5 more)	No outcomes identified
Development of end stage kidney disease	1 study (n=1010), Very low quality, 2 more per 1000 (2 fewer to 6 more)	No outcomes identified
Death from renal cause	No outcomes identified.	1 study (n=423), High quality, 0 fewer per 1000 (9 fewer to 9 more)
Cardiac arrhythmia	2 studies (n=1515), Very low quality, 0 fewer per 1000 (5 fewer to 5 more)	No outcomes identified
Diabetic ketoacidosis	No outcomes identified.	No outcomes identified
Falls requiring hospitalisation	No outcomes identified.	No outcomes identified
Progression of liver disease	No outcomes identified.	No outcomes identified

Outcomes for drugs compared to insulin	Insulin degludec/liraglutide	Insulin glargine/lixisenatide
Remission	No outcomes identified.	No outcomes identified
Hypoglycaemia episodes	6 studies (n=3318), Moderate quality, 82 fewer per 1000 (109 fewer to 52 fewer)	7 studies (n=4142), Moderate quality, 1 more per 1000 (19 fewer to 24 more)
At night hypoglycaemic episodes	3 studies (n=1443), Very low quality, 58 fewer per 1000 (87 fewer to 10 more)	No outcomes identified
Severe hypoglycaemic episodes	6 studies (n=2238), Very low quality, 2 fewer per 1000 (14 fewer to 9 more)	4 studies (n=2412), Very low quality, 2 more per 1000 (4 fewer to 7 more)
HbA1c change	11 studies (n=5672), Very low quality, MD 0.65% lower (0.82 lower to 0.48 lower) HbA1c change (mmol/mol) 1 study (n=540), Moderate quality, MD 6.50 mmol/mol lower (7.96 lower to 5.04 lower)	7 studies (n=4138), Very low quality, MD 0.50% lower (0.64 lower to 0.35 lower)
Weight change	12 studies (n=6718), Very low quality, MD 2.21 kg lower (2.79 lower to 1.63 lower)	7 studies (n=4138), High quality, MD 1.16 kg lower (1.32 lower to 0.99 lower)
BMI change	No outcomes identified.	No outcomes identified

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1.1.7.4.28. Switching — Switching to monotherapy compared to switching to placebo

Table 48: A summary matrix showing the outcomes for switching to monotherapy compared to switching to placebo for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to switching to placebo	Switching to sitagliptin
Health-related quality of life	No outcomes identified
All-cause mortality	No outcomes identified
Cardiovascular mortality	No outcomes identified
3-item MACE	No outcomes identified
4-item MACE	No outcomes identified
5-item MACE	No outcomes identified
Non-fatal stroke	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified
Unstable angina	No outcomes identified
Hospitalisation for heart failure	No outcomes identified
Acute kidney injury	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified
Development of end stage kidney disease	No outcomes identified
Death from renal cause	No outcomes identified

Outcomes for drugs compared to switching to placebo	Switching to sitagliptin
Cardiac arrhythmia	No outcomes identified
Diabetic ketoacidosis	No outcomes identified
Falls requiring hospitalisation	No outcomes identified
Progression of liver disease	No outcomes identified
Remission	No outcomes identified
Hypoglycaemia episodes	1 study (n=21), Very low quality, 9 more per 1000 (84 fewer to 1305 more)
At night hypoglycaemic episodes	No outcomes identified
Severe hypoglycaemic episodes	No outcomes identified
HbA1c change	No outcomes identified
Weight change	No outcomes identified
BMI change	No outcomes identified

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1.1.7.4.29. Switching — Switching to metformin slow release compared to staying on metformin standard release

Table 49: A summary matrix showing the outcomes for switching to metformin slow release compared to staying on metformin standard release for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to staying on Metformin standard release	Switching to metformin slow release
Health-related quality of life	No outcomes identified
All-cause mortality	1 study (n=221), Very low quality, 7 more per 1000 (7 fewer to 20 more)
Cardiovascular mortality	No outcomes identified
3-item MACE	No outcomes identified
4-item MACE	No outcomes identified
5-item MACE	No outcomes identified
Non-fatal stroke	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified
Unstable angina	No outcomes identified
Hospitalisation for heart failure	No outcomes identified
Acute kidney injury	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified
Development of end stage kidney disease	No outcomes identified

Outcomes for drugs compared to staying on Metformin standard release	Switching to metformin slow release
Death from renal cause	No outcomes identified
Cardiac arrhythmia	No outcomes identified
Diabetic ketoacidosis	No outcomes identified
Falls requiring hospitalisation	No outcomes identified
Progression of liver disease	No outcomes identified
Remission	No outcomes identified
Hypoglycaemia episodes	1 study (n=221), Very low quality, 6 fewer per 1000 (13 fewer to 95 more)
At night hypoglycaemic episodes	No outcomes identified
Severe hypoglycaemic episodes	1 study (n=221), Very low quality, 0 fewer per 1000 (20 fewer to 20 more)
HbA1c change	No outcomes identified
Weight change	No outcomes identified
BMI change	No outcomes identified

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1.1.7.4.30. Switching — Switching to fixed-dose combination glimepiride/metformin slow release compared to staying on fixed-dose combination glimepiride/metformin standard release

Table 50: A summary matrix showing the outcomes for switching to glimepiride + metformin slow release compared to staying on glimepiride + metformin standard release for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to staying on glimepiride + metformin standard release	Switching to glimepiride + metformin slow release
Health-related quality of life	No outcomes identified
All-cause mortality	No outcomes identified
Cardiovascular mortality	No outcomes identified
3-item MACE	No outcomes identified
4-item MACE	No outcomes identified
5-item MACE	No outcomes identified
Non-fatal stroke	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified
Unstable angina	No outcomes identified
Hospitalisation for heart failure	No outcomes identified
Acute kidney injury	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified
Development of end stage kidney disease	No outcomes identified

Outcomes for drugs compared to staying on glimepiride + metformin standard release	Switching to glimepiride + metformin slow release
Death from renal cause	No outcomes identified
Cardiac arrhythmia	No outcomes identified
Diabetic ketoacidosis	No outcomes identified
Falls requiring hospitalisation	No outcomes identified
Progression of liver disease	No outcomes identified
Remission	No outcomes identified
Hypoglycaemia episodes	1 study (n=172), Very low quality, 105 more per 1000 (7 fewer to 331 more)
At night hypoglycaemic episodes	1 study (n=172), Very low quality, 23 fewer per 1000 (50 fewer to 83 more)
Severe hypoglycaemic episodes	No outcomes identified
HbA1c change	No outcomes identified
Weight change	No outcomes identified
BMI change	No outcomes identified

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1.1.7.4.31. Switching — Switching to monotherapy compared to switching to alogliptin

