

## Type 2 diabetes in adults: management

**[F7] Evidence reviews for subsequent pharmacological management of type 2 diabetes**

*NICE guideline*

*Evidence reviews underpinning recommendations 1.9.1 to 1.9.5, 1.10.1 to 1.18.4, 1.19.1 to 1.19.2, 1.20.1 to 1.20.2, 1.21.3 to 1.31.1 and recommendations for research in the NICE guideline*

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*Final*

*This evidence review was developed by NICE*



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# Contents

<b>Appendices</b> .....	<b>6</b>
Appendix L   GRADE tables – Model 5: Type 2 diabetes and higher cardiovascular risk .....	6



# Appendices

## Appendix L GRADE tables – Model 5: Type 2 diabetes and higher cardiovascular risk

### L.1 Adding

#### L.1.1 Metformin

##### L.1.1.1 Adding metformin compared to adding placebo

**Table 1: Clinical evidence profile: Adding metformin compared to adding placebo**

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerat ions	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>all-cause mortality at end of follow up Mean follow-up: 35 month(s)</b>											
2	RC T	serio us <sup>1</sup>	not seriou s	serious <sup>2</sup>	very seriou s <sup>3</sup>	NA	11/402	6/40 0	PETO OR 1.82 (0.69, 4.78)	12 more per 1000 (8 fewer to 32 more)	very low
<b>cardiovascular mortality at end of follow up Mean follow-up: 52 month(s)</b>											
1 (kooy 2009)	RC T	serio us <sup>1</sup>	not seriou s	NA <sup>4</sup>	very seriou s <sup>3</sup>	NA	3/196	1/19 4	RR 2.97 (0.31, 28.30)	10 more per 1000 (4 fewer to 141 more)	very low
<b>hospitalisation for heart failure at end of follow up Mean follow-up: 52 month(s)</b>											

1 (kooy 2009)	RC T	serious <sup>1</sup>	not serious	NA <sup>4</sup>	very serious <sup>3</sup>	NA	3/196	4/194	RR 0.74 (0.17, 3.27)	5 fewer per 1000 (17 fewer to 47 more)	very low
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 14.9 month(s)</b>											
4	RC T	not serious	not serious	not serious	not serious	NA	291/394	285/395	RR 1.03 (0.90, 1.17)	21 more per 1000 (70 fewer to 125 more)	high
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 15 month(s)</b>											
2	RC T	not serious	not serious	very serious <sup>5</sup>	very serious <sup>3</sup>	NA	17/283	8/279	RR 2.62 (0.27, 25.56)	46 more per 1000 (21 fewer to 704 more)	very low
<b>hba1c change (% , lower values are better, mean difference) at end of follow up Mean follow-up: 19.6 month(s)</b>											
6	RC T	serious <sup>1</sup>	not serious	very serious <sup>5</sup>	serious <sup>6</sup>	NA	611	610	MD -0.47 (-0.80, -0.13)	MD 0.47 lower (0.80 lower to 0.13 lower)	very low
<b>weight change (kg, lower values are better, mean difference) at end of follow up Mean follow-up: 14.9 month(s)</b>											
4	RC T	serious <sup>1</sup>	not serious	very serious <sup>5</sup>	serious <sup>7</sup>	NA	388	393	MD -1.19 (-3.92, 1.54)	MD 1.19 lower (3.92 lower to 1.54 higher)	very low
<b>bmi change (kg/m2, lower values are better, mean difference) at end of follow up Mean follow-up: 35 month(s)</b>											

2	RC T	not serious	not serious	not serious	not serious	NA	402	400	MD -0.99 (-1.18, - 0.80)	MD 0.99 lower (1.18 lower to 0.80 lower)	high
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1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
4. Only one study so no inconsistency
5. I<sup>2</sup> > 75%
6. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
7. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

#### L.1.1.2 Adding metformin compared to adding insulin

**Table 2: Clinical evidence profile: Adding metformin compared to adding insulin**

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>all-cause mortality at end of follow up Mean follow-up: 6 month(s)</b>											
1 (civera 2008)	RC T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	0/12	1/13	PETO OR 0.15 (0.00, 7.39)	77 fewer per 1000 (222 fewer to 68 more)	very low
<b>cardiovascular mortality at end of follow up Mean follow-up: 6 month(s)</b>											

1 (civera 2008)	RC T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	0/12	1/13	PETO OR 0.15 (0.00, 7.39)	77 fewer per 1000 (222 fewer to 68 more)	very low
<b>hba1c change (% , lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)</b>											
1 (civera 2008)	RC T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>4</sup>	NA	12	13	MD 0.70 (-0.40, 1.80)	MD 0.70 higher (0.40 lower to 1.80 higher)	low
<b>weight change (kg, lower values are better, change score) at end of follow up Mean follow-up: 5.5 month(s)</b>											
1 (civera 2008)	RC T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>5</sup>	NA	12	13	MD -1.30 (-3.42, 0.82)	MD 1.30 lower (3.42 lower to 0.82 higher)	low

1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
2. Only one study so no inconsistency
3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
4. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
5. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

## L.1.2 DPP-4 inhibitors

## L.1.2.1 Adding alogliptin compared to adding placebo

Table 3: Clinical evidence profile: Adding alogliptin compared to adding placebo

	De sig n	Risk of bias	Indir ectn ess	Incon sisten cy	Impr ecisi on	Other consider ations	Interv entio n N	Con trol N	Relative effect (95% CI)	Absolute effect	Cer tain ty
<b>No of studies</b>											
<b>all-cause mortality at end of follow up Mean follow-up: 6 month(s)</b>											
4	R CT	very serio us <sup>1</sup>	not serio us	serio us <sup>2</sup>	very serio us <sup>3</sup>	NA	3/148 1	0/4 30	RD 0.00 (- 0.01, 0.01)	2 more per 1000 (5 fewer to 10 more)	ver y low
<b>cardiovascular mortality at end of follow up Mean follow-up: 6 month(s)</b>											
3	R CT	very serio us <sup>1</sup>	not serio us	serio us <sup>2</sup>	very serio us <sup>4</sup>	NA	2/108 4	0/3 33	RD 0.00 (- 0.01, 0.01)	2 more per 1000 (6 fewer to 10 more)	ver y low
<b>non-fatal myocardial infarction at end of follow up Mean follow-up: 6 month(s)</b>											
1 (pratley 2009a)	R CT	not serio us	not serio us	NA <sup>5</sup>	very serio us <sup>6</sup>	NA	3/397	0/9 7	PETO OR 3.49 (0.20, 60.57)	8 more per 1000 (1 fewer to 16 more)	low
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 6 month(s)</b>											
4	R CT	very serio us <sup>1</sup>	not serio us	not serio us	serio us <sup>7</sup>	NA	148/1 481	50/ 429	RR 1.07 (0.80, 1.44)	9 more per 1000 (23 fewer to 51 more)	ver y low
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 6 month(s)</b>											
3	R CT	very serio us <sup>1</sup>	not serio us	serio us <sup>2</sup>	very serio us <sup>8</sup>	NA	3/108 4	3/3 33	RD -0.01 (- 0.02, 0.01)	6 fewer per 1000 (17 fewer to 6 more)	ver y low

<b>hba1c change (%), lower values are better, mean difference) at end of follow up Mean follow-up: 6 month(s)</b>											
3	R CT	very serious <sup>1</sup>	not serious	not serious	serious <sup>9</sup>	NA	1084	333	MD -0.53 (-0.63, -0.42)	MD 0.53 lower (0.63 lower to 0.42 lower)	very low
<b>weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)</b>											
4	R CT	not serious	not serious	not serious	not serious	NA	1480	430	MD 0.17 (-0.09, 0.43)	MD 0.17 higher (0.09 lower to 0.43 higher)	high

- >33.3% of the studies in the meta-analysis were at high risk of bias
- Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.5 (0.8-0.9 = serious, <0.8 = very serious).
- Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.37 (0.8-0.9 = serious, <0.8 = very serious).
- Only one study so no inconsistency
- 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.58 (0.8-0.9 = serious, <0.8 = very serious).
- 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

## L.1.2.2 Adding linagliptin compared to adding placebo

Table 4: Clinical evidence profile: Adding linagliptin compared to adding placebo

No of studies	De sig n	Risk of bias	Indir ectn ess	Incon siste ncy	Impr ecisio n	Other consider ations	Interv entio n N	Con trol N	Relative effect (95% CI)	Absolute effect	Cer tain ty
<b>all-cause mortality at end of follow up Mean follow-up: 8.5 month(s)</b>											
10	R C T	not serio us	not serio us	serio us <sup>1</sup>	very serio us <sup>2</sup>	NA	373/5 274	380/ 499 6	RD -0.00 (- 0.01, 0.01)	2 fewer per 1000 (12 fewer to 8 more)	ver y low
<b>all-cause mortality at end of follow up Mean follow-up: 26.4 month(s)</b>											
1 (rosenstock 2019a)	R C T	not serio us	not serio us	NA <sup>3</sup>	not serio us	NA	3494	348 5	HR 0.98 (0.84, 1.14)	Not estimable	hig h
<b>cardiovascular mortality at end of follow up Mean follow-up: 8.5 month(s)</b>											
10	R C T	not serio us	not serio us	serio us <sup>1</sup>	very serio us <sup>4</sup>	NA	261/5 274	266/ 499 6	RD 0.00 (- 0.00, 0.01)	2 more per 1000 (3 fewer to 6 more)	ver y low
<b>cardiovascular mortality at end of follow up Mean follow-up: 26.4 month(s)</b>											
1 (rosenstock 2019a)	R C T	not serio us	not serio us	NA <sup>3</sup>	not serio us	NA	3494	348 5	HR 0.96 (0.81, 1.14)	Not estimable	hig h
<b>4-point mace at end of follow up Mean follow-up: 15.9 month(s)</b>											
2	R C T	not serio us	not serio us	not serio us	not serio us	NA	466/3 645	460/ 363 7	RR 1.01 (0.90, 1.14)	1 more per 1000 (13 fewer to 18 more)	hig h
<b>4-point mace at end of follow up Mean follow-up: 26.4 month(s)</b>											

1 (rosenstock 2019a)	R C T	not serio us	not serio us	NA <sup>3</sup>	not serio us	NA	3494	348 6	HR 1.00 (0.88, 1.14)	Not estimable	high
<b>5-point mace at end of follow up Mean follow-up: 9.9 month(s)</b>											
2	R C T	very serio us <sup>5</sup>	not serio us	serio us <sup>1</sup>	very serio us <sup>6</sup>	NA	18/83 6	11/7 30	RD 0.01 (- 0.00, 0.02)	9 more per 1000 (5 fewer to 23 more)	very low
<b>non-fatal stroke at end of follow up Mean follow-up: 10.7 month(s)</b>											
4	R C T	not serio us	not serio us	serio us <sup>1</sup>	very serio us <sup>7</sup>	NA	67/39 90	74/3 804	RD -0.00 (- 0.01, 0.00)	2 fewer per 1000 (8 fewer to 4 more)	very low
<b>non-fatal stroke at end of follow up Mean follow-up: 26.4 month(s)</b>											
1 (rosenstock 2019a)	R C T	not serio us	not serio us	NA <sup>3</sup>	serio us <sup>8</sup>	NA	3494	348 5	HR 0.88 (0.63, 1.23)	Not estimable	moderate
<b>non-fatal myocardial infarction at end of follow up Mean follow-up: 10.7 month(s)</b>											
4	R C T	not serio us	not serio us	serio us <sup>1</sup>	very serio us <sup>9</sup>	NA	158/3 956	135/ 385 6	RD 0.01 (- 0.00, 0.01)	6 more per 1000 (3 fewer to 14 more)	very low
<b>non-fatal myocardial infarction at end of follow up Mean follow-up: 26.4 month(s)</b>											
1 (rosenstock 2019a)	R C T	not serio us	not serio us	NA <sup>3</sup>	serio us <sup>8</sup>	NA	3494	348 5	HR 1.15 (0.91, 1.45)	Not estimable	moderate
<b>unstable angina at end of follow up Mean follow-up: 12.5 month(s)</b>											
3	R C T	not serio us	not serio us	serio us <sup>1</sup>	very serio us <sup>10</sup>	NA	43/38 39	47/3 652	RD -0.00 (- 0.01, 0.00)	1 fewer per 1000 (6 fewer to 4 more)	very low
<b>unstable angina at end of follow up Mean follow-up: 26.4 month(s)</b>											