Table 51: A summary matrix showing the outcomes for switching to individual drugs compared to switching to alogliptin for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to switching to alogliptin	Switching to vildagliptin
Health-related quality of life	No outcomes identified
All-cause mortality	No outcomes identified
Cardiovascular mortality	No outcomes identified
3-item MACE	No outcomes identified
4-item MACE	No outcomes identified
5-item MACE	No outcomes identified
Non-fatal stroke	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified
Unstable angina	No outcomes identified
Hospitalisation for heart failure	No outcomes identified
Acute kidney injury	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified
Development of end stage kidney disease	No outcomes identified
Death from renal cause	No outcomes identified
Cardiac arrhythmia	No outcomes identified
Diabetic ketoacidosis	No outcomes identified
Falls requiring hospitalisation	No outcomes identified
Progression of liver disease	No outcomes identified
Remission	No outcomes identified
Hypoglycaemia episodes	1 study (n=130), Low quality, 0 fewer per 1000 (29 fewer to 30 more)
At night hypoglycaemic episodes	No outcomes identified
Severe hypoglycaemic episodes	1 study (n=130), Very low quality, 0 fewer per 1000 (30 fewer to 30 more)
HbA1c change	1 study (n=125), Low quality, MD 0.20% lower (0.43 lower to 0.03 higher)

Outcomes for drugs compared to switching to alogliptin	Switching to vildagliptin
Weight change	1 study (n=125), Low quality, MD 0.10 kg lower (0.74 lower to 0.54 higher)
BMI change	No outcomes identified

1.1.7.4.32. Switching — Switching monotherapy compared to staying on sitagliptin

Table 52: A summary matrix showing the outcomes for individual drugs compared to sitagliptin for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to staying on sitagliptin	Switching to liraglutide	Switching to semaglutide
Health-related quality of life	No outcomes identified	No outcomes identified
All-cause mortality	1 study (n=406), Very low quality, 5 more per 1000 (5 fewer to 14 more)	1 study (n=197), Moderate quality, 0 fewer per 1000 (20 fewer to 20 more)
Cardiovascular mortality	No outcomes identified	1 study (n=197), Moderate quality, 0 fewer per 1000 (20 fewer to 20 more)
3-item MACE	No outcomes identified	No outcomes identified
4-item MACE	No outcomes identified	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified
Non-fatal stroke	No outcomes identified	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified	1 study (n=197), Moderate quality, 0 fewer per 1000 (20 fewer to 20 more)
Unstable angina	No outcomes identified	No outcomes identified
Hospitalisation for heart failure	No outcomes identified	1 study (n=197), Low quality, 10 fewer per 1000 (30 fewer to 10 more)
Acute kidney injury	No outcomes identified	1 study (n=197), Moderate quality, 0 fewer per 1000 (20 fewer to 20 more)
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified

Outcomes for drugs compared to staying on sitagliptin	Switching to liraglutide	Switching to semaglutide
Development of end stage kidney disease	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified
Cardiac arrhythmia	No outcomes identified	No outcomes identified
Diabetic ketoacidosis	No outcomes identified	No outcomes identified
Falls requiring hospitalisation	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified
Remission	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	1 study (n=406), Very low quality, 15 fewer per 1000 (32 fewer to 2 more)	No outcomes identified
At night hypoglycaemic episodes	No outcomes identified	1 study (n=197), Moderate quality, 0 fewer per 1000 (20 fewer to 20 more)
Severe hypoglycaemic episodes	1 study (n=406), Moderate quality, 0 fewer per 1000 (10 fewer to 10 more)	1 study (n=197), Moderate quality, 0 fewer per 1000 (20 fewer to 20 more)
HbA1c change	1 study (n=406), Low quality, MD 0.61% lower (0.82 lower to 0.40 lower)	1 study (n=198), Low quality, MD 0.30% lower (0.60 lower to 0.00 higher)
Weight change	1 study (n=406), Moderate quality, MD 1.67 kg lower (2.34 lower to 1.00 lower)	1 study (n=198), Low quality, MD 1.50 kg lower (2.85 lower to 0.15 lower)
BMI change	No outcomes identified	1 study (n=198), Low quality, MD 0.40 kg/m^2 lower (0.90 lower to 0.10 higher)

1.1.7.4.33. Switching — Switching to monotherapy compared to switching to dulaglutide

Table 53: A summary matrix showing the outcomes for switching to individual drugs compared to switching to dulaglutide for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to switching to dulaglutide	Switching to semaglutide
Health-related quality of life	No outcomes identified

Outcomes for drugs compared to switching to dulaglutide	Switching to semaglutide
All-cause mortality	No outcomes identified
Cardiovascular mortality	No outcomes identified
3-item MACE	No outcomes identified
4-item MACE	No outcomes identified
5-item MACE	No outcomes identified
Non-fatal stroke	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified
Unstable angina	No outcomes identified
Hospitalisation for heart failure	No outcomes identified
Acute kidney injury	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified
Development of end stage kidney disease	No outcomes identified
Death from renal cause	No outcomes identified
Cardiac arrhythmia	No outcomes identified
Diabetic ketoacidosis	No outcomes identified
Falls requiring hospitalisation	No outcomes identified
Progression of liver disease	No outcomes identified
Remission	No outcomes identified
Hypoglycaemia episodes	1 study (n=32), Very low quality, 0 fewer per 1000 (114 fewer to 114 more)
At night hypoglycaemic episodes	No outcomes identified
Severe hypoglycaemic episodes	No outcomes identified
HbA1c change	1 study (n=32), Low quality, MD 0.42% lower (0.71 lower to 0.13 lower)
Weight change	1 study (n=32), Low quality, MD 2.50 kg lower (4.70 lower to 0.30 lower)
BMI change	No outcomes identified

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1.1.7.4.34. Switching — Switching to monotherapy compared to switching to liraglutide

Table 54: A summary matrix showing the outcomes for switching to individual drugs compared to switching to liraglutide for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to switching to liraglutide	Switching to glimepiride	Switching to canagliflozin
Health-related quality of life	No outcomes identified	Overall (DTR-QOL [Diabetes Therapy-related Quality of Life]) 1 study (n=34), Very low quality, MD 6.50 higher (0.14 higher to 12.86 higher)
All-cause mortality	No outcomes identified	No outcomes identified
Cardiovascular mortality	No outcomes identified	No outcomes identified
3-item MACE	No outcomes identified	No outcomes identified
4-item MACE	No outcomes identified	No outcomes identified
5-item MACE	No outcomes identified	No outcomes identified
Non-fatal stroke	No outcomes identified	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified	No outcomes identified
Unstable angina	No outcomes identified	No outcomes identified
Hospitalisation for heart failure	No outcomes identified	No outcomes identified
Acute kidney injury	No outcomes identified	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified	No outcomes identified
Development of end stage kidney disease	No outcomes identified	No outcomes identified
Death from renal cause	No outcomes identified	No outcomes identified
Cardiac arrhythmia	No outcomes identified	No outcomes identified
Diabetic ketoacidosis	No outcomes identified	No outcomes identified
Falls requiring hospitalisation	No outcomes identified	No outcomes identified
Progression of liver disease	No outcomes identified	No outcomes identified

Outcomes for drugs compared to switching to liraglutide	Switching to glimepiride	Switching to canagliflozin
Remission	No outcomes identified	No outcomes identified
Hypoglycaemia episodes	No outcomes identified	No outcomes identified
At night hypoglycaemic episodes	No outcomes identified	No outcomes identified
Severe hypoglycaemic episodes	No outcomes identified	1 study (n=39), Very low quality, 0 fewer per 1000 (95 fewer to 95 more)
HbA1c change	1 study (n=474) Very low quality, MD 0.42% higher (0.21 higher to 0.63 higher)	1 study (n=34), Very low quality, MD 0.10% higher (0.30 lower to 0.50 higher)
Weight change	No outcomes identified	1 study (n=34), Low quality, MD 0.20 kg higher (1.89 lower to 2.29 higher)
BMI change	No outcomes identified	1 study (n=34), Very low quality, MD 0.10 kg/m^2 higher (0.61 lower to 0.81 higher)

1.1.7.4.35. Switching — Staying on monotherapy compared to switching to dapagliflozin

Table 55: A summary matrix showing the outcomes for staying on individual drugs compared to switching to dapagliflozin for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to switching to dapagliflozin	Staying on pioglitazone
Health-related quality of life	No outcomes identified
All-cause mortality	No outcomes identified
Cardiovascular mortality	No outcomes identified
3-item MACE	No outcomes identified
4-item MACE	No outcomes identified
5-item MACE	No outcomes identified
Non-fatal stroke	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified
Unstable angina	No outcomes identified
Hospitalisation for heart failure	No outcomes identified

Outcomes for drugs compared to switching to dapagliflozin	Staying on pioglitazone
Acute kidney injury	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified
Development of end stage kidney disease	No outcomes identified
Death from renal cause	No outcomes identified
Cardiac arrhythmia	No outcomes identified
Diabetic ketoacidosis	No outcomes identified
Falls requiring hospitalisation	No outcomes identified
Progression of liver disease	No outcomes identified
Remission	No outcomes identified
Hypoglycaemia episodes	1 study (n=71), Very low quality, 63 more per 1000 (87 fewer to 420 more)
At night hypoglycaemic episodes	No outcomes identified
Severe hypoglycaemic episodes	1 study (n=71), Low quality, 0 fewer per 1000 (53 fewer to 53 more)
HbA1c change	1 study (n=71), Moderate quality, MD 0.10% higher (0.25 lower to 0.45 higher)
Weight change	1 study (n=71), Very low quality, MD 3.90 kg higher (2.85 lower to 10.65 higher)
BMI change	No outcomes identified

1.1.7.4.36. Switching — Switched to monotherapy compared to switched to glimepiride

Table 56: A summary matrix showing the outcomes for switching to individual drugs compared to switching to glimepiride for people with type 2 diabetes at high cardiovascular risk with no other comorbidities

Outcomes for drugs compared to switched to glimepiride	Switched to pioglitazone
Health-related quality of life	No outcomes identified
All-cause mortality	No outcomes identified
Cardiovascular mortality	No outcomes identified
3-item MACE	No outcomes identified
4-item MACE	No outcomes identified

Outcomes for drugs compared to switched to glimepiride	Switched to pioglitazone
5-item MACE	No outcomes identified
Non-fatal stroke	No outcomes identified
Non-fatal myocardial infarction	No outcomes identified
Unstable angina	No outcomes identified
Hospitalisation for heart failure	No outcomes identified
Acute kidney injury	No outcomes identified
Persistent signs of worsening kidney disease	No outcomes identified
Development of end stage kidney disease	No outcomes identified
Death from renal cause	No outcomes identified
Cardiac arrhythmia	No outcomes identified
Diabetic ketoacidosis	No outcomes identified
Falls requiring hospitalisation	No outcomes identified
Progression of liver disease	No outcomes identified
Remission	No outcomes identified
Hypoglycaemia episodes	1 study (n=244), Moderate quality, 152 fewer per 1000 (213 fewer to 53 fewer)
At night hypoglycaemic episodes	No outcomes identified
Severe hypoglycaemic episodes	No outcomes identified
HbA1c change	1 study (n=218), Low quality, MD 0.10% lower (1.49 lower to 1.29 higher)
Weight change	No outcomes identified
BMI change	No outcomes identified

See reports F3 (appendix F), F4 (appendix H), F5 (appendix J) and F7 (appendix L) for full GRADE tables.

1.1.8. Economic evidence

1.1.8.1. Included studies

Two health economic studies with relevant comparisons were included in this review:

1 comparing metformin, sulfonylurea, insulins, exenatide, linagliptin, liraglutide, pioglitazone, repaglinide, sitagliptin and vildagliptin in various combinations; and

1 comparing metformin, sulfonylurea, insulin, alogliptin, canagliflozin, dapagliflozin,
2 dulaglutide, empagliflozin, ertugliflozin, exenatide, linagliptin, liraglutide, lixisenatide,
3 pioglitazone, saxagliptin, semaglutide (oral and subcutaneous) and sitagliptin in various
4 combinations.

5 These are summarised in the health economic evidence profile/s below (Table 1 to Table 5)
6 and the health economic evidence tables in Appendix C.

7 1.1.8.2. Excluded studies

8 23 economic studies (26 papers) relating to this review question were identified but were
9 selectively excluded due to the availability of more applicable evidence. These are listed in
10 Appendix E, with reasons for exclusion given.