1 (rosenstock 2019a)	R C T	not serio us	not serio us	NA <sup>3</sup>	very serio us <sup>11</sup>	NA	3494	348 4	HR 0.87 (0.57, 1.33)	Not estimable	low
<b>hospitalisation for heart failure at end of follow up Mean follow-up: 10.7 month(s)</b>											
4	R C T	not serio us	not serio us	serio us <sup>1</sup>	very serio us <sup>12</sup>	NA	210/4 033	228/ 382 5	RD -0.00 (- 0.01, 0.01)	5 fewer per 1000 (15 fewer to 5 more)	ver y low
<b>hospitalisation for heart failure at end of follow up Mean follow-up: 26.4 month(s)</b>											
1 (rosenstock 2019a)	R C T	not serio us	not serio us	NA <sup>3</sup>	serio us <sup>8</sup>	NA	3494	348 4	HR 0.90 (0.74, 1.09)	Not estimable	mo der ate
<b>acute kidney injury at end of follow up Mean follow-up: 26.4 month(s)</b>											
1 (rosenstock 2019a)	R C T	not serio us	not serio us	NA <sup>3</sup>	serio us <sup>8</sup>	NA	96/34 94	102/ 348 5	RR 0.94 (0.71, 1.24)	2 fewer per 1000 (8 fewer to 7 more)	mo der ate
<b>persistent signs of worsening kidney disease at end of follow up Mean follow-up: 26.4 month(s)</b>											
1 (rosenstock 2019a)	R C T	not serio us	not serio us	NA <sup>3</sup>	not serio us	NA	763/3 494	819/ 348 5	RR 0.93 (0.85, 1.01)	17 fewer per 1000 (35 fewer to 3 more)	hig h
<b>persistent signs of worsening kidney disease at end of follow up Mean follow-up: 26.4 month(s)</b>											
1 (rosenstock 2019a)	R C T	not serio us	not serio us	NA <sup>3</sup>	serio us <sup>8</sup>	NA	3494	348 5	HR 0.86 (0.78, 0.95)	Not estimable	mo der ate
<b>development of end stage kidney disease at end of follow up Mean follow-up: 15.9 month(s)</b>											
2	R C T	not serio us	not serio us	serio us <sup>1</sup>	very serio us <sup>13</sup>	NA	63/36 99	64/3 585	RD -0.00 (- 0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	ver y low

<b>death from renal causes at end of follow up Mean follow-up: 26.4 month(s)</b>												
1 (rosenstock 2019a)	R C T	not serio us	not serio us	NA <sup>3</sup>	very serio us <sup>11</sup>	NA	1/349 4	1/34 85	PETO OR 1.00 (0.06, 15.95)	0 fewer per 1000 (1 fewer to 1 more)	low	
<b>cardiac arrhythmia at end of follow up Mean follow-up: 5.5 month(s)</b>												
1 (barnett 2013)	R C T	not serio us	not serio us	NA <sup>3</sup>	very serio us <sup>11</sup>	NA	1/162	0/79	PETO OR 4.43 (0.07, 288.02)	6 more per 1000 (6 fewer to 18 more)	low	
<b>diabetic ketoacidosis at end of follow up Mean follow-up: 5.5 month(s)</b>												
2	R C T	not serio us	not serio us	not serio us	not serio us	NA	0/238	0/24 0	RD 0.00 (- 0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	high	
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 7.2 month(s)</b>												
12	R C T	not serio us	not serio us	serio us <sup>1</sup>	very serio us <sup>14</sup>	NA	1450/ 6589	126 1/54 36	RD 0.00 (- 0.01, 0.02)	4 more per 1000 (11 fewer to 20 more)	very low	
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 7.2 month(s)</b>												
12	R C T	not serio us	not serio us	serio us <sup>1</sup>	very serio us <sup>15</sup>	NA	116/6 589	116/ 543 6	RD -0.00 (- 0.01, 0.00)	1 fewer per 1000 (6 fewer to 4 more)	very low	
<b>hba1c change (% , lower values are better, change scores) at end of follow up Mean follow-up: 7.2 month(s)</b>												
12	R C T	not serio us	not serio us	serio us <sup>16</sup>	serio us <sup>17</sup>	NA	6495	519 5	MD -0.53 (- 0.62, -0.44)	MD 0.53 lower (0.62 lower to 0.44 lower)	low	
<b>weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)</b>												

10	R C T	serious <sup>18</sup>	not serious	not serious	not serious	NA	2783	168 0	MD 0.10 (- 0.08, 0.28)	MD 0.10 higher (0.08 lower to 0.28 higher)	moderate
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1. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
2. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.31 (0.8-0.9 = serious, <0.8 = very serious).
3. Only one study so no inconsistency
4. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.23 (0.8-0.9 = serious, <0.8 = very serious).
5. >33.3% of the studies in the meta-analysis were at high risk of bias
6. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.27 (0.8-0.9 = serious, <0.8 = very serious).
7. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.24 (0.8-0.9 = serious, <0.8 = very serious).
8. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
9. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.37 (0.8-0.9 = serious, <0.8 = very serious).
10. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.15 (0.8-0.9 = serious, <0.8 = very serious).
11. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
12. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.54 (0.8-0.9 = serious, <0.8 = very serious).
13. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.06 (0.8-0.9 = serious, <0.8 = very serious).

14. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.6 (0.8-0.9 = serious, <0.8 = very serious).
15. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.55 (0.8-0.9 = serious, <0.8 = very serious).
16. I<sup>2</sup> between 50% and 75%
17. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
18. >33.3% of the studies in the meta-analysis were at moderate risk of bias

## L.1.2.3 Adding linagliptin compared to adding metformin

Table 5: Adding linagliptin compared to adding metformin

No of studies	De sig n	Risk of bias	Indir ectn ess	Incon siste ncy	Impr ecisi on	Other consider ations	Interv entio n N	Con trol N	Relative effect (95% CI)	Absolute effect	Cer tai nty
<b>all-cause mortality at end of follow up Mean follow-up: 12 month(s)</b>											
1 (komorizono 2020)	R C T	not serio us	not serio us	NA <sup>1</sup>	very serio us <sup>2</sup>	NA	0/25	0/25	RD 0.00 (- 0.07, 0.07)	0 fewer per 1000 (75 fewer to 75 more)	low
<b>cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)</b>											
1 (komorizono 2020)	R C T	not serio us	not serio us	NA <sup>1</sup>	very serio us <sup>2</sup>	NA	0/25	0/25	RD 0.00 (- 0.07, 0.07)	0 fewer per 1000 (75 fewer to 75 more)	low
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 12 month(s)</b>											
1 (inagaki 2013)	R C T	serio us <sup>3</sup>	not serio us	NA <sup>1</sup>	very serio us <sup>4</sup>	NA	1/185	0/124	PETO OR 5.31 (0.10, 289.71)	5 more per 1000 (5 fewer to 16 more)	ver y low
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)</b>											
1 (inagaki 2013)	R C T	serio us <sup>3</sup>	not serio us	NA <sup>1</sup>	serio us <sup>2</sup>	NA	0/185	0/124	RD 0.00 (- 0.01, 0.01)	0 fewer per 1000 (13 fewer to 13 more)	low
<b>hba1c change (% , lower values are better, change scores and final values) at end of follow up Mean follow-up: 12 month(s)</b>											
2	R C T	serio us <sup>3</sup>	not serio us	not serio us	not serio us	NA	208	165	MD 0.10 (0.08, 0.12)	MD 0.10 higher (0.08 higher to 0.12 higher)	mo der ate

weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)											
1 (komorizono 2020)	R C T	not serio ous	not serio us	NA <sup>1</sup>	serio us <sup>5</sup>	NA	23	25	MD 2.60 (1.21, 3.99)	MD 2.60 higher (1.21 higher to 3.99 higher)	mo der ate

1. Only one study so no inconsistency
2. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
3. >33.3% of the studies in the meta-analysis were at moderate risk of bias
4. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
5. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

#### L.1.2.4 Adding saxagliptin compared to adding placebo

**Table 6: Clinical evidence profile: Adding saxagliptin compared to adding placebo**

No of studies	De sig n	Risk of bias	Indir ectn ess	Inco nsist ency	Impr ecisi on	Other consider ations	Inter venti on N	Con trol N	Relative effect (95% CI)	Absolute effect	Cer tai nty
<b>all-cause mortality at end of follow up Mean follow-up: 12 month(s)</b>											
7	R C T	very serio us <sup>1</sup>	not serio us	serio us <sup>2</sup>	very serio us <sup>3</sup>	NA	425/1 0043	381 /92 46	RD 0.00 (- 0.00, 0.01)	4 more per 1000 (2 fewer to 10 more)	ver y low
<b>all-cause mortality at end of follow up Mean follow-up: 25.2 month(s)</b>											
1 (scirica 2013)	R C T	very serio us <sup>1</sup>	not serio us	NA <sup>4</sup>	serio us <sup>5</sup>	NA	8280	821 2	HR 1.11 (0.96, 1.28)	Not estimable	ver y low

<b>cardiovascular mortality at end of follow up</b>												
<b>Mean follow-up: 11.9 month(s)</b>												
5	R C T	very serious <sup>1</sup>	not serious	serious <sup>2</sup>	very serious <sup>3</sup>	NA	271/9 586	261 /89 33	RD 0.00 (- 0.00, 0.01)	1 more per 1000 (4 fewer to 6 more)	ver y low	
<b>cardiovascular mortality at end of follow up</b>												
<b>Mean follow-up: 25.2 month(s)</b>												
1 (scirica 2013)	R C T	very serious <sup>1</sup>	not serious	NA <sup>4</sup>	not serious	NA	8280	821 2	HR 1.03 (0.87, 1.22)	Not estimable	low	
<b>3-point mace at end of follow up</b>												
<b>Mean follow-up: 25.2 month(s)</b>												
1 (scirica 2013)	R C T	very serious <sup>1</sup>	not serious	NA <sup>4</sup>	not serious	NA	613/8 280	609 /82 12	RR 1.00 (0.90, 1.11)	0 fewer per 1000 (8 fewer to 8 more)	low	
<b>3-point mace at end of follow up</b>												
<b>Mean follow-up: 25.2 month(s)</b>												
1 (scirica 2013)	R C T	very serious <sup>1</sup>	not serious	NA <sup>4</sup>	not serious	NA	8280	821 2	HR 1.00 (0.89, 1.12)	Not estimable	low	
<b>non-fatal stroke at end of follow up</b>												
<b>Mean follow-up: 15.3 month(s)</b>												
2	R C T	very serious <sup>1</sup>	not serious	not serious	serious <sup>5</sup>	NA	158/8 523	142 /84 60	RR 1.10 (0.88, 1.38)	2 more per 1000 (2 fewer to 6 more)	ver y low	
<b>non-fatal stroke at end of follow up</b>												
<b>Mean follow-up: 25.2 month(s)</b>												
1 (scirica 2013)	R C T	very serious <sup>1</sup>	not serious	NA <sup>4</sup>	serious <sup>5</sup>	NA	8240	817 3	HR 1.11 (0.88, 1.40)	Not estimable	ver y low	
<b>non-fatal myocardial infarction at end of follow up</b>												
<b>Mean follow-up: 15.6 month(s)</b>												
2	R C T	very serious <sup>1</sup>	not serious	serious <sup>2</sup>	not serious	NA	266/8 474	278 /84 04	RR 0.95 (0.80, 1.12)	2 fewer per 1000 (6 fewer to 4 more)	Ver y low	

<b>non-fatal myocardial infarction at end of follow up</b> <b>Mean follow-up: 25.2 month(s)</b>											
1 (scirica 2013)	R C T	very serio us <sup>1</sup>	not serio us	NA <sup>4</sup>	serio us <sup>5</sup>	NA	8240	817 3	HR 0.95 (0.80, 1.13)	Not estimable	ver y low
<b>unstable angina at end of follow up</b> <b>Mean follow-up: 25.2 month(s)</b>											
1 (scirica 2013)	R C T	very serio us <sup>1</sup>	not serio us	NA <sup>4</sup>	serio us <sup>5</sup>	NA	97/82 80	81/ 821 2	RR 1.19 (0.89, 1.59)	2 more per 1000 (1 fewer to 6 more)	ver y low
<b>unstable angina at end of follow up</b> <b>Mean follow-up: 25.2 month(s)</b>											
1 (scirica 2013)	R C T	very serio us <sup>1</sup>	not serio us	NA <sup>4</sup>	serio us <sup>5</sup>	NA	8280	821 2	HR 1.19 (0.89, 1.59)	Not estimable	ver y low
<b>hospitalisation for heart failure at end of follow up</b> <b>Mean follow-up: 25.2 month(s)</b>											
1 (scirica 2013)	R C T	very serio us <sup>1</sup>	not serio us	NA <sup>4</sup>	serio us <sup>5</sup>	NA	289/8 240	228 /81 73	RR 1.26 (1.06, 1.49)	7 more per 1000 (2 more to 14 more)	ver y low
<b>hospitalisation for heart failure at end of follow up</b> <b>Mean follow-up: 25.2 month(s)</b>											
1 (scirica 2013)	R C T	very serio us <sup>1</sup>	not serio us	NA <sup>4</sup>	serio us <sup>5</sup>	NA	8240	817 3	HR 1.27 (1.07, 1.51)	Not estimable	ver y low
<b>persistent signs of worsening kidney disease at end of follow up</b> <b>Mean follow-up: 25.2 month(s)</b>											
1 (scirica 2013)	R C T	very serio us <sup>1</sup>	not serio us	NA <sup>4</sup>	serio us <sup>5</sup>	NA	183/8 280	166 /82 12	RR 1.09 (0.89, 1.35)	2 more per 1000 (2 fewer to 7 more)	ver y low
<b>persistent signs of worsening kidney disease at end of follow up</b> <b>Mean follow-up: 25.2 month(s)</b>											
1 (scirica 2013)	R C T	very serio us <sup>1</sup>	not serio us	NA <sup>4</sup>	serio us <sup>5</sup>	NA	8280	821 2	HR 1.10 (0.89, 1.36)	Not estimable	ver y low

<b>development of end stage kidney disease at end of follow up</b> Mean follow-up: 25.2 month(s)											
1 (scirica 2013)	R C T	very serious <sup>1</sup>	not serious	NA <sup>4</sup>	very serious <sup>6</sup>	NA	51/82 80	55/ 821 2	PETO OR 0.92 (0.63, 1.35)	1 fewer per 1000 (3 fewer to 2 more)	very low
<b>development of end stage kidney disease at end of follow up</b> Mean follow-up: 25.2 month(s)											
1 (scirica 2013)	R C T	very serious <sup>1</sup>	not serious	NA <sup>4</sup>	very serious <sup>6</sup>	NA	8280	821 2	HR 0.90 (0.61, 1.33)	Not estimable	very low
<b>death from renal causes at end of follow up</b> Mean follow-up: 25.2 month(s)											
1 (scirica 2013)	R C T	very serious <sup>1</sup>	not serious	NA <sup>4</sup>	very serious <sup>6</sup>	NA	10/82 80	5/8 212	PETO OR 1.93 (0.70, 5.32)	1 more per 1000 (0 more to 2 more)	very low
<b>cardiac arrhythmia at end of follow up</b> Mean follow-up: 12 month(s)											
1 (matthaei 2015a)	R C T	serious <sup>7</sup>	not serious	NA <sup>4</sup>	very serious <sup>6</sup>	NA	0/153	1/1 62	PETO OR 0.14 (0.00, 7.22)	6 fewer per 1000 (18 fewer to 6 more)	very low
<b>hypoglycaemia episodes at end of follow up</b> Mean follow-up: 11.2 month(s)											
8	R C T	very serious <sup>1</sup>	not serious	serious <sup>2</sup>	very serious <sup>8</sup>	NA	1310/ 1032 8	113 4/9 534	RD 0.00 (- 0.01, 0.01)	2 more per 1000 (10 fewer to 15 more)	very low
<b>severe hypoglycaemic episodes at end of follow up</b> Mean follow-up: 11 month(s)											
6	R C T	very serious <sup>1</sup>	not serious	serious <sup>2</sup>	very serious <sup>9</sup>	NA	180/9 818	143 /92 22	RD 0.00 (- 0.00, 0.01)	4 more per 1000 (0 more to 7 more)	very low
<b>severe hypoglycaemic episodes at end of follow up</b> Mean follow-up: 25.2 month(s)											
1 (scirica 2013)	R C T	very serious <sup>1</sup>	not serious	NA <sup>4</sup>	serious <sup>5</sup>	NA	8280	821 2	HR 1.22 (0.82, 1.82)	Not estimable	very low

<b>hba1c change (% , lower values are better, change scores and final values) at end of follow up Mean follow-up: 11.2 month(s)</b>											
8	R C T	very serious <sup>1</sup>	not serious	very serious <sup>10</sup>	serious <sup>11</sup>	NA	1023 4	948 7	MD -0.50 (-0.67, -0.33)	MD 0.50 lower (0.67 lower to 0.33 lower)	very low
<b>weight change (kg, lower values are better, change scores and final values) at end of follow up Mean follow-up: 11.9 month(s)</b>											
6	R C T	very serious <sup>1</sup>	not serious	serious <sup>12</sup>	not serious	NA	9545	916 0	MD 0.21 (-0.15, 0.57)	MD 0.21 higher (0.15 lower to 0.57 higher)	very low
<b>bmi change (kg/m2, lower values are better, change scores and final values) at end of follow up Mean follow-up: 12.2 month(s)</b>											
4	R C T	very serious <sup>1</sup>	not serious	not serious	not serious	NA	9035	884 7	MD 0.02 (-0.06, 0.10)	MD 0.02 higher (0.06 lower to 0.10 higher)	low

- >33.3% of the studies in the meta-analysis were at high risk of bias
- Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.08 (0.8-0.9 = serious, <0.8 = very serious).
- Only one study so no inconsistency
- 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- >33.3% of the studies in the meta-analysis were at moderate risk of bias
- Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.67 (0.8-0.9 = serious, <0.8 = very serious).

9. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.57 (0.8-0.9 = serious, <0.8 = very serious).

10. I<sup>2</sup> > 75%

11. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

12. I<sup>2</sup> between 50% and 75%

#### L.1.2.5 Adding sitagliptin compared to adding placebo

**Table 7: Clinical evidence profile: Adding sitagliptin compared to adding placebo**

No of studies	De sig n	Risk of bias	Indir ectn ess	Incon siste ncy	Impr ecisi on	Other consider ations	Interv entio n N	Con trol N	Relative effect (95% CI)	Absolute effect	Cer tain ty
<b>health-related quality of life - overall (iwqol lite scores, higher values are better, change scores) at end of follow up</b>											
1 (gadde 2017)	R C T	very serio us <sup>1</sup>	not serio us	NA <sup>2</sup>	not serio us	NA	122	61	MD 0.30 (-3.83, 4.43)	MD 0.30 higher (3.83 lower to 4.43 higher)	low
<b>health-related quality of life - subscale well being (dmsat well being scores, higher values are better, change scores) at end of follow up</b>											
1 (gadde 2017)	R C T	very serio us <sup>1</sup>	not serio us	NA <sup>2</sup>	not serio us	NA	122	61	MD -1.10 (-9.37, 7.17)	MD 1.10 lower (9.37 lower to 7.17 higher)	low
<b>all-cause mortality at end of follow up</b>											

16	R C T	not serio us	not serio us	serio us <sup>3</sup>	very serio us <sup>4</sup>	NA	3/348 3	6/3 080	RD -0.00 (-0.00, 0.00)	1 fewer per 1000 (3 fewer to 2 more)	ver y low
<b>cardiovascular mortality at end of follow up</b>											
11	R C T	not serio us	not serio us	serio us <sup>3</sup>	very serio us <sup>5</sup>	NA	0/230 5	3/2 087	RD -0.00 (-0.00, 0.00)	1 fewer per 1000 (5 fewer to 2 more)	ver y low
<b>non-fatal stroke at end of follow up</b>											
1 (ba 2017)	R C T	not serio us	not serio us	NA <sup>2</sup>	very serio us <sup>6</sup>	NA	0/248	1/2 49	PETO OR 0.14 (0.00, 6.85)	4 fewer per 1000 (12 fewer to 4 more)	low
<b>non-fatal myocardial infarction at end of follow up</b>											
3	R C T	serio us <sup>7</sup>	not serio us	serio us <sup>3</sup>	very serio us <sup>6</sup>	NA	1/678	2/7 13	PETO OR 0.56 (0.06, 5.41)	1 fewer per 1000 (6 fewer to 4 more)	ver y low
<b>unstable angina at end of follow up</b>											
2	R C T	not serio us	not serio us	serio us <sup>3</sup>	very serio us <sup>6</sup>	NA	1/570	1/5 68	PETO OR 1.00 (0.06, 15.95)	0 fewer per 1000 (5 fewer to 5 more)	ver y low
<b>diabetic ketoacidosis at end of follow up</b>											
1 (shankar 2017a)	R C T	serio us <sup>7</sup>	not serio us	NA <sup>2</sup>	very serio us <sup>6</sup>	NA	0/234	1/2 33	RR 0.33 (0.01, 8.11)	3 fewer per 1000 (4 fewer to 30 more)	ver y low
<b>hypoglycaemia episodes at the end of follow up</b>											
20	R C T	not serio us	not serio us	serio us <sup>3</sup>	very serio us <sup>8</sup>	NA	608/4 022	535 /34 45	RD 0.02 (0.00, 0.04)	18 more per 1000 (1 more to 35 more)	ver y low

<b>severe hypoglycaemic episodes at the end of follow up</b>											
16	R C T	not serio us	not serio us	serio us <sup>3</sup>	very serio us <sup>9</sup>	NA	38/32 52	36/ 300 1	RD 0.00 (-0.01, 0.01)	1 more per 1000 (5 fewer to 6 more)	ver y low
<b>hba1c change (% , lower values are better, mean difference) at end of follow up</b>											
23	R C T	very serio us <sup>1</sup>	not serio us	very serio us <sup>10</sup>	not serio us	NA	4055	356 8	MD -0.71 (-0.80, - 0.61)	MD 0.71 lower (0.80 lower to 0.61 lower)	ver y low
<b>weight change (kg, lower values are better, mean difference) at end of follow up</b>											
20	R C T	not serio us	not serio us	very serio us <sup>10</sup>	not serio us	NA	3221	295 1	MD 0.13 (-0.13, 0.39)	MD 0.13 higher (0.13 lower to 0.39 higher)	low
<b>bmi change (kg/m2, lower values are better, final values) at end of follow up</b>											
3	R C T	very serio us <sup>1</sup>	not serio us	very serio us <sup>10</sup>	serio us <sup>11</sup>	NA	237	229	MD -1.50 (-2.35, - 0.66)	MD 1.50 lower (2.35 lower to 0.66 lower)	ver y low

- >33.3% of the studies in the meta-analysis were at high risk of bias
- Only one study so no inconsistency
- Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.38 (0.8-0.9 = serious, <0.8 = very serious).

5. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.71 (0.8-0.9 = serious, <0.8 = very serious).
6. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
7. >33.3% of the studies in the meta-analysis were at moderate risk of bias
8. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.1 (0.8-0.9 = serious, <0.8 = very serious).
9. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.04 (0.8-0.9 = serious, <0.8 = very serious).
10. I<sup>2</sup> > 75%
11. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

#### L.1.2.6 Adding sitagliptin compared to adding metformin

**Table 8: Clinical evidence profile: Adding sitagliptin compared to adding metformin**

No of studies	De sig n	Risk of bias	Indir ectn ess	Incon siste ncy	Impr ecisi on	Other consider ations	Interv entio n N	Con trol N	Relative effect (95% CI)	Absolute effect	Cer tai nty
<b>hypoglycaemia episodes at end of follow-up Mean follow-up: 12 month(s)</b>											
1 (derosa 2010b)	R C T	very serio us <sup>1</sup>	not serio us	NA <sup>2</sup>	very serio us <sup>3</sup>	NA	2/75	0/7 6	PETO OR 7.59 (0.47, 122.49)	27 more per 1000 (10 fewer to 63 more)	ver y low
<b>hba1c change (% , lower values are better, final and change scores) at end of follow-up Mean follow-up: 9 month(s)</b>											
2	R C T	very serio us <sup>1</sup>	not serio us	very serio us <sup>4</sup>	very serio us <sup>5</sup>	NA	104	103	MD -0.33 (- 1.25, 0.60)	MD 0.33 lower (1.25 lower to 0.60 higher)	ver y low

<b>weight change (kg, lower values are better, final and change values) at end of follow-up Mean follow-up: 9 month(s)</b>												
2	R C T	very serious <sup>1</sup>	not serious	very serious <sup>4</sup>	serious <sup>6</sup>	NA	104	103	MD 1.47 (-0.53, 3.47)	MD 1.47 higher (0.53 lower to 3.47 higher)	very low	
<b>bmi change (kg/m2, lower values are better, final and change values) at end of follow-up Mean follow-up: 9 month(s)</b>												
2	R C T	very serious <sup>1</sup>	not serious	serious <sup>7</sup>	serious <sup>8</sup>	NA	104	103	MD 0.41 (0.02, 0.80)	MD 0.41 higher (0.02 higher to 0.80 higher)	very low	

1. >33.3% of the studies in the meta-analysis were at high risk of bias
2. Only one study so no inconsistency
3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
4. I<sup>2</sup> > 75%
5. 95% confidence intervals cross both ends of the defined MIDs (-0.50, 0.50)
6. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)
7. I<sup>2</sup> between 50% and 75%
8. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

## L.1.2.7 Adding sitagliptin compared to adding insulin

Table 9: Clinical evidence profile: Adding sitagliptin compared to adding insulin

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
<b>health-related quality of life - subscale mental component (sf36, higher values are better, change scores) at end of follow up Mean follow-up: 24 month(s)</b>											
1 (group 2022)	RCT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	1236	1209	MD 0.12 (-0.48, 0.72)	MD 0.12 higher (0.48 lower to 0.72 higher)	low
<b>health-related quality of life - subscale physical component (sf36, higher values are better, change scores) at end of follow up Mean follow-up: 12 month(s)</b>											
1 (group 2022)	RCT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	1236	1209	MD 0.23 (-0.32, 0.78)	MD 0.23 higher (0.32 lower to 0.78 higher)	low
<b>all-cause mortality at end of follow-up Mean follow-up: 33 month(s)</b>											
2	RCT	serious <sup>3</sup>	not serious	serious <sup>4</sup>	very serious <sup>5</sup>	NA	41/1495	43/1489	PETO OR 0.95 (0.61, 1.47)	1 fewer per 1000 (13 fewer to 10 more)	very low
<b>all-cause mortality at end of follow up Mean follow-up: 60 month(s)</b>											