11 See also the health economic study selection flow chart in Appendix C.

12

1.1.9. Summary of included economic evidence

Table 57: Health economic evidence profile: NICE clinical guidelines

Study	Applicability	Limitations	Other comments	Total cost[(c)]	Total QALYs	Cost effectiveness	Uncertainty
NICE NG28 2015 (UK)	Directly applicable [(a)]	Minor limitations [(b)]	• Probabilistic model based on meta analysis of • Cost-utility analysis (QALYs) Population: Subsequent therapy in adults aged 18 years and over with type 2 diabetes. • Comparators: **First intensification** 1: Metformin- exenatide 2: Metformin- linagliptin 3: Metformin- liraglutide 4: Metformin-pioglitazone 5: Metformin-sitagliptin 6: Metformin-sulfonylurea 7: Metformin-vildagliptin **Second intensification** 8: Biphasic insulin aspart-metformin	**First intensification** 4: £20,390 6: £20,522 7: £21,569 2: £21,654 5: £21,685 1: £23,213 3: £23,614 **Second intensification** 24: £17,279 26: £21,636 25: £21,763 23: £22,000 21: £22,108 10: £22,738 16: £22,870 27: £22,896 22: £22,899 17: £23,260	**First intensification** 4: 8.217 6: 8.213 7: 8.249 2: 8.252 5: 8.243 1: 8.255 3: 8.284 **Second intensification** 24: 7.147 26: 7.097 25: 7.126 23: 7.02 21: 7.23 10: 6.979 16: 7.173 27: 7.06 22: 7.161 17: 7.135	**First intensification** 4: Baseline 6: Dominated 7: Extendedly dominated 2: £36,788 5: Dominated 1: Extendedly dominated 3: £61,381 **Second intensification** 24: Baseline 26: Dominated 25: Dominated 23: Dominated 21: Extendedly dominated 10: Dominated	**First intensification** Probability metformin-pioglitazone cost effective versus all other interventions (£20K/30K threshold): 48%/30%. Metformin-sulfonylurea was most cost-effective option at £20k in 19% of iterations. For people who could not take metformin-pioglitazone or metformin-sulfonylurea, metformin with either linagliptin, vildagliptin or sitagliptin were considered acceptable treatment options. **Second intensification** Probability metformin-pioglitazone-sulfonylurea cost effective versus all other interventions

Study	Applicability	Limitations	Other comments	Total cost[(c)]	Total QALYs	Cost effectiveness	Uncertainty
			9: Biphasic insulin aspart-metformin/sulfonylurea 10: Biphasic insulin aspart-repaglinide 11: Exenatide-metformin-sulfonylurea 12: Insulin degludec/aspart mix-metformin 13: Insulin degludec-metformin 14: Insulin determir-metformin 15: Insulin glargine-metformin 16: Insulin glargine-metformin-sulfonylurea 17: Insulin glargine-sulfonylurea 18: Insulin lispro mix 50 and mix 25 19: Insulin lispro mix 50/50-metformin 20: Liraglutide-metformin-sulfonylurea 21: Metformin-NPH insulin 22: Metformin- NPH insulin-repaglinide 23: Metformin-NPH insulin-sulfonylurea	12: £23,263 9: £23,303 15: £23,716 8: £24,028 19: £24,136 14: £24,228 11: £25,795 13: £26,097 18: £26,307 20: £30,166	12: 7.134 9: 7.051 15: 7.27 8: 7.013 19: 7.126 14: 7.317 11: 7.229 23: 7.32 18: 6.818 20: 7.352	16: Dominated 27: Dominated 22: Dominated 17: Dominated 12: Dominated 9: Dominated 15: Extendedly dominated 8: Dominated 19: Dominated 14: £40,778 11: Dominated 13: Extendedly dominated 18: Dominated 20: £172,890	(£20K/30K threshold): 75%/56% **Analysis of uncertainty:** **First intensification:** Metformin-pioglitazone remained the most cost-effective treatment option at £20k when 2-year treatment effects data for HbA1c and weight change were applied. **Second intensification:** Metformin-pioglitazone-sulfonylurea remained the most cost-effective treatment option at £20k when 2-year treatment effects data for HbA1c and weight change were applied.

Study	Applicability	Limitations	Other comments	Total cost[(c)]	Total QALYs	Cost effectiveness	Uncertainty
			24: Metformin-pioglitazone-sulfonylurea 25: Metformin-sitagliptin-sulfonylurea 26: NPH insulin 27: NPH insulin • Time horizon: 40 years				
NICE NG28 2022 (UK)	Directly applicable [(a)]	Minor limitations [(b)]	• Probabilistic model based on meta-analysis of RCTs • Cost-utility analysis (QALYs) • Population: Subsequent therapy in adults aged 18 years and over with type 2 diabetes. • Comparators: **First intensification CVOTs as additions (compared to metformin + sulfonylurea)** 1: Alogliptin + metformin + sulfonylurea 2: Canagliflozin + metformin + sulfonylurea 3: Dapagliflozin + metformin + sulfonylurea	**Total costs (mean per patient):** **First intensification CVOTs as additions (compared to metformin + sulfonylurea)** 11: £18,612 12: £20,467 1: £22,878 6: £23,026 8: £23,516 3: £24,035 16: £24,181 5: £24,454	11: 8.768 12: 8.64 1: 8.705 6: 8.967 8: 8.795 3: 9.141 16: 8.792 5: 9.006 13: 8.487 2: 8.97 10: 8.518 4: 8.937 14: 9.23 7: 8.825 15: 8.413 9: 8.79 **First intensification CVOTs**	**First intensification CVOTs as additions (compared to metformin + sulfonylurea)** 11: Baseline 12: Dominated 1: Dominated 6: £22,153 8: £179,895 3: £14,540 16: £231,735 5: £24,584 13: Dominated 2: £33,152 10: Dominated 4: £70,257 14: £25,974 7: £213,122	Subgroup analyses are conducted in people with: (a) High cardiovascular risk- no prior event (b) High cardiovascular risk- prior event (c) All high cardiovascular risk (d) High BMI Results are presented in Appendix C.

Study	Applicability	Limitations	Other comments	Total cost[(c)]	Total QALYs	Cost effectiveness	Uncertainty
			4: Dulaglutide + metformin + sulfonylurea 5: Empagliflozin + metformin + sulfonylurea 6: Ertugliflozin + metformin + sulfonylurea 7: Exenatide + metformin + sulfonylurea 8: Linagliptin + metformin + sulfonylurea 9: Liraglutide + metformin + sulfonylurea 10: Lixisenatide + metformin + sulfonylurea 11: Metformin + sulfonylurea 12: Pioglitazone + metformin + sulfonylurea 13: Saxagliptin + metformin + sulfonylurea 14: Semaglutide (injection) + metformin + sulfonylurea 15: Semaglutide (oral) + metformin + sulfonylurea 16: Sitagliptin + metformin + sulfonylurea **First intensification CVOTs as replacements (compared to metformin alone)**	13: £24,592 2: £25,297 10: £26,908 4: £30,453 14: £30,622 7: £30,832 15: £32,300 9: £36,412 (95% CI: NR; p=NR) **First intensification CVOTs as replacements (compared to metformin alone)** 27: £18,474 28: £19,780 17: £22,657 22: £23,001 24: £23,409 32: £23,933 19: £24,158 29: £24,261	**as replacements (compared to metformin alone)** 27: 8.995 28: 8.973 17: 8.95 22: 9.171 24: 9.017 32: 9.044 19: 9.32 29: 8.752 22: 9.209 18: 9.244 26: 8.68 20: 9.144 30: 9.477 23: 9.073 31: 8.743 25: 8.979 **Second intensification CVOTs as additions (compared to**	15: Dominated 9: £808,413 **First intensification CVOTs as replacements (compared to metformin alone)** 27: Baseline 28: Dominated 17: Dominated 22: £25,755 24: £221,103 32: £112,315 19: £17,497 29: Dominated 21: £27,927 18: £25,882 26: Dominated 20: £80,490 30: £24,908 23: £155,507 31: Dominated 25: Dominated	