1 (group 2022)	RCT	serious <sup>3</sup>	not serious	NA <sup>2</sup>	very serious <sup>5</sup>	NA	1267	12/63	HR 0.98 (0.68, 1.41)	Not estimable	very low
<b>cardiovascular mortality at end of follow-up Mean follow-up: 60 month(s)</b>											
1 (group 2022)	RCT	serious <sup>3</sup>	not serious	NA <sup>2</sup>	very serious <sup>5</sup>	NA	21/264	12/57	RR 0.99 (0.55, 1.81)	0 fewer per 1000 (8 fewer to 14 more)	very low
<b>cardiovascular mortality at end of follow up Mean follow-up: 60 month(s)</b>											
1 (group 2022)	RCT	serious <sup>3</sup>	not serious	NA <sup>2</sup>	very serious <sup>5</sup>	NA	1264	12/57	HR 1.00 (0.55, 1.82)	Not estimable	very low
<b>3-point mace at end of follow-up Mean follow-up: 60 month(s)</b>											
1 (group 2022)	RCT	serious <sup>3</sup>	not serious	NA <sup>2</sup>	very serious <sup>5</sup>	NA	69/264	12/57	RR 1.06 (0.76, 1.47)	3 more per 1000 (12 fewer to 24 more)	very low
<b>3-point mace at end of follow up Mean follow-up: 60 month(s)</b>											
1 (group 2022)	RCT	serious <sup>3</sup>	not serious	NA <sup>2</sup>	very serious <sup>5</sup>	NA	1264	12/57	HR 1.06 (0.76, 1.48)	Not estimable	very low
<b>4-point mace at end of follow up Mean follow-up: 60 month(s)</b>											

1 (group 2022)	RCT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>6</sup>	NA	78/1268	71/1263	RR 1.09 (0.80, 1.49)	5 more per 1000 (11 fewer to 28 more)	very low
<b>non-fatal myocardial infarction</b>											
<b>Mean follow-up: 5.5 month(s)</b>											
1 (aschner 2012)	RCT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>5</sup>	NA	1/264	0/237	PETO OR 6.67 (0.13, 338.11)	4 more per 1000 (4 fewer to 11 more)	very low
<b>unstable angina at the end of follow-up</b>											
<b>Mean follow-up: 32.8 month(s)</b>											
2	RCT	very serious <sup>1</sup>	not serious	serious <sup>4</sup>	very serious <sup>5</sup>	NA	15/1532	11/1500	PETO OR 1.35 (0.62, 2.92)	2 more per 1000 (4 fewer to 9 more)	very low
<b>hospitalisation for heart failure at end of follow-up</b>											
<b>Mean follow-up: 60 month(s)</b>											
1 (group 2022)	RCT	serious <sup>3</sup>	not serious	NA <sup>2</sup>	very serious <sup>5</sup>	NA	1264	1257	HR 1.15 (0.67, 1.96)	Not estimable	very low
<b>hospitalisation for heart failure at end of follow-up</b>											
<b>Mean follow-up: 60 month(s)</b>											
1 (group 2022)	RCT	serious <sup>3</sup>	not serious	NA <sup>2</sup>	very serious <sup>5</sup>	NA	30/264	26/1257	RR 1.15 (0.68, 1.93)	3 more per 1000 (7 fewer to 19 more)	very low
<b>hypoglycaemia episodes at end of follow-up</b>											
<b>Mean follow-up: 16.6 month(s)</b>											

5	RCT	very serious <sup>1</sup>	not serious	very serious <sup>7</sup>	not serious	NA	398/1833	69/179/5	RR 0.41 (0.23, 0.72)	227 fewer per 1000 (295 fewer to 107 fewer)	very low
<b>hypoglycaemia episodes at end of follow-up</b>											
<b>Mean follow-up: 60 month(s)</b>											
1 (group 2022)	RCT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	1253	12/45	HR 0.63 (0.59, 0.67)	Not estimable	low
<b>at night hypoglycaemic episodes</b>											
<b>Mean follow-up: 5.8 month(s)</b>											
2	RCT	serious <sup>3</sup>	not serious	serious <sup>8</sup>	not serious	NA	21/492	70/463	RR 0.28 (0.11, 0.71)	108 fewer per 1000 (134 fewer to 43 fewer)	low
<b>severe hypoglycaemic episodes at end of follow-up</b>											
<b>Mean follow-up: 19.2 month(s)</b>											
4	RCT	very serious <sup>1</sup>	not serious	serious <sup>4</sup>	serious <sup>6</sup>	NA	11/1821	24/1789	PETO OR 0.47 (0.24, 0.91)	7 fewer per 1000 (14 fewer to 1 fewer)	very low
<b>hba1c change (% , lower values are better, mean difference) at end of follow-up</b>											
<b>Mean follow-up: 14.4 month(s)</b>											
7	RCT	very serious <sup>1</sup>	not serious	serious <sup>8</sup>	not serious	NA	880	99/8	MD 0.18 (-0.09, 0.46)	MD 0.18 higher (0.09 lower to 0.46 higher)	very low
<b>bmi change (kg/m2, lower values are better, change scores and final values) at end of follow-up</b>											
<b>Mean follow-up: 7.8 month(s)</b>											

3	RCT	not serious	not serious	not serious	serious <sup>9</sup>	NA	60	57	MD -0.39 (-1.00, 0.23)	MD 0.39 lower (1.00 lower to 0.23 higher)	moderate
<b>weight change (kg, lower values are better, mean difference) at end of follow-up Mean follow-up: 6.8 month(s)</b>											
6	RCT	very serious <sup>1</sup>	not serious	serious <sup>8</sup>	serious <sup>10</sup>	NA	603	576	MD -1.89 (-2.62, -1.16)	MD 1.89 lower (2.62 lower to 1.16 lower)	very low

1. >33.3% of the studies in the meta-analysis were at high risk of bias
2. Only one study so no inconsistency
3. >33.3% of the studies in the meta-analysis were at moderate risk of bias
4. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
5. 95% confidence intervals cross both ends of the defined MIDd (0.80, 1.25)
6. 95% confidence intervals cross one end of the defined MIDd (0.80, 1.25)
7. I<sup>2</sup> > 75%
8. I<sup>2</sup> between 50% and 75%
9. 95% confidence intervals cross one end of the defined MIDd (-0.80, 0.80)
10. 95% confidence intervals cross one end of the defined MIDd (-2.40, 2.40)

#### L.1.2.8 Adding vildagliptin compared to adding placebo

**Table 10: Clinical evidence profile: Adding vildagliptin compared to adding placebo**

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
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<b>all-cause mortality at end of follow-up Mean follow-up: 6.1 month(s)</b>											
12	R C T	Very serious <sup>1</sup>	not serious	serious <sup>2</sup>	very serious <sup>3</sup>	NA	3/2191	5/1659	RD -0.00 (-0.01, 0.00)	1 fewer per 1000 (6 fewer to 3 more)	very low
<b>cardiovascular mortality at end of follow-up Mean follow-up: 6.4 month(s)</b>											
8	R C T	serious <sup>4</sup>	not serious	serious <sup>2</sup>	very serious <sup>5</sup>	NA	1/1304	1/971	RD 0.00 (-0.01, 0.01)	0 more per 1000 (6 fewer to 6 more)	very low
<b>non-fatal stroke at end of follow-up Mean follow-up: 5.5 month(s)</b>											
3	R C T	serious <sup>4</sup>	not serious	serious <sup>2</sup>	very serious <sup>6</sup>	NA	1/797	3/61	PETO OR 0.19 (0.02, 1.48)	5 fewer per 1000 (13 fewer to 2 more)	very low
<b>progression of liver disease at end of follow-up Mean follow-up: 5.5 month(s)</b>											
1 (strain 2013)	R C T	not serious	serious <sup>7</sup>	NA <sup>8</sup>	serious <sup>9</sup>	NA	0/139	0/139	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	low
<b>hypoglycaemia episodes at end of follow-up Mean follow-up: 6.4 month(s)</b>											
15	R C T	very serious <sup>1</sup>	not serious	serious <sup>2</sup>	very serious <sup>10</sup>	NA	116/3031	93/2229	RD 0.01 (-0.01, 0.01)	4 more per 1000 (6 fewer to 15 more)	very low
<b>severe hypoglycaemic episodes at end of follow-up Mean follow-up: 6.0 month(s)</b>											
13	R C T	serious <sup>4</sup>	not serious	serious <sup>2</sup>	very serious <sup>11</sup>	NA	6/2642	11/1840	RD -0.00 (-0.01, 0.00)	3 fewer per 1000 (8 fewer to 2 more)	very low
<b>hba1c change (% , lower values are better, mean difference) at end of follow-up Mean follow-up: 6.0 month(s)</b>											
14	R C T	very serious <sup>1</sup>	not serious	very serious <sup>12</sup>	not serious	NA	2601	1894	MD -0.69 (-0.77, -0.62)	MD 0.69 lower (0.77 lower to 0.62 lower)	very low

weight change (kg, lower values are better, change and final scores) at end of follow-up Mean follow-up: 5.8 month(s)											
7	R C T	very serious <sup>1</sup>	not serious	very serious <sup>12</sup>	not serious	NA	1108	835	MD 0.07 (- 0.89, 1.04)	MD 0.7 higher (0.89 lower to 1.04 higher)	ver y low

1. >33.3% of the studies in the meta-analysis were at high risk of bias
2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
3. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.3 (0.8-0.9 = serious, <0.8 = very serious).
4. >33.3% of the studies in the meta-analysis were at moderate risk of bias
5. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.05 (0.8-0.9 = serious, <0.8 = very serious).
6. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
7. Largest proportion of studies in the meta-analysis came from partially direct studies
8. Only one study so no inconsistency
9. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
10. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.07 (0.8-0.9 = serious, <0.8 = very serious).
11. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.59 (0.8-0.9 = serious, <0.8 = very serious).
12. I<sup>2</sup> > 75%

## L.1.2.9 Adding vildagliptin compared to adding metformin

Table 11: Clinical evidence profile: Adding vildagliptin compared to adding metformin

No of studies	De sig n	Risk of bias	Indire ctnes s	Incons istenc y	Impre cision	Other considerat ions	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>all-cause mortality at end of follow-up</b> Mean follow-up: 5.5 month(s)											
1 (ji 2016b)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	not seriou s	NA	0/2562	0/50 0	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (3 fewer to 3 more)	low
<b>cardiovascular mortality at end of follow-up</b> Mean follow-up: 5.5 month(s)											
1 (ji 2016b)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	not seriou s	NA	0/2562	0/50 0	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (3 fewer to 3 more)	low
<b>acute kidney injury at end of follow-up</b> Mean follow-up: 5.5 month(s)											
1 (filozof 2010b)	RC T	not seriou s	seriou s <sup>3</sup>	NA <sup>2</sup>	very seriou s <sup>4</sup>	NA	1/456	0/45 8	PETO OR 7.42 (0.15, 374.03)	2 more per 1000 (2 fewer to 6 more)	very low
<b>hypoglycaemia episodes at end of follow-up</b> Mean follow-up: 5.5 month(s)											
2	RC T	very seriou s <sup>1</sup>	not seriou s	not seriou s	very seriou s <sup>4</sup>	NA	27/301 8	9/95 8	RR 0.66 (0.31, 1.41)	3 fewer per 1000 (6 fewer to 4 more)	very low
<b>hba1c change (% , lower values are better, change and final scores) at end of follow-up</b> Mean follow-up: 5.5 month(s)											

2	RC T	very serious <sup>1</sup>	not serious	not serious	not serious	NA	2957	942	MD -0.14 (-0.20, - 0.08)	MD 0.14 lower (0.20 lower to 0.08 lower)	low
<b>weight change (kg, lower values are better, change scores) at end of follow-up Mean follow-up: 5.5 month(s)</b>											
1 (ji 2016b)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	2501	484	MD -0.51 (-0.77, - 0.25)	MD 0.51 lower (0.77 lower to 0.25 lower)	low

- >33.3% of the studies in the meta-analysis were at high risk of bias
- Only one study so no inconsistency
- Largest proportion of studies in the meta-analysis came from partially direct studies
- 95% confidence intervals cross both ends of the defined MID (0.80, 1.25)

#### L.1.2.10 Adding vildagliptin compared to adding insulin

**Table 12: Clinical evidence profile: Adding vildagliptin compared to adding insulin**

No of studies	De sig n	Risk of bias	Indir ectn ess	Incon sisten cy	Impr ecisi on	Other consider ations	Interv entio n N	Con trol N	Relative effect (95% CI)	Absolute effect	Cer tain ty
<b>all-cause mortality at end of follow-up Mean follow-up: 5.5 month(s)</b>											
1 (forst 2015)	R CT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	0/82	1/7 9	PETO OR 0.13 (0.00, 6.57)	13 fewer per 1000 (37 fewer to 12 more)	ver y low
<b>hypoglycaemia episodes at end of follow-up Mean follow-up: 5.5 month(s)</b>											

1 (forst 2015)	R CT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>4</sup>	NA	12/82	23/ 79	RR 0.50 (0.27, 0.94)	145 fewer per 1000 (213 fewer to 18 fewer)	ver y low
<b>severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.5 month(s)</b>											
1 (forst 2015)	R CT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>5</sup>	NA	0/82	0/7 9	RD 0.00 (- 0.02, 0.02)	0 fewer per 1000 (24 fewer to 24 more)	ver y low
<b>hba1c change (% , lower values are better, mean difference) at end of follow-up Mean follow-up: 5.5 month(s)</b>											
1 (forst 2015)	R CT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>6</sup>	NA	82	79	MD 0.30 (0.05, 0.55)	MD 0.30 higher (0.05 higher to 0.55 higher)	ver y low

- >33.3% of the studies in the meta-analysis were at high risk of bias
- Only one study so no inconsistency
- 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
- 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

#### L.1.2.11 Adding vildagliptin compared to adding saxagliptin

**Table 13: Clinical evidence profile: Adding vildagliptin compared to adding saxagliptin**

No of studies	De sig n	Risk of bias	Indir ectn ess	Incon sisten cy	Impr ecisi on	Other consider ations	Interv entio n N	Con trol N	Relative effect (95% CI)	Absolute effect	Cer tain ty
<b>all-cause mortality at end of follow-up Mean follow-up: 5.5 month(s)</b>											

2	R CT	very serious <sup>1</sup>	not serious	not serious	serious <sup>2</sup>	NA	0/100	0/1 02	RD 0.00 (- 0.03, 0.03)	0 fewer per 1000 (27 fewer to 27 more)	ver y low
<b>cardiovascular mortality at end of follow-up Mean follow-up: 5.5 month(s)</b>											
2	R CT	very serious <sup>1</sup>	not serious	not serious	serious <sup>2</sup>	NA	0/100	0/1 02	RD 0.00 (- 0.03, 0.03)	0 fewer per 1000 (27 fewer to 27 more)	ver y low
<b>hospitalisation for heart failure at end of follow-up Mean follow-up: 5.5 month(s)</b>											
1 (chen 2016)	R CT	very serious <sup>1</sup>	not serious	NA <sup>3</sup>	serious <sup>2</sup>	NA	0/37	0/3 6	RD 0.00 (- 0.05, 0.05)	0 fewer per 1000 (52 fewer to 52 more)	ver y low
<b>hypoglycaemia episodes at end of follow-up Mean follow-up: 5.5 month(s)</b>											
3	R CT	very serious <sup>1</sup>	not serious	not serious	very serious <sup>4</sup>	NA	7/157	9/1 62	RR 0.81 (0.25, 2.65)	11 fewer per 1000 (42 fewer to 92 more)	ver y low
<b>at night hypoglycaemic episodes Mean follow-up: 5.5 month(s)</b>											
1 (chen 2016)	R CT	very serious <sup>1</sup>	not serious	NA <sup>3</sup>	serious <sup>2</sup>	NA	0/37	0/3 6	RD 0.00 (- 0.05, 0.05)	0 fewer per 1000 (52 fewer to 52 more)	ver y low
<b>severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.5 month(s)</b>											
2	R CT	very serious <sup>1</sup>	not serious	not serious	serious <sup>2</sup>	NA	0/94	0/9 6	RD 0.00 (- 0.03, 0.03)	0 fewer per 1000 (29 fewer to 29 more)	ver y low
<b>hba1c change (% , lower values are better, change scores) at end of follow-up Mean follow-up: 5.5 month(s)</b>											
3	R CT	very serious <sup>1</sup>	not serious	not serious	not serious	NA	157	162	MD -0.08 (-0.20, 0.04)	MD 0.08 lower (0.20 lower to 0.04 higher)	low

weight change (kg, lower values are better, change scores) at end of follow-up Mean follow-up: 5.5 month(s)											
1 (li 2014a)	RCT	very serious <sup>1</sup>	not serious	NA <sup>3</sup>	not serious	NA	57	60	MD 0.10 (-0.63, 0.83)	MD 0.10 higher (0.63 lower to 0.83 higher)	low
bmi change (kg/m2, lower values are better, change scores) at end of follow-up Mean follow-up: 5.5 month(s)											
2	RCT	very serious <sup>1</sup>	not serious	not serious	not serious	NA	94	96	MD -0.01 (-0.25, 0.24)	MD 0.01 lower (0.25 lower to 0.24 higher)	low

- >33.3% of the studies in the meta-analysis were at high risk of bias
- Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
- Only one study so no inconsistency
- 95% confidence intervals cross both ends of the defined MIDd (0.80, 1.25)

### L.1.3 GLP-1 receptor agonist

#### L.1.3.1 Adding dulaglutide compared to adding placebo

Table 14: Clinical evidence profile: Adding dulaglutide compared to adding placebo

No of studies	D e s i g n	Risk of bias	Indi rect ness	Inco nsist ency	Impr ecisi on	Other conside rations	Inter venti on N	Co ntr ol N	Relative effect (95% CI)	Absolute effect	Cer tai nty
health-related quality of life - overall (eq-5d-5l uk index, -0.59-1, higher values are better, changes scores) at end of follow up Mean follow-up: 6.5 month(s)											

1 (pozzilli 2017)	R C T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	150	150	MD -0.01 (-0.07, 0.05)	MD 0.01 lower (0.07 lower to 0.05 higher)	very low
<b>all-cause mortality at end of follow up Mean follow-up: 13.3 month(s)</b>											
8	R C T	not serious	not serious	serious <sup>4</sup>	not serious	NA	320/6428	349/5696	RD -0.01 (-0.01, 0.00)	5 fewer per 1000 (14 fewer to 3 more)	moderate
<b>all-cause mortality at end of follow up Mean follow-up: 64.8 month(s)</b>											
1 (gerstein 2019a)	R C T	not serious	not serious	NA <sup>2</sup>	serious <sup>5</sup>	NA	4949	4952	HR 0.90 (0.80, 1.01)	Not estimable	moderate
<b>cardiovascular mortality at end of follow up Mean follow-up: 17.8 month(s)</b>											
8	R C T	not serious	not serious	serious <sup>4</sup>	not serious	NA	541/6428	595/5696	RD -0.01 (-0.02, 0.00)	10 fewer per 1000 (20 fewer to 1 more)	moderate
<b>cardiovascular mortality at end of follow up Mean follow-up: 64.8 month(s)</b>											
1 (gerstein 2019a)	R C T	not serious	not serious	NA <sup>2</sup>	serious <sup>5</sup>	NA	4949	4952	HR 0.91 (0.78, 1.06)	Not estimable	moderate
<b>3-point mace at end of follow up Mean follow-up: 64.8 month(s)</b>											
1 (gerstein 2019a)	R C T	not serious	not serious	NA <sup>2</sup>	not serious	NA	594/949	663/4952	RR 0.90 (0.81, 0.99)	14 fewer per 1000 (26 fewer to 1 fewer)	high
<b>3-point mace at end of follow up Mean follow-up: 64.8 month(s)</b>											
1 (gerstein 2019a)	R C T	not serious	not serious	NA <sup>2</sup>	serious <sup>5</sup>	NA	4949	4952	HR 0.88 (0.79, 0.99)	Not estimable	moderate

<b>non-fatal stroke at end of follow up Mean follow-up: 25.6 month(s)</b>											
3	R C T	not seri ous	not seri ous	serio us <sup>4</sup>	serio us <sup>5</sup>	NA	138/5 338	17 5/5 16 2	RR 0.78 (0.63, 0.98)	7 fewer per 1000 (13 fewer to 1 fewer)	low
<b>non-fatal stroke at end of follow up Mean follow-up: 64.8 month(s)</b>											
1 (gerstein 2019a)	R C T	not seri ous	not seri ous	NA <sup>2</sup>	serio us <sup>5</sup>	NA	4949	49 52	HR 0.76 (0.61, 0.95)	Not estimable	mo der ate
<b>non-fatal myocardial infarction at end of follow up Mean follow-up: 25.6 month(s)</b>											
3	R C T	not seri ous	not seri ous	serio us <sup>4</sup>	serio us <sup>5</sup>	NA	206/5 382	21 4/5 24 2	RR 0.96 (0.80, 1.16)	2 fewer per 1000 (8 fewer to 6 more)	low
<b>non-fatal myocardial infarction at end of follow up Mean follow-up: 64.8 month(s)</b>											
1 (gerstein 2019a)	R C T	not seri ous	not seri ous	NA <sup>2</sup>	serio us <sup>5</sup>	NA	4949	49 52	HR 0.96 (0.79, 1.16)	Not estimable	mo der ate
<b>unstable angina at end of follow up Mean follow-up: 25.6 month(s)</b>											
3	R C T	not seri ous	not seri ous	serio us <sup>4</sup>	serio us <sup>5</sup>	NA	89/53 82	79/ 52 42	RR 1.12 (0.83, 1.51)	2 more per 1000 (3 fewer to 8 more)	low
<b>unstable angina at end of follow up Mean follow-up: 64.8 month(s)</b>											
1 (gerstein 2019a)	R C T	not seri ous	not seri ous	NA <sup>2</sup>	serio us <sup>5</sup>	NA	4949	49 52	HR 1.14 (0.84, 1.54)	Not estimable	mo der ate
<b>hospitalisation for heart failure at end of follow up Mean follow-up: 64.8 month(s)</b>											

1 (gerstein 2019a)	R C T	not seri ous	not seri ous	NA <sup>2</sup>	serio us <sup>5</sup>	NA	213/4 949	22 6/4 95 2	RR 0.94 (0.79, 1.13)	3 fewer per 1000 (10 fewer to 6 more)	mo der ate
<b>hospitalisation for heart failure at end of follow up Mean follow-up: 64.8 month(s)</b>											
1 (gerstein 2019a)	R C T	not seri ous	not seri ous	NA <sup>2</sup>	serio us <sup>5</sup>	NA	4949	49 52	HR 0.93 (0.77, 1.12)	Not estimable	mo der ate
<b>acute kidney injury at end of follow up Mean follow-up: 35.6 month(s)</b>											
2	R C T	not seri ous	not seri ous	serio us <sup>4</sup>	very serio us <sup>6</sup>	NA	61/50 93	67/ 50 99	RR 0.91 (0.65, 1.29)	1 fewer per 1000 (5 fewer to 4 more)	Ver y low
<b>persistent signs of worsening kidney disease at end of follow up Mean follow-up: 64.8 month(s)</b>											
1 (gerstein 2019a)	R C T	not seri ous	not seri ous	NA <sup>2</sup>	not serio us	NA	453/4 949	50 0/4 95 2	RR 0.91 (0.80, 1.02)	9 fewer per 1000 (20 fewer to 2 more)	hig h
<b>persistent signs of worsening kidney disease at end of follow up Mean follow-up: 64.8 month(s)</b>											
1 (gerstein 2019a)	R C T	not seri ous	not seri ous	NA <sup>2</sup>	serio us <sup>5</sup>	NA	4949	49 52	HR 0.89 (0.78, 1.01)	Not estimable	mo der ate
<b>development of end stage kidney disease at end of follow up Mean follow-up: 64.8 month(s)</b>											
1 (gerstein 2019a)	R C T	not seri ous	not seri ous	NA <sup>2</sup>	very serio us <sup>6</sup>	NA	3/494 9	6/4 95 2	PETO OR 0.51 (0.14, 1.90)	1 fewer per 1000 (2 fewer to 1 more)	low
<b>cardiac arrhythmia at end of follow up Mean follow-up: 35.4 month(s)</b>											
2	R C T	not seri ous	not seri ous	serio us <sup>4</sup>	very serio us <sup>7</sup>	NA	216/4 999	19 2/5	RD 0.00 (-0.00, 0.01)	5 more per 1000 (3 fewer to 13 more)	ver y low

								007			
<b>diabetic ketoacidosis at end of follow up Mean follow-up: 5.8 month(s)</b>											
2	RCT	not serious	not serious	not serious	not serious	NA	0/333	0/195	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	high
<b>progression of liver disease at end of follow up Mean follow-up: 64.8 month(s)</b>											
1 (gerstein 2019a)	RCT	not serious	not serious	NA <sup>2</sup>	serious <sup>5</sup>	NA	25/49	40/49	PETO OR 0.63 (0.39, 1.02)	3 fewer per 1000 (6 fewer to 0 more)	moderate
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 6 month(s)</b>											
6	RCT	not serious	not serious	not serious	serious <sup>5</sup>	NA	159/920	101/603	RR 1.22 (0.97, 1.54)	38 more per 1000 (5 fewer to 91 more)	moderate
<b>at night hypoglycaemic episodes at end of follow up Mean follow-up: 6.1 month(s)</b>											
3	RCT	not serious	not serious	not serious	very serious <sup>6</sup>	NA	69/533	63/357	RR 0.94 (0.68, 1.29)	11 fewer per 1000 (56 fewer to 51 more)	low
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 14.4 month(s)</b>											
7	RCT	not serious	not serious	serious <sup>4</sup>	very serious <sup>8</sup>	NA	66/5869	74/5555	RD -0.00 (-0.01, 0.00)	1 fewer per 1000 (6 fewer to 3 more)	very low
<b>hba1c change (% , lower values are better, change scores) at end of follow up Mean follow-up: 12.5 month(s)</b>											
9	RCT	not serious	not serious	very serious <sup>9</sup>	not serious	NA	7034	5873	MD -0.90 (-1.08, -0.73)	MD 0.90 lower (1.08 lower to 0.73 lower)	low
<b>weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 12.5 month(s)</b>											

9	R C T	not seri ous	not seri ous	not serio us	not serio us	NA	6559	57 29	MD -1.44 (-1.60, - 1.27)	MD 1.44 lower (1.60 lower to 1.27 lower)	high
<b>bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 25.6 month(s)</b>											
3	R C T	not seri ous	not seri ous	not serio us	not serio us	NA	5053	50 58	MD -0.53 (-0.61, - 0.46)	MD 0.53 lower (0.61 lower to 0.46 lower)	high

- >33.3% of the studies in the meta-analysis were at moderate risk of bias
- Only one study so no inconsistency
- 95% confidence intervals cross both ends of the defined MIDs (-0.03, 0.03)
- Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.41 (0.8-0.9 = serious, <0.8 = very serious).
- Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.3 (0.8-0.9 = serious, <0.8 = very serious).
- I2 > 75%