Study	Applicability	Limitations	Other comments	Total cost[(c)]	Total QALYs	Cost effectiveness	Uncertainty
			17: Alogliptin + metformin 18: Canagliflozin + metformin 19: Dapagliflozin + metformin 20: Dulaglutide + metformin 21: Empagliflozin + metformin 22: Ertugliflozin + metformin 23: Exenatide + metformin 24: Linagliptin + metformin 25: Liraglutide + metformin 26: Lixisenatide + metformin 27: Metformin 28: Pioglitazone + metformin 29: Saxagliptin + metformin 30: Semaglutide (injection) + metformin 31: Semaglutide (oral) + metformin 32: Sitagliptin + metformin **Second intensification CVOTs as additions**	21: £24,435 18: £24,916 26: £27,112 20: £30,450 30: £30,470 23: £30,614 31: £31,586 25: £36,517 **Second intensification CVOTs as additions (compared to metformin + sulfonylurea + NPH insulin)** 43: £19,604 44: £21,665 33: £23,553 38: £23,616 40: £24,080 35: £24,523 48: £24,814 37: £24,973	**metformin + sulfonylurea + NPH insulin)** 43: 7.875 44: 7.722 33: 7.81 38: 8.066 40: 7.903 35: 8.243 48: 7.891 37: 8.098 45: 7.592 34: 8.048 42: 7.668 36: 8.048 36: 8.325 39: 7.926 47: 7.491 41: 7.922 **Second intensification CVOTs as replacements (compared to**	**Second intensification CVOTs as additions (compared to metformin + sulfonylurea + NPH insulin)** 43: Baseline 44: Dominated 33: Dominated 38: £20,983 40: £156,837 35: £13,357 48: £329,076 37: £24,011 45: Dominated 34: £36,849 42: Dominated 36: £62,654 46: £24,950 39: £222,593 47: Dominated 41: £343,276 **Second intensification CVOTs as**	

Study	Applicability	Limitations	Other comments	Total cost[(c)]	Total QALYs	Cost effectiveness	Uncertainty
			(compared to metformin + sulfonylurea + NPH insulin) 33: Alogliptin + metformin + sulfonylurea + NPH insulin 34: Canagliflozin + metformin + sulfonylurea + NPH insulin 35: Dapagliflozin + metformin + sulfonylurea + NPH insulin 36: Dulaglutide + metformin + sulfonylurea + NPH insulin 37: Empagliflozin + metformin + sulfonylurea + NPH insulin 38: Ertugliflozin + metformin + sulfonylurea + NPH insulin 39: Exenatide + metformin + sulfonylurea + NPH insulin 40: Linagliptin + metformin + sulfonylurea + NPH insulin	45: £25,161 34: £25,972 42: £27,020 36: £30,453 46: £30,833 39: £30,922 47: £32,385 41: £35,927 **Second intensification CVOTs as replacements (compared to metformin + NPH insulin)** 59: £19,828 60: £21,314 49: £23,704 54: £23,967 56: £24,350 64: £24,936 51: £25,030 61: £25,203 53: £25,329	**metformin + NPH insulin)** 59: 8.124 60: 8.073 49: 8.077 54: 8.296 56: 8.15 64: 8.163 51: 8.448 61: 7.878 53: 8.328 50: 8.344 58: 7.856 52: 8.276 62: 8.584 55: 8.194 63: 7.846 57: 8.133	**replacements (compared to metformin + NPH insulin)** 59: Baseline 60: Dominated 49: Dominated 54: £24,052 56: £175,448 64: £130,822 51: £16,088 61: Dominated 53: £26,958 50: £27,851 58: Dominated 52: £72,742 62: £24,453 55: £161,775 63: Dominated 57: £1,984,769	

Study	Applicability	Limitations	Other comments	Total cost[(c)]	Total QALYs	Cost effectiveness	Uncertainty
			41: Liraglutide + metformin + sulfonylurea + NPH insulin 42: Lixisenatide + metformin + sulfonylurea + NPH insulin 43: Metformin + sulfonylurea + NPH insulin 44: Pioglitazone + metformin + sulfonylurea + NPH insulin 45: Saxagliptin + metformin + sulfonylurea + NPH insulin 46: Semaglutide (injection) + metformin + sulfonylurea + NPH insulin 47: Semaglutide (oral) + metformin + sulfonylurea + NPH insulin 48: Sitagliptin + metformin + sulfonylurea + NPH insulin **Second intensification CVOTs as replacements (compared to metformin + NPH insulin)** 49: Alogliptin + metformin + NPH insulin	50: £25,950 58: £27,630 52: £30,853 62: £31,067 55: £31,095 63: £32,049 57: £36,453			

Study	Applicability	Limitations	Other comments	Total cost[(c)]	Total QALYs	Cost effectiveness	Uncertainty
			50: Canagliflozin + metformin + NPH insulin 51: Dapagliflozin + metformin + NPH insulin 52: + metformin + NPH insulin 53: Empagliflozin + metformin + NPH insulin 54: Ertugliflozin + metformin + NPH insulin 55: Exenatide + metformin + NPH insulin 56: Linagliptin + metformin + NPH insulin 57: Liraglutide + metformin + NPH insulin 58: Lixisenatide + metformin + NPH insulin 59: Metformin + NPH insulin 60: Pioglitazone + metformin + NPH insulin 61: Saxagliptin + metformin + NPH insulin 62: Semaglutide (injection) + metformin + NPH insulin 63: Semaglutide (oral) + metformin + NPH insulin 64: Sitagliptin + metformin + NPH insulin				

Study	Applicability	Limitations	Other comments	Total cost[(c)]	Total QALYs	Cost effectiveness	Uncertainty
			• Time horizon: 40 years				

Abbreviations: BMI= body mass index; CVOT= cardiovascular outcome trials; GLP-1= glucagon-like peptide-1; ICER= incremental cost-effectiveness ratio; NPH= neutral protamine Hagedorn; QALY= quality-adjusted life years; RCT= randomised controlled trial; SGLT-2i= sodium-glucose cotransporter-2 inhibitor

(a) Newer GLP-1 agonists and SGLT-2 inhibitors are missing from the analysis.

(b) The validity of HbA1c as a surrogate marker used to predict cardiovascular outcomes and mortality has been questioned. Sources of costs are dated and do not accurately reflect current NHS conditions. The proportion of hypoglycaemic episodes that are severe (2%) and (therefore incur costs to the NHS) was assumed to be the same across all treatments.

(c) 2012/13 UK pounds. Cost components incorporated: Drug costs, drug consumables (needles, self-monitoring blood glucose strips and lancets, sharps bins), staff time for GLP-1 and insulin initiation, diabetes-related complications costs

(d) Only CVOT drugs are included in the incremental analysis; drug classes such as sulfonylureas and insulin are included as background treatments only.

(e) Probabilistic analysis was only conducted for the second intensification stage due to a lack of time. The analysis assumes that non-cardiovascular (microvascular) treatment-related outcomes are the same between comparator arms. The timing of treatment intensification does not differ between different treatment options, meaning between-treatment effects on HbA1c are not fully captured.

(f) 2022 UK pounds. Cost components incorporated: Drug costs, drug consumables (needles, self-monitoring blood glucose strips and lancets [for sulfonylureas and insulins only], sharps bins), staff time for GLP-1 and insulin drug class initiation, diabetes-related complications costs

1.1.10. Economic model

Population and strategies evaluated

The modelled population were adults with type 2 diabetes mellitus (T2DM) and one of the following risk factors:

- Atherosclerotic cardiovascular disease (ASCVD)
- Chronic kidney disease (CKD) stages 1-3
- CKD stage 4
- Heart failure (HF)
- Aged under 40 years
- High risk of CVD and living with obesity
- High risk of CVD and living with overweight

The interventions explored were:

- Biguanide
  - Modified-release metformin monotherapy
- DPP-4 inhibitors
  - Alogliptin
  - Linagliptin
  - Saxagliptin
  - Sitagliptin
  - Vildagliptin
- GLP-1 receptor agonists
  - Dulaglutide
  - Exenatide
  - Liraglutide
  - Semaglutide (oral)
  - Semaglutide (subcutaneous)
- Insulin
- SGLT2 inhibitors
  - Canagliflozin
  - Dapagliflozin
  - Empagliflozin
  - Ertugliflozin
- Sulfonylurea
  - Gliclazide
- Thiazolidinedione
  - Pioglitazone

Treatments other than modified-release metformin monotherapy were assumed to be in addition to modified-release metformin. All analyses were conducted in the UKPDS OM2.2 model with cardiovascular and renal outcomes calibrated to match outcomes reported from guideline review network meta-analysis (NMA).

Methods and data sources (Summary)

Baseline

The UKPDS OM2.2 model requires 13 inputs at baseline consisting of demographics, clinical risk factors and pre-existing conditions. These were obtained from the Clinical Practice Research Datalink (CPRD) AURUM, which accounts for around 13 million patients, or around 20% of the UK population. The UKPDS 90 risk factor time path equations were used to estimate the change over time to the baseline dataset.

Treatment effects

Two types of treatment effects applied in the model; effects on surrogate measures (HbA1c and weight) and effects on cardiovascular and renal outcomes such as those reported in CVOT trials.

HbA1c

The treatment effect on HbA1c was modelled in a linear manner over one year. Following this, change was dictated in line with the UKPDS risk equations. The treatment effect of metformin on HbA1C was set to 0 as the UKPDS risk equations already accounted for the effects of metformin during treatment intensification in the original cohort, and so applying an effect here would lead to double counting.

Weight

Treatment effects in year one was assumed to occur in a linear manner. For years 2-4, weight loss from baseline at time 0 were based on real-world data from CPRD AURUM. From year 4 onwards, weight rebound to baseline was modelled in a linear manner over one year with GLP-1 agonists and two years with SGLT-2 inhibitors, in line with committee assumptions.

Cardiovascular and renal outcomes

Treatment effects on cardiovascular and renal outcomes (specifically angina, heat failure, myocardial infarction, stroke, established kidney disease and cardiovascular mortality) predicted by the model were calibrated to those reported in the clinical review NMA. This was done because external validation studies of the UKPDS model have reported that it overpredicts cardiovascular outcomes such as myocardial infarction and mortality and underestimated the cardiovascular benefits of newer drug classes like the GLP-1 agonists and SGLT-2 inhibitors.

Utilities

- Baseline utility with T2DM was taken from a systematic literature review and meta-analysis. It was assumed that the baseline utility applied to model cohort starting age (67 years). The ratio difference between this T2DM-specific utility and the population-level utility at 67 years was applied to the general population life-table to give age- and sex-specific utility scores for people with T2DM

- Utility detriments for diabetic events were matched to those referenced in NG28 2022.

Resource use and costs

- Medication costs were obtained from the NHS Electronic Drug Tariff (accessed 13/07/2024). The NHS Prescription Costs Analysis (PCA) 2023/24 was then referenced to calculate a weighted average cost for each treatment based on the total amount of each formulation dispensed in primary care.
- Diabetic event costs were obtained from Alva 2015, which reported costs specific to a T2DM population based on the UKPDS study. An algorithm within it that enabled the calculation of costs that were dependent on age, sex event type and history of comorbidities was applied to generate event costs age- and sex-specific costs.

Computations

- All analyses were conducted in the UKPDS Global beta model with risk equations modified in line with the clinical evidence review.

Results

Table 58. Results: base-case analysis (ASCVD)

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Metformin	£45,193	4.71	Reference	Reference	Reference	£0	5
SGLT-2 inhibitor	£50,430	4.95	£5,237	0.2394	£21,877	-£449	6
Dulaglutide	£49,724	4.83	£4,531	0.1211	£37,434	-£2,110	11
Exenatide	£49,601	4.87	£4,408	0.1672	£26,363	-£1,064	9
Liraglutide	£55,160	5.01	£9,967	0.3067	£32,499	-£3,833	16
Semaglutide; Oral	£63,340	5.30	£18,147	0.5962	£30,436	-£6,223	19
Semaglutide; Subcutaneous	£47,583	4.87	£2,390	0.1645	£14,529	£900	1
Alogliptin	£49,903	4.83	£4,711	0.1213	£38,835	-£2,285	14
Linagliptin	£46,522	4.73	£1,329	0.0243	£54,772	-£844	8
Saxagliptin	£46,727	4.67	£1,534	-0.0347	Dominated	-£2,227	13
Sitagliptin	£45,933	4.64	£740	-0.0701	Dominated	-£2,141	12
Vildagliptin	£46,124	4.72	£931	0.0103	£90,279	-£725	7
Gliclazide	£45,181	4.71	-£12	0.0058	Dominant	£127	4
Insulin	£49,966	4.70	£4,774	-0.0059	Dominated	-£4,892	17
Pioglitazone	£46,232	4.79	£1,039	0.0837	£12,422	£634	2
SGLT-2i + Dulaglutide	£54,982	5.05	£9,789	0.3417	£28,647	-£2,955	15
SGLT-2i + Exenatide	£54,534	5.10	£9,341	0.3908	£23,901	-£1,525	10
SGLT-2i + Liraglutide	£61,350	5.25	£16,157	0.5398	£29,931	-£5,361	18
SGLT-2i + Semaglutide; Oral	£71,236	5.56	£26,043	0.8557	£30,435	-£8,929	20
SGLT-2i	£51,709	5.05	£6,516	0.3406	£19,134	£295	3

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
+ Semaglutide; Subcutaneous							