**L.1.3.2 Adding dulaglutide compared to adding insulin**

**Table 15: Clinical evidence profile: Adding dulaglutide compared to adding insulin**

No of studies	De sig n	Risk of bias	Indir ectn ess	Incon siste ncy	Impr ecisi on	Other consider ations	Interv entio n N	Con trol N	Relative effect (95% CI)	Absolute effect	Cer tain ty
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<b>all-cause mortality at end of follow up</b>											
<b>Mean follow-up: 13.9 month(s)</b>											
3	R C T	very serious <sup>1</sup>	not serious	serious <sup>2</sup>	very serious <sup>3</sup>	NA	4/164 8	5/8 11	PETO OR 0.36 (0.09, 1.45)	4 fewer per 1000 (10 fewer to 2 more)	very low
<b>cardiovascular mortality at end of follow up</b>											
<b>Mean follow-up: 17.7 month(s)</b>											
1 (giorgino 2015)	R C T	not serious	not serious	NA <sup>4</sup>	very serious <sup>3</sup>	NA	1/545	0/2 62	PETO OR 4.40 (0.07, 289.01)	2 more per 1000 (2 fewer to 5 more)	low
<b>non-fatal stroke at end of follow up</b>											
<b>Mean follow-up: 6 month(s)</b>											
1 (araki 2015b)	R C T	not serious	not serious	NA <sup>4</sup>	very serious <sup>3</sup>	NA	2/181	0/1 80	PETO OR 7.39 (0.46, 118.59)	11 more per 1000 (4 fewer to 26 more)	low
<b>non-fatal myocardial infarction at end of follow up</b>											
<b>Mean follow-up: 6 month(s)</b>											
1 (araki 2015b)	R C T	not serious	not serious	NA <sup>4</sup>	very serious <sup>3</sup>	NA	1/181	0/1 80	PETO OR 7.35 (0.15, 370.34)	6 more per 1000 (5 fewer to 16 more)	low
<b>falls requiring hospitalisation at end of follow up</b>											
<b>Mean follow-up: 6 month(s)</b>											
1 (araki 2015b)	R C T	not serious	not serious	NA <sup>4</sup>	very serious <sup>3</sup>	NA	1/181	0/1 80	PETO OR 7.35 (0.15, 370.34)	6 more per 1000 (5 fewer to 16 more)	low
<b>hypoglycaemia episodes at end of follow up</b>											
<b>Mean follow-up: 11.9 month(s)</b>											
3	R C T	not serious	not serious	serious <sup>5</sup>	serious <sup>6</sup>	NA	361/1 241	297 /69 5	RR 0.66 (0.51, 0.84)	147 fewer per 1000 (208 fewer to 70 fewer)	low
<b>at night hypoglycaemic episodes at end of follow up</b>											
<b>Mean follow-up: 11.9 month(s)</b>											
3	R C T	not serious	not serious	not serious	not serious	NA	156/1 241	181 /69 5	RR 0.47 (0.39, 0.57)	138 fewer per 1000 (159 fewer to 112 fewer)	high





## L.1.3.3 Adding dulaglutide compared to adding exenatide

Table 16: Clinical evidence profile: Adding dulaglutide compared to adding exenatide

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>all-cause mortality at end of follow up</b> Mean follow-up: 12 month(s)											
1 (wysham 2014 52 weeks)	RC T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	2/559	0/27 6	RR 2.47 (0.12, 51.34)	0 fewer per 1000 (0 more to 0 more)	very low
<b>cardiovascular mortality at end of follow up</b> Mean follow-up: 12 month(s)											
1 (wysham 2014 52 weeks)	RC T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	Very serious <sup>3</sup>	NA	2/559	0/27 6	PETO OR 4.46 (0.23, 85.07)	4 more per 1000 (1 fewer to 9 more)	very low
<b>hypoglycaemia episodes at end of follow up</b> Mean follow-up: 6 month(s)											
1 (wysham 2014 26 weeks)	RC T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>4</sup>	NA	59/559	44/2 76	RR 0.66 (0.46, 0.95)	54 fewer per 1000 (86 fewer to 8 fewer)	low
<b>severe hypoglycaemic episodes at end of follow up</b> Mean follow-up: 12 month(s)											
1 (wysham 2014 52 weeks)	RC T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>4</sup>	NA	0/559	2/27 6	PETO OR 0.05 (0.00, 0.92)	7 fewer per 1000 (17 fewer to 3 more)	low

<b>hba1c change (% , lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)</b>											
1 (wysham 2014 52 weeks)	RC T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	559	276	MD -0.13 (-0.32, 0.06)	MD 0.13 lower (0.32 lower to 0.06 higher)	moderate
<b>weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)</b>											
1 (wysham 2014 26 weeks)	RC T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	559	276	MD 0.52 (-0.18, 1.22)	MD 0.52 higher (0.18 lower to 1.22 higher)	moderate

1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
2. Only one study so no inconsistency
3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
4. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)

## L.1.3.4 Adding dulaglutide compared to adding sitagliptin

Table 17: Clinical evidence profile: Adding dulaglutide compared to adding sitagliptin

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>all-cause mortality at end of follow up</b> Mean follow-up: 12 month(s)											
1 (nauck 2014 dulaglutide v sitagliptin)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	1/606	2/31 5	RR 0.26 (0.02, 2.86)	5 fewer per 1000 (6 fewer to 12 more)	very low
<b>cardiovascular mortality at end of follow up</b> Mean follow-up: 12 month(s)											
1 (nauck 2014 dulaglutide v sitagliptin)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	0/606	1/31 5	PETO OR 0.05 (0.00, 3.35)	3 fewer per 1000 (9 fewer to 3 more)	very low
<b>severe hypoglycaemic episodes at end of follow up</b> Mean follow-up: 12 month(s)											
1 (nauck 2014 dulaglutide v sitagliptin)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	0/606	0/31 5	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (5 fewer to 5 more)	low
<b>hba1c change (% , lower values are better, change scores) at end of follow up</b> Mean follow-up: 12 month(s)											
1 (nauck 2014 dulaglutide v sitagliptin)	RC T	serious <sup>4</sup>	not serious	NA <sup>2</sup>	serious <sup>5</sup>	NA	606	315	MD -0.53 (-0.68, - 0.38)	MD 0.53 lower	low

										(0.68 lower to 0.38 lower)	
<b>weight change (kg, lower values are better, change scores) at end of follow up</b>											
<b>Mean follow-up: 12 month(s)</b>											
1 (nauck 2014 dulaglutide v sitagliptin)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	606	315	MD -0.89 (-1.49, -0.29)	MD 0.89 lower (1.49 lower to 0.29 lower)	low

1. >33.3% of the studies in the meta-analysis were at high risk of bias
2. Only one study so no inconsistency
3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
4. >33.3% of the studies in the meta-analysis were at moderate risk of bias
5. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

## L.1.3.5 Adding exenatide compared to adding placebo

Table 18: Clinical evidence profile: Adding exenatide compared to adding placebo

	D es ig n	Risk of bias	Indir ectn ess	Inco nsist ency	Impr ecisi on	Other conside rations	Inter venti on N	Co ntr ol N	Relative effect (95% CI)	Absolute effect	Cer tai nty
<b>No of studies</b>											
<b>health-related quality of life - overall (iqwol-lite, 0-100, higher values are better, changes scores) at end of follow up Mean follow-up: 6.5 month(s)</b>											
1 (gadde 2017)	R C T	very serio us <sup>1</sup>	not serio us	NA <sup>2</sup>	not serio us	NA	181	61	MD -1.00 (-5.13, 3.13)	MD 1.00 lower (5.13 lower to 3.13 higher)	low
<b>health-related quality of life - subscale barriers to activity (diabetes health profile, 0-100, lower values are better, changes scores) at end of follow up Mean follow-up: 6 month(s)</b>											
1 (joubert 2021)	R C T	serio us <sup>3</sup>	not serio us	NA <sup>2</sup>	serio us <sup>4</sup>	NA	28	18	MD -4.30 (-9.75, 1.15)	MD 4.30 lower (9.75 lower to 1.15 higher)	low
<b>health-related quality of life - subscale disinhibited eating (diabetes health profile, 0-100, lower values are better, changes scores) at end of follow up Mean follow-up: 6 month(s)</b>											
1 (joubert 2021)	R C T	serio us <sup>3</sup>	not serio us	NA <sup>2</sup>	serio us <sup>5</sup>	NA	28	18	MD -8.09 (-19.75, 3.57)	MD 8.09 lower	low

										(19.75 lower to 3.57 higher)	
<b>health-related quality of life - subscale well being (dmsat, 0-100, higher values are better, changes scores) at end of follow up</b> <b>Mean follow-up: 6.5 month(s)</b>											
1 (gadde 2017)	R C T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>6</sup>	NA	181	61	MD 7.10 (-0.95, 15.15)	MD 7.10 higher (0.95 lower to 15.15 higher)	very low
<b>health-related quality of life - subscale psychological distress (diabetes health profile, 0-100, lower values are better, changes scores) at end of follow up</b> <b>Mean follow-up: 6 month(s)</b>											
1 (joubert 2021)	R C T	serious <sup>3</sup>	not serious	NA <sup>2</sup>	serious <sup>7</sup>	NA	28	18	MD 2.73 (-3.04, 8.50)	MD 2.73 higher (3.04 lower to 8.50 higher)	low
<b>all-cause mortality at end of follow up</b> <b>Mean follow-up: 10.6 month(s)</b>											
8	R C T	not serious	not serious	serious <sup>8</sup>	not serious	NA	508/8590	587/8151	RD -0.01 (-0.02, -0.00)	9 fewer per 1000 (17 fewer to 2 fewer)	moderate
<b>all-cause mortality at end of follow up</b> <b>Mean follow-up: 38.4 month(s)</b>											
1 (holman 2017)	R C T	not serious	not serious	NA <sup>2</sup>	serious <sup>9</sup>	NA	7356	7396	HR 0.86 (0.77, 0.97)	Not estimable	moderate
<b>cardiovascular mortality at end of follow up</b>											

<b>Mean follow-up: 10.6 month(s)</b>											
8	R C T	not serio us	not serio us	serio us <sup>8</sup>	not serio us	NA	340/8 590	384 /81 51	RD -0.01 (-0.01, 0.00)	5 fewer per 1000 (11 fewer to 1 more)	mo der ate
<b>cardiovascular mortality at end of follow up Mean follow-up: 38.4 month(s)</b>											
1 (holman 2017)	R C T	not serio us	not serio us	NA <sup>2</sup>	serio us <sup>9</sup>	NA	7356	739 6	HR 0.88 (0.76, 1.02)	Not estimable	mo der ate
<b>3-point mace at end of follow up Mean follow-up: 38.4 month(s)</b>											
1 (holman 2017)	R C T	not serio us	not serio us	NA <sup>2</sup>	not serio us	NA	839/7 356	905 /73 96	RR 0.93 (0.85, 1.02)	8 fewer per 1000 (18 fewer to 2 more)	hig h
<b>3-point mace at end of follow up Mean follow-up: 38.4 month(s)</b>											
1 (holman 2017)	R C T	not serio us	not serio us	NA <sup>2</sup>	not serio us	NA	7356	739 6	HR 0.91 (0.83, 1.00)	Not estimable	hig h
<b>non-fatal myocardial infarction at end of follow up Mean follow-up: 6.8 month(s)</b>											
2	R C T	very serio us <sup>1</sup>	not serio us	serio us <sup>8</sup>	very serio us <sup>10</sup>	NA	1/435	1/1 84	PETO OR 0.36 (0.02, 7.65)	3 fewer per 1000 (15 fewer to 8 more)	ver y low
<b>unstable angina at end of follow up Mean follow-up: 38.4 month(s)</b>											
1 (holman 2017)	R C T	not serio us	serio us <sup>11</sup>	NA <sup>2</sup>	serio us <sup>9</sup>	NA	171/7 356	151 /73 96	RR 1.14 (0.92, 1.41)	3 more per 1000 (2 fewer to 8 more)	low
<b>hospitalisation for heart failure at end of follow up Mean follow-up: 22.2 month(s)</b>											

2	R C T	not serio us	not serio us	serio us <sup>8</sup>	serio us <sup>9</sup>	NA	220/7 384	231 /74 14	RR 0.96 (0.80, 1.15)	1 fewer per 1000 (6 fewer to 5 more)	low
<b>hospitalisation for heart failure at end of follow up</b> Mean follow-up: 38.4 month(s)											
1 (holman 2017)	R C T	not serio us	not serio us	NA <sup>2</sup>	serio us <sup>9</sup>	NA	7356	739 6	HR 0.94 (0.78, 1.13)	Not estimable	mo der ate
<b>acute kidney injury at end of follow up</b> Mean follow-up: 6.4 month(s)											
1 (guja 2017)	R C T	not serio us	not serio us	NA <sup>2</sup>	very serio us <sup>10</sup>	NA	1/232	0/2 31	PETO OR 7.36 (0.15, 370.79)	4 more per 1000 (4 fewer to 13 more)	low
<b>development of end stage kidney disease at end of follow up</b> Mean follow-up: 38.4 month(s)											
1 (holman 2017)	R C T	not serio us	not serio us	NA <sup>2</sup>	serio us <sup>9</sup>	NA	55/73 56	65/ 739 6	PETO OR 0.85 (0.59, 1.22)	1 fewer per 1000 (4 fewer to 2 more)	mo der ate
<b>death from renal causes at end of follow up</b> Mean follow-up: 38.4 month(s)											
1 (holman 2017)	R C T	not serio us	not serio us	NA <sup>2</sup>	very serio us <sup>10</sup>	NA	5/735 6	5/7 396	PETO OR 1.01 (0.29, 3.47)	0 more per 1000 (1 fewer to 1 more)	low
<b>cardiac arrhythmia at end of follow up</b> Mean follow-up: 38.4 month(s)											
1 (holman 2017)	R C T	not serio us	not serio us	NA <sup>2</sup>	serio us <sup>9</sup>	NA	322/7 356	350 /73 96	RR 0.93 (0.80, 1.07)	4 fewer per 1000 (10 fewer to 3 more)	mo der ate
<b>diabetic ketoacidosis at end of follow up</b> Mean follow-up: 5.5 month(s)											