Abbreviations: ASCVD= atherosclerotic cardiovascular disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2; SW= south-west

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

Table 59. Results: base-case analysis (CKD 1-3)

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Metformin	£41,595	5.60	Reference	Reference	Reference	£0	4
SGLT-2 inhibitor	£45,538	5.86	£3,943	0.27	£14,716	£1,416	1
Dulaglutide	£46,613	5.69	£5,018	0.09	£53,197	-£3,132	11
Exenatide	£45,952	5.74	£4,358	0.15	£29,469	-£1,400	7
Liraglutide	£51,572	5.90	£9,978	0.30	£33,239	-£3,974	12
Semaglutide; Oral	£57,648	6.15	£16,054	0.55	£28,934	-£4,957	14
Semaglutide; Subcutaneous	£52,199	5.90	£10,604	0.30	£35,328	-£4,601	13
Alogliptin	£45,976	5.72	£4,382	0.13	£34,567	-£1,847	8
Linagliptin	£42,991	5.64	£1,397	0.04	£33,546	-£564	5
Saxagliptin	£43,336	5.55	£1,741	-0.04	Dominated	-£2,606	10
Sitagliptin	£42,230	5.52	£635	-0.08	Dominated	-£2,221	9
Vildagliptin	£42,669	5.61	£1,075	0.01	£94,453	-£847	6
Gliclazide	£41,547	5.59	-£47	0.00	SW Quadrant	£2	3
Insulin	£47,200	5.59	£5,605	-0.01	Dominated	-£5,758	15
Pioglitazone	£42,468	5.66	£874	0.07	£12,567	£517	2

Abbreviations: CKD= chronic kidney disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2; SW= south-west

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

Table 60. Results: base-case analysis (CKD 4)

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Standard Care	£34,466	3.39	Reference	Reference	Reference	£0	4
SGLT-2 inhibitor	£37,847	3.68	£3,381	0.29	£11,666	£2,415	1
Dulaglutide	£38,254	3.50	£3,787	0.11	£33,030	-£1,494	8
Exenatide	£37,723	3.53	£3,257	0.15	£22,053	-£303	6
Liraglutide	£41,390	3.61	£6,924	0.22	£31,097	-£2,471	11

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Semaglutide; Oral	£50,592	3.87	£16,125	0.49	£33,196	-£6,410	15
Semaglutide; Subcutaneous	£43,075	3.61	£8,609	0.23	£37,838	-£4,059	14
Alogliptin	£37,914	3.45	£3,447	0.07	£51,244	-£2,102	10
Linagliptin	£35,392	3.44	£926	0.05	£17,598	£126	2
Saxagliptin	£35,631	3.35	£1,164	-0.03	Dominated	-£1,857	9
Sitagliptin	£35,487	3.31	£1,020	-0.08	Dominated	-£2,562	12
Vildagliptin	£35,337	3.41	£871	0.02	£47,798	-£506	7
Gliclazide	£34,584	3.40	£118	0.01	£12,628	£69	3
Insulin	£38,225	3.39	£3,759	0.00	£1,711,758	-£3,715	13
Pioglitazone	£35,073	3.41	£606	0.03	£22,815	-£75	5

Abbreviations: CKD= chronic kidney disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2; SW= south-west

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

Table 61. Results: base-case analysis (HF)

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Metformin	£47,554	3.133	Reference	Reference	Reference	£0	4
SGLT-2 inhibitor	£50,709	3.250	£3,154	0.117	£26,919	-£811	6
Dulaglutide	£51,054	3.226	£3,500	0.093	£37,812	-£1,649	10
Exenatide	£50,975	3.242	£3,421	0.109	£31,320	-£1,236	9
Liraglutide	£52,777	3.294	£5,223	0.160	£32,571	-£2,016	12
Semaglutide; Oral	£61,055	3.489	£13,501	0.355	£37,993	-£6,394	14
Semaglutide; Subcutaneous	£49,246	3.298	£1,691	0.165	£10,274	£1,601	1
Alogliptin	£52,130	3.261	£4,575	0.128	£35,674	-£2,010	11
Linagliptin	£48,879	3.153	£1,325	0.020	£66,787	-£928	8
Saxagliptin	£48,215	3.123	£661	-0.010	Dominated	-£870	7
Sitagliptin	£46,779	3.151	-£776	0.018	Dominant	£1,127	2
Vildagliptin	£48,154	3.149	£600	0.015	£38,780	-£290	5
Gliclazide	£47,500	3.142	-£55	0.009	Dominant	£239	3
Insulin	£50,821	3.144	£3,266	0.011	£291,349	-£3,042	13
Pioglitazone	Contra-indicated						

Abbreviations: HF= heart failure; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2; SW= south-west

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

Table 62. Results: base-case analysis (high risk of CVD and living with obesity)

Treatment[a]	Cost[b]	QALY [b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Metformin	£51,289	8.38	Reference	Reference	Reference	£0	2
SGLT-2 inhibitor	£56,013	8.62	£4,724	0.237	£19,942	£14	1
Dulaglutide	£59,067	8.51	£7,779	0.127	£61,348	-£5,243	13
Exenatide	£56,574	8.54	£5,285	0.151	£34,938	-£2,260	9
Liraglutide	£62,362	8.66	£11,073	0.271	£40,787	-£5,643	14
Semaglutide; Oral	£62,531	8.79	£11,242	0.406	£27,693	-£3,123	11
Semaglutide; Subcutaneous	£58,363	8.64	£7,074	0.252	£28,117	-£2,042	7
Alogliptin	£54,241	8.43	£2,953	0.043	£69,077	-£2,098	8
Linagliptin	£53,548	8.42	£2,259	0.034	£65,790	-£1,572	6
Saxagliptin	£53,194	8.28	£1,905	-0.101	Dominated	-£3,931	12
Sitagliptin	£51,061	8.24	-£228	-0.146	SW Quadrant	-£2,686	10
Vildagliptin	£52,955	8.39	£1,666	0.005	£326,586	-£1,564	5
Gliclazide	£51,452	8.38	£163	-0.006	Dominated	-£280	4
Insulin	£59,394	8.35	£8,105	-0.031	Dominated	-£8,716	15
Pioglitazone	£51,369	8.38	£80	-0.004	Dominated	-£158	3

Abbreviations: CVD= cardiovascular disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

Table 63. Results: base-case analysis (high risk of CVD and living with overweight)