2	R C T	very serio us <sup>1</sup>	not serio us	serio us <sup>8</sup>	very serio us <sup>12</sup>	NA	1/160	0/4 9	RD 0.01 (-0.04, 0.05)	5 more per 1000 (38 fewer to 49 more)	ver y low
<b>hypoglycaemia episodes at end of follow up</b> <b>Mean follow-up: 6.9 month(s)</b>											
13	R C T	serio us <sup>3</sup>	not serio us	serio us <sup>8</sup>	not serio us	NA	455/2 480	171 /13 98	RD 0.06 (0.01, 0.10)	56 more per 1000 (10 more to 102 more)	low
<b>at night hypoglycaemic episodes at end of follow up</b> <b>Mean follow-up: 7 month(s)</b>											
1 (buse 2011)	R C T	serio us <sup>3</sup>	not serio us	NA <sup>2</sup>	serio us <sup>9</sup>	NA	23/13 7	32/ 122	RR 0.64 (0.40, 1.03)	94 fewer per 1000 (158 fewer to 8 more)	low
<b>severe hypoglycaemic episodes at end of follow up</b> <b>Mean follow-up: 9.5 month(s)</b>											
11	R C T	not serio us	not serio us	serio us <sup>8</sup>	very serio us <sup>13</sup>	NA	248/9 363	220 /85 14	RD 0.00 (-0.00, 0.01)	3 more per 1000 (2 fewer to 8 more)	ver y low
<b>hba1c change (% , lower values are better, change scores) at end of follow up</b> <b>Mean follow-up: 10.9 month(s)</b>											
13	R C T	very serio us <sup>1</sup>	not serio us	serio us <sup>14</sup>	not serio us	NA	9820	868 2	MD -0.72 (-0.82, - 0.63)	MD 0.72 lower (0.82 lower to 0.63 lower)	ver y low
<b>hba1c change (mmol/l, lower values are better, change scores) at end of follow up</b> <b>Mean follow-up: 5.5 month(s)</b>											

1 (harreiter 2021)	R C T	serious <sup>3</sup>	not serious	NA <sup>2</sup>	not serious	NA	16	14	MD -0.52 (-0.86, -0.17)	MD 0.52 lower (0.86 lower to 0.17 lower)	moderate
<b>weight change (kg, lower values are better, change scores) at end of follow up</b> <b>Mean follow-up: 10.6 month(s)</b>											
14	R C T	very serious <sup>1</sup>	not serious	serious <sup>14</sup>	not serious	NA	9846	8719	MD -1.58 (-2.00, -1.17)	MD 1.58 lower (2.00 lower to 1.17 lower)	very low
<b>bmi change (kg/m2, lower values are better, change and final scores) at end of follow up</b> <b>Mean follow-up: 7.8 month(s)</b>											
3	R C T	very serious <sup>1</sup>	serious <sup>11</sup>	not serious	not serious	NA	125	114	MD -1.28 (-1.51, -1.06)	MD 1.28 lower (1.51 lower to 1.06 lower)	very low

1. >33.3% of the studies in the meta-analysis were at high risk of bias
2. Only one study so no inconsistency
3. >33.3% of the studies in the meta-analysis were at moderate risk of bias
4. 95% confidence intervals cross one end of the defined MIDs (-8.33, 8.33)
5. 95% confidence intervals cross one end of the defined MIDs (-11.68, 11.68)
6. 95% confidence intervals cross one end of the defined MIDs (-11.43, 11.43)

7. 95% confidence intervals cross one end of the defined MIDs (-7.78, 7.78)
8. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
9. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
10. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
11. Largest proportion of studies in the meta-analysis came from partially direct studies
12. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.21 (0.8-0.9 = serious, <0.8 = very serious).
13. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.06 (0.8-0.9 = serious, <0.8 = very serious).
14. I2 between 50% and 75%

#### L.1.3.6 Adding exenatide compared to adding insulin

**Table 19: Clinical evidence profile: Adding exenatide compared to adding insulin**

No of studies	D e s i g n	Risk of bias	Indi rect ness	Inco nsist ency	Impr ecisi on	Other conside rations	Inter venti on N	Co ntr ol N	Relative effect (95% CI)	Absolute effect	Cer tai nty
health-related quality of life - overall (eq-5d, -0.59-1.0, higher values are better, change scores) at end of follow up Mean follow-up: 20.8 month(s)											
2	R C T	very serio us <sup>1</sup>	not serio us	not serio us	not serio us	NA	450	438	MD -0.00 (- 0.03, 0.02)	MD 0.00 lower (0.03 lower to 0.02 higher)	low
health-related quality of life - overall (iwqol, 0-100, higher values are better, change scores) at end of follow up Mean follow-up: 6.5 month(s)											

2	R C T	serious <sup>2</sup>	not serious	not serious	not serious	NA	358	368	MD 3.71 (1.95, 5.46)	MD 3.71 higher (1.95 higher to 5.46 higher)	moderate
<b>all-cause mortality at end of follow up Mean follow-up: 12.2 month(s)</b>											
6	R C T	very serious <sup>1</sup>	not serious	serious <sup>3</sup>	very serious <sup>4</sup>	NA	5/1251	2/1224	RD 0.00 (-0.00, 0.01)	2 more per 1000 (3 fewer to 8 more)	very low
<b>cardiovascular mortality at end of follow up Mean follow-up: 6.2 month(s)</b>											
4	R C T	serious <sup>2</sup>	not serious	serious <sup>3</sup>	very serious <sup>5</sup>	NA	2/765	0/753	RD 0.00 (-0.00, 0.01)	3 more per 1000 (4 fewer to 9 more)	very low
<b>non-fatal stroke at end of follow up Mean follow-up: 6 month(s)</b>											
1 (inagaki 2012)	R C T	not serious	not serious	NA <sup>6</sup>	very serious <sup>7</sup>	NA	1/215	0/212	PETO OR 7.29 (0.14, 367.26)	5 more per 1000 (4 fewer to 14 more)	low
<b>non-fatal myocardial infarction at end of follow up Mean follow-up: 7 month(s)</b>											
1 (diamant 2014)	R C T	serious <sup>2</sup>	not serious	NA <sup>6</sup>	very serious <sup>7</sup>	NA	0/315	2/312	PETO OR 0.13 (0.01, 2.14)	6 fewer per 1000 (15 fewer to 2 more)	very low
<b>acute kidney injury at end of follow up Mean follow-up: 7 month(s)</b>											
1 (diamant 2014)	R C T	serious <sup>2</sup>	not serious	NA <sup>6</sup>	very serious <sup>7</sup>	NA	1/315	0/312	PETO OR 7.32 (0.15, 368.87)	3 more per 1000 (3 fewer to 9 more)	very low
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 7.6 month(s)</b>											
8	R C T	serious <sup>2</sup>	not serious	not serious	not serious	NA	178/1081	269/1071	RR 0.66 (0.56, 0.77)	86 fewer per 1000 (111 fewer to 58 fewer)	moderate
<b>at night hypoglycaemic episodes at end of follow up Mean follow-up: 7.2 month(s)</b>											

6	R C T	serious <sup>2</sup>	not serious	serious <sup>8</sup>	not serious	NA	150/147	257/1130	RR 0.54 (0.38, 0.76)	105 fewer per 1000 (141 fewer to 55 fewer)	low
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 10.9 month(s)</b>											
10	R C T	very serious <sup>1</sup>	not serious	serious <sup>3</sup>	very serious <sup>9</sup>	NA	11/1738	21/1704	RD -0.01 (-0.01, 0.00)	6 fewer per 1000 (13 fewer to 1 more)	very low
<b>hba1c change (% , lower values are better, change scores) at end of follow up Mean follow-up: 9.2 month(s)</b>											
15	R C T	serious <sup>2</sup>	not serious	very serious <sup>10</sup>	not serious	NA	2059	2010	MD -0.09 (-0.24, 0.06)	MD 0.09 lower (0.24 lower to 0.06 higher)	very low
<b>weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 9.2 month(s)</b>											
15	R C T	very serious <sup>1</sup>	not serious	very serious <sup>10</sup>	not serious	NA	2015	1976	MD -4.26 (-5.05, -3.48)	MD 4.26 lower (5.05 lower to 3.48 lower)	very low
<b>bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 7.1 month(s)</b>											
6	R C T	serious <sup>2</sup>	not serious	very serious <sup>10</sup>	serious <sup>11</sup>	NA	604	594	MD -1.34 (-1.88, -0.79)	MD 1.34 lower (1.88 lower to 0.79 lower)	very low

1. >33.3% of the studies in the meta-analysis were at high risk of bias
2. >33.3% of the studies in the meta-analysis were at moderate risk of bias
3. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
4. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.35 (0.8-0.9 = serious, <0.8 = very serious).

5. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.51 (0.8-0.9 = serious, <0.8 = very serious).
6. Only one study so no inconsistency
7. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
8. I2 between 50% and 75%
9. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.73 (0.8-0.9 = serious, <0.8 = very serious).
10. I2 > 75%
11. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

#### L.1.3.7 Adding exenatide compared to adding liraglutide

**Table 20: Clinical evidence profile: Adding exenatide compared to adding liraglutide**

No of studies	De sig n	Risk of bias	Indir ectn ess	Incon sisten cy	Impr ecisi on	Other consider ations	Interv entio n N	Con trol N	Relative effect (95% CI)	Absolute effect	Cer tain ty
<b>all-cause mortality at end of follow up Mean follow-up: 6 month(s)</b>											
1 (buse 2013)	R CT	serio us <sup>1</sup>	not serio us	NA 2	very serio us <sup>3</sup>	NA	2/461	2/4 50	PETO OR 0.98 (0.14, 6.95)	0 fewer per 1000 (9 fewer to 8 more)	ver y low
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 6 month(s)</b>											
2	R CT	not serio us	not serio us	not serio us	serio us <sup>4</sup>	NA	129/6 93	100 /68 5	RR 1.29 (1.02, 1.62)	42 more per 1000 (3 more to 91 more)	mo der ate
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 6 month(s)</b>											

2	R CT	serious <sup>1</sup>	not serious	serious <sup>5</sup>	very serious <sup>6</sup>	NA	1/693	0/6 85	RD 0.00 (- 0.00, 0.01)	1 more per 1000 (3 fewer to 6 more)	very low
<b>hba1c change (% , lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)</b>											
2	R CT	serious <sup>1</sup>	not serious	not serious	not serious	NA	621	621	MD 0.26 (0.16, 0.35)	MD 0.26 higher (0.16 higher to 0.35 higher)	moderate
<b>weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)</b>											
2	R CT	serious <sup>1</sup>	not serious	not serious	not serious	NA	635	633	MD 0.69 (0.30, 1.07)	MD 0.69 higher (0.30 higher to 1.07 higher)	moderate

- >33.3% of the studies in the meta-analysis were at moderate risk of bias
- Only one study so no inconsistency
- 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.29 (0.8-0.9 = serious, <0.8 = very serious).