Treatment[a]	Cost[b]	QALY [b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Metformin	£48,193	7.60	Reference	Reference	Reference	£0	2
SGLT-2 inhibitor	£52,410	7.79	£4,218	0.18	£23,039	-£556	4
Dulaglutide	£55,285	7.70	£7,092	0.10	£71,570	-£5,110	13
Exenatide	£52,875	7.71	£4,682	0.10	£45,397	-£2,620	10
Liraglutide	£58,218	7.81	£10,025	0.21	£47,165	-£5,774	14
Semaglutide; Oral	£57,169	7.87	£8,976	0.27	£33,843	-£3,671	12
Semaglutide; Subcutaneous	£54,684	7.82	£6,491	0.22	£29,243	-£2,052	9
Alogliptin	£50,563	7.63	£2,370	0.03	£88,111	-£1,832	8
Linagliptin	£50,223	7.62	£2,030	0.02	£106,214	-£1,648	7
Saxagliptin	£49,999	7.53	£1,806	-0.07	Dominated	-£3,237	11
Sitagliptin	£47,825	7.52	-£368	-0.09	SW Quadrant	-£1,367	5

Vildagliptin	£49,788	7.61	£1,596	0.01	£159,244	-£1,395	6
Gliclazide	£48,469	7.61	£276	0.01	£40,612	-£140	3
Insulin	£55,825	7.59	£7,632	-0.01	Dominated	-£7,796	15
Pioglitazone	£48,325	7.65	£132	0.05	£2,568	£898	1

Abbreviations: CVD= cardiovascular disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

Table 64. Results: base-case analysis (aged under 40 years)

Treatment[(a)]	Cost[(b)]	QALY [(b)]	Inc. cost[(b)]	Inc. QALYs[(b)]	ICER[(b)]	INMB[(c)]	Rank[(d)]
Metformin	£75,441	16.18	Reference	Reference	Reference	£0	3
SGLT-2 inhibitor	£82,329	16.43	£6,888	0.25	£28,056	-£1,978	4
Dulaglutide	£88,632	16.31	£13,191	0.13	£102,108	-£10,607	16
Exenatide	£83,329	16.29	£7,888	0.11	£73,521	-£5,742	11
Liraglutide	£92,931	16.48	£17,491	0.29	£59,398	-£11,601	17
Semaglutide; Oral	£89,433	16.54	£13,992	0.35	£39,537	-£6,914	12
Semaglutide; Subcutaneous	£87,036	16.41	£11,595	0.23	£50,900	-£7,039	13
Alogliptin	£79,133	16.20	£3,692	0.02	£191,240	-£3,306	8
Linagliptin	£79,458	16.22	£4,017	0.04	£99,942	-£3,213	7
Saxagliptin	£78,596	16.06	£3,156	-0.13	Dominated	-£5,700	10
Sitagliptin	£74,860	16.05	-£581	-0.14	SW Quadrant	-£2,144	5
Vildagliptin	£78,436	16.20	£2,996	0.02	£197,044	-£2,691	6
Gliclazide	£75,798	16.20	£358	0.02	£18,100	£38	2
Insulin	£89,694	16.16	£14,254	-0.03	Dominated	-£14,833	20
Pioglitazone	£75,581	16.20	£141	0.02	£7,212	£250	1
SGLT-2i + Dulaglutide	£96,716	16.64	£21,275	0.45	£46,884	-£12,199	18
SGLT-2i + Exenatide	£90,073	16.64	£14,632	0.45	£32,394	-£5,598	9
SGLT-2i + Liraglutide	£101,262	16.77	£25,822	0.59	£44,015	-£14,089	19
SGLT-2i + Semaglutide; Oral	£97,310	16.82	£21,869	0.63	£34,533	-£9,204	15
SGLT-2i + Semaglutide; Subcutaneous	£96,253	16.77	£20,812	0.59	£35,552	-£9,104	14

Abbreviations: CVD= cardiovascular disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2; SW= south-west

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

1.1.11. Economic evidence statements

- One cost-utility analysis reported that adding pioglitazone to metformin was the most cost-effective option in a full incremental analysis that included exenatide, linagliptin, liraglutide, sitagliptin, a sulfonylurea and vildagliptin. At second intensification, the combination of metformin, pioglitazone and a sulfonylurea was most cost-effective in a full incremental analysis that included 19 other interventions of various combinations of insulins, liraglutide, metformin, pioglitazone, sitagliptin and a sulfonylurea. This analysis was assessed as directly applicable with potentially serious limitations.
- One cost-utility analysis reported that dapagliflozin was cost effective when added to various background therapy combinations, specifically metformin alone, metformin plus a sulfonylurea, metformin plus neutral protamine Hagedorn (NPH) insulin and metformin plus a sulfonylurea plus NPH insulin. Other interventions included alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin, dulaglutide, exenatide, liraglutide, lixisenatide, oral semaglutide, subcutaneous semaglutide, canagliflozin, empagliflozin, ertugliflozin and pioglitazone. This analysis was assessed as directly applicable with minor limitations.
- One original model assessed the following interventions: alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin, dulaglutide, exenatide, liraglutide, oral semaglutide, subcutaneous semaglutide, SGLT-2 inhibitors, gliclazide, insulin and pioglitazone. All interventions were assessed as additive therapy to modified release (MR) metformin and were compared to MR metformin alone. Triple therapy (metformin concurrent with SGLT-2 inhibitor and GLP-1 agonist) was assessed in select populations. Comparisons were made across seven sub-populations and reported that:
    - In people with ASCVD, subcutaneous was the most cost-effective intervention with pioglitazone, gliclazide and triple therapy with an SGLT-2 inhibitor and subcutaneous semaglutide being the only other cost-effective treatments when compared directly to metformin monotherapy
    - In both people with CKD 1-3 and CKD 4, SGLT-2 inhibitors were the most cost-effective intervention. Compared to metformin monotherapy, gliclazide was cost-effective when compared to metformin monotherapy in both populations with pioglitazone cost-effective in CKD 1-3 and linagliptin in CKD4.
    - In people with HF, subcutaneous semaglutide was the most cost-effective option with sitagliptin and gliclazide also cost-effective compared to metformin monotherapy
    - In people with high risk of CVD and living with obesity SGLT-2 inhibitors were the only intervention cost-effective compared to metformin monotherapy.
    - In people with high risk of CVD and living with overweight pioglitazone was the only intervention cost effective compared to metformin
    - In people aged under 40 years only pioglitazone and gliclazide were cost-effective compared to metformin monotherapy with pioglitazone being the most cost-effective

  This analysis was assessed as directly applicable with minor limitations.

1.1.12. The committee's discussion and interpretation of the evidence

For more information, please see the committee discussion report.

1.1.13. Recommendations supported by this evidence review

This evidence review supports recommendations 1.8.6-1.8.32, 1.8.34,1.8.38-1.8.60 and the recommendation for research on treatment strategies for people with type 2 diabetes and frailty and access to SGLT-2 inhibitors and management of early onset type 2 diabetes. Other evidence supporting these recommendations can be found in the evidence reviews on initial therapy (evidence review E).

1.1.14. References

National Institute for Health and Care Excellence (NICE). Type 2 Diabetes in Adults: Management. NICE guideline [NG28], 2022. Available: https://www.nice.org.uk/guidance/ng28