#### L.1.3.8 Adding exenatide compared to adding sitagliptin

**Table 21: Clinical evidence profile: Adding exenatide compared to adding sitagliptin**

No of studies	D es ig n	Risk of bias	Indir ectn ess	Inco nsist ency	Impr ecisi on	Other conside rations	Inter venti on N	Co ntr ol N	Relative effect (95% CI)	Absolute effect	Cer tai nty
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<b>health-related quality of life - overall (ed-5d index, -0.59-1, higher values are better, changes scores) Mean follow-up: 6 month(s)</b>											
1 (bergenstal 2010)	R C T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	129	139	MD -0.01 (-0.07, 0.05)	MD 0.01 lower (0.07 lower to 0.05 higher)	very low
<b>health-related quality of life - overall (iqwol, 0-100, higher values are better, changes scores) Mean follow-up: 6.5 month(s)</b>											
1 (gadde 2017)	R C T	serious <sup>4</sup>	not serious	NA <sup>2</sup>	not serious	NA	181	122	MD -1.30 (-4.35, 1.75)	MD 1.30 lower (4.35 lower to 1.75 higher)	moderate
<b>health-related quality of life - subscale well being (dmsat, 0-100, higher values are better, changes scores) Mean follow-up: 6.5 month(s)</b>											
1 (gadde 2017)	R C T	serious <sup>4</sup>	not serious	NA <sup>2</sup>	not serious	NA	181	122	MD 8.20 (1.54, 14.86)	MD 8.20 higher (1.54 higher to 14.86 higher)	moderate
<b>all-cause mortality at end of follow up Mean follow-up: 6 month(s)</b>											
1 (bergenstal 2010)	R C T	serious <sup>4</sup>	not serious	NA <sup>2</sup>	very serious <sup>5</sup>	NA	0/160	1/166	PETO OR 0.14 (0.00, 7.08)	6 fewer per 1000 (18 fewer to 6 more)	very low
<b>cardiovascular mortality at end of follow up Mean follow-up: 6 month(s)</b>											
1 (bergenstal 2010)	R C T	serious <sup>4</sup>	not serious	NA <sup>2</sup>	very serious <sup>5</sup>	NA	0/160	1/166	PETO OR 0.14 (0.00, 7.08)	6 fewer per 1000 (18 fewer to 6 more)	very low
<b>non-fatal myocardial infarction at end of follow up Mean follow-up: 6.5 month(s)</b>											
1 (gadde 2017)	R C T	not serious	not serious	NA <sup>2</sup>	serious <sup>6</sup>	NA	0/181	0/122	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	moderate
<b>unstable angina at end of follow up Mean follow-up: 6 month(s)</b>											

1 (bergenstal 2010)	R C T	serious <sup>4</sup>	not serious	NA <sup>2</sup>	serious <sup>6</sup>	NA	0/160	0/166	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	low
<b>acute kidney injury at end of follow up</b> Mean follow-up: 6 month(s)											
1 (bergenstal 2010)	R C T	serious <sup>4</sup>	not serious	NA <sup>2</sup>	serious <sup>6</sup>	NA	0/160	0/166	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	low
<b>hypoglycaemia episodes at end of follow up</b> Mean follow-up: 6.2 month(s)											
2	R C T	serious <sup>4</sup>	not serious	serious <sup>7</sup>	very serious <sup>5</sup>	NA	2/341	6/288	PETO OR 0.35 (0.09, 1.44)	15 fewer per 1000 (33 fewer to 3 more)	very low
<b>severe hypoglycaemic episodes at end of follow up</b> Mean follow-up: 6.2 month(s)											
2	R C T	serious <sup>4</sup>	not serious	not serious	not serious	NA	0/341	0/288	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	moderate
<b>hba1c change (% , lower values are better, change scores) at end of follow up</b> Mean follow-up: 6.2 month(s)											
2	R C T	not serious	not serious	not serious	serious <sup>8</sup>	NA	341	288	MD -0.44 (-0.74, -0.14)	MD 0.44 lower (0.74 lower to 0.14 lower)	moderate
<b>weight change (kg, lower values are better, change scores) at end of follow up</b> Mean follow-up: 6.2 month(s)											
2	R C T	not serious	not serious	very serious <sup>9</sup>	not serious	NA	341	288	MD -0.69 (-2.26, 0.88)	MD 0.69 lower (2.26 lower to 0.88 higher)	low

1. >33.3% of the studies in the meta-analysis were at high risk of bias
2. Only one study so no inconsistency
3. 95% confidence intervals cross both ends of the defined MIDs (-0.03, 0.03)

4. >33.3% of the studies in the meta-analysis were at moderate risk of bias
5. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
6. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
7. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
8. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
9. I<sup>2</sup> > 75%

### L.1.3.9 Adding liraglutide compared to adding placebo

**Table 22: Adding liraglutide compared to adding placebo**

	D e s i g n	R i s k o f b i a s	I n d i r e c t n e s s	I n c o n s i s t e n c y	I m p r e c i s i o n	O t h e r c o n s i d e r a t i o n s	I n t e r v e n t i o n N	C o n t r o l N	R e l a t i v e e f f e c t ( 95% C I)	A b s o l u t e e f f e c t	C e r t a i n t y
<b>No of studies</b>											
<b>health-related quality of life - overall (iwqol, higher values are better, change score) at end of follow-up Mean follow-up: 12.8 month(s)</b>											
1 (davies 2015)	R C T	ver y ser i o u s <sup>1</sup>	not ser i o u s	NA <sup>2</sup>	not ser i o u s	NA	615	21 1	MD 3.23 (1.18, 5.28)	MD 3.23 higher (1.18 higher to 5.28 higher)	lo w
<b>health-related quality of life - subscale barriers to activity (sf-36 physical role subscale, higher values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)</b>											
1 (miras 2019)	R C T	ser i o u s <sup>3</sup>	not ser i o u s	NA <sup>2</sup>	ver y ser i o u s	NA	53	27	MD 14.20 (- 5.77, 34.17)	MD 14.20 higher (5.77 lower to	ve r y lo w

					ous <sup>4</sup>					34.17 higher)	
<b>health-related quality of life - subscale barriers to activity (modified diabetes quality of life clinical trial questionnaire - lifestyle flexibility subscale, lower values are better, change score) at end of follow-up</b> Mean follow-up: 6 month(s)											
1 (vanderheiden 2016a)	R C T	seri ous <sup>3</sup>	not ser iou s	NA <sup>2</sup>	seri ous <sup>5</sup>	NA	32	34	MD - 0.10 (- 0.51, 0.31)	MD 0.10 lower (0.51 lower to 0.31 higher)	lo w
<b>health-related quality of life - subscale blood glucose control (modified diabetes quality of life clinical trial questionnaire - glycaemia control perception subscale, lower values are better, change score) at end of follow-up</b> Mean follow-up: 6 month(s)											
1 (vanderheiden 2016a)	R C T	seri ous <sup>3</sup>	not ser iou s	NA <sup>2</sup>	seri ous <sup>6</sup>	NA	32	34	MD - 1.10 (- 1.78, - 0.42)	MD 1.10 lower (1.78 lower to 0.42 lower)	lo w
<b>health-related quality of life - subscale current health perception (modified diabetes quality of life clinical trial questionnaire - current health perception subscale, lower values are better, change score) at end of follow-up</b> Mean follow-up: 6 month(s)											
1 (vanderheiden 2016a)	R C T	seri ous <sup>3</sup>	not ser iou s	NA <sup>2</sup>	seri ous <sup>7</sup>	NA	32	34	MD - 0.30 (- 0.88, 0.28)	MD 0.30 lower (0.88 lower to 0.28 higher)	lo w
<b>health-related quality of life - subscale emotional effects (sf-36 emotional role functioning subscale, higher values are better, change score) at end of follow-up</b> Mean follow-up: 5.5 month(s)											
1 (miras 2019)	R C T	seri ous <sup>3</sup>	not ser iou s	NA <sup>2</sup>	ver y seri ous <sup>8</sup>	NA	53	27	MD 6.30 (- 9.49, 22.09)	MD 6.30 higher (9.49 lower to 22.09 higher)	ve ry lo w

<b>health-related quality of life - subscale fatigue (sf-36 vitality subscale, higher values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)</b>											
1 (miras 2019)	R C T	seri ous <sup>3</sup>	not seri ous	NA <sup>2</sup>	ver y seri ous <sup>4</sup>	NA	53	27	MD 0.20 (- 8.77, 9.17)	MD 0.20 higher (8.77 lower to 9.17 higher)	ve ry lo w
<b>health-related quality of life - subscale general health (sf-36 general health perception, higher values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)</b>											
1 (miras 2019)	R C T	seri ous <sup>3</sup>	not seri ous	NA <sup>2</sup>	seri ous <sup>9</sup>	NA	53	27	MD 6.20 (- 1.66, 14.06)	MD 6.20 higher (1.66 lower to 14.06 higher)	lo w
<b>health related-quality of life - subscale general health (modified diabetes quality of life clinical trial questionnaire - general health perception subscale, lower values are better, change score) at end of follow-up Mean follow-up: 6 month(s)</b>											
1 (vanderheiden 2016a)	R C T	seri ous <sup>3</sup>	not seri ous	NA <sup>2</sup>	seri ous <sup>10</sup>	NA	32	34	MD - 0.30 (- 0.68, 0.08)	MD 0.30 lower (0.68 lower to 0.08 higher)	lo w
<b>health-related quality of life - subscale hypoglycaemia fear (modified diabetes quality of life clinical trial questionnaire - hypoglycaemia subscale, lower values are better, change score) at end of follow-up Mean follow-up: 6 month(s)</b>											
1 (vanderheiden 2016a)	R C T	seri ous <sup>3</sup>	not seri ous	NA <sup>2</sup>	not seri ous	NA	32	34	MD 0.00 (- 0.27, 0.27)	MD 0.00 lower (0.27 lower to 0.27 higher)	m od er at e
<b>health-related quality of life - lifestyle impact (modified diabetes quality of life clinical trial questionnaire - treatment impact subscale, lower</b>											

<b>values are better, change score) at end of follow-up Mean follow-up: 6 month(s)</b>											
1 (vanderheiden 2016a)	R C T	seri ous <sup>3</sup>	not seri ous	NA <sup>2</sup>	seri ous <sup>11</sup>	NA	32	34	MD - 0.20 (- 0.41, 0.01)	MD 0.20 lower (0.41 lower to 0.01 higher)	lo w
<b>health-related quality of life - subscale pain (sf-36 bodily pain subscale, higher values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)</b>											
1 (miras 2019)	R C T	seri ous <sup>3</sup>	not seri ous	NA <sup>2</sup>	ver y seri ous <sup>12</sup>	NA	53	27	MD - 3.40 (- 17.95, 11.15)	MD 3.40 lower (17.95 lower to 11.15 higher)	ve ry lo w
<b>health-related quality of life - subscale physical functioning (sf-36 physical function subscale, higher values are better, change scores) at end of follow-up Mean follow-up: 9.2 month(s)</b>											
2	R C T	not seri ous	not seri ous	not seri ous	not seri ous	NA	251	22 5	MD 0.36 (- 1.00, 1.71)	MD 0.36 higher (1.00 lower to 1.71 higher)	hi gh
<b>health-related quality of life - subscale satisfaction (modified diabetes quality of life clinical trial questionnaire - treatment satisfaction subscale, lower values are better, change score) at end of follow-up Mean follow-up: 6 month(s)</b>											
1 (vanderheiden 2016a)	R C T	seri ous <sup>3</sup>	not seri ous	NA <sup>2</sup>	seri ous <sup>13</sup>	NA	32	34	MD - 0.30 (- 0.57, - 0.03)	MD 0.30 lower (0.57 lower to 0.03 lower)	lo w
<b>health-related quality of life - subscale social (sf-36 social role functioning subscale, higher values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)</b>											
1 (miras 2019)	R C T	seri ous <sup>3</sup>	not seri ous	NA <sup>2</sup>	ver y seri ous	NA	53	27	MD - 5.60 (- 17.15, 5.95)	MD 5.60 lower (17.15 lower to 5.95 higher)	ve ry lo w

					ous <sup>12</sup>						
<b>health-related quality of life - subscale social or vocational worry (modified diabetes quality of life clinical questionnaire - social or vocational worry subscale, lower values are better, change score) at end of follow-up Mean follow-up: 6 month(s)</b>											
1 (vanderheiden 2016a)	R C T	seri ous <sup>3</sup>	not seri ous	NA <sup>2</sup>	seri ous <sup>14</sup>	NA	32	34	MD - 0.30 (- 0.64, 0.04)	MD 0.30 lower (0.64 lower to 0.04 higher)	lo w
<b>health-related quality of life - subscale social stigma (modified diabetes quality of life clinical questionnaire - social stigma subscale, lower values are better, change score) at end of follow-up Mean follow-up: 6 month(s)</b>											
1 (vanderheiden 2016a)	R C T	seri ous <sup>3</sup>	not seri ous	NA <sup>2</sup>	seri ous <sup>15</sup>	NA	32	34	MD 0.30 (- 0.14, 0.74)	MD 0.30 higher (0.14 lower to 0.74 higher)	lo w
<b>health-related quality of life - subscale wellbeing (sf-36 mental health subscale, higher values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)</b>											
1 (miras 2019)	R C T	seri ous <sup>3</sup>	not seri ous	NA <sup>2</sup>	ver y seri ous <sup>12</sup>	NA	53	27	MD 0.60 (- 7.31, 8.51)	MD 0.60 higher (7.31 lower to 8.51 higher)	ve ry lo w
<b>all-cause mortality at end of follow up Mean follow-up: 12.1 month(s)</b>											
11	R C T	ver y seri ous <sup>1</sup>	not seri ous	seri ous <sup>16</sup>	not seri ous	NA	387 /72 14	45 0/ 58 82	RD - 0.00 (- 0.01, 0.01)	1 fewer per 1000 (9 fewer to 6 more)	ve ry lo w
<b>all-cause mortality at end of follow up (hazard ratio) Mean follow-up: 45.6 month(s)</b>											

1 (marso 2016a)	RCT	not serious	not serious	NA <sup>2</sup>	serious <sup>17</sup>	NA	468	4672	HR 0.85 (0.74, 0.98)	Not estimable	moderate
<b>cardiovascular mortality at end of follow up Mean follow-up: 13.5 month(s)</b>											
9	RCT	not serious	not serious	serious <sup>16</sup>	not serious	NA	222/6936	278/5630	RD - 0.00 (-0.01, 0.01)	1 fewer per 1000 (9 fewer to 7 more)	moderate
<b>cardiovascular mortality at end of follow up (hazard ratio) Mean follow-up: 45.6 month(s)</b>											
1 (marso 2016a)	RCT	not serious	not serious	NA <sup>2</sup>	serious <sup>17</sup>	NA	468	4672	HR 0.78 (0.66, 0.92)	Not estimable	moderate
<b>3-point mace at end of follow up Mean follow-up: 45.6 month(s)</b>											
1 (marso 2016a)	RCT	not serious	not serious	NA <sup>2</sup>	serious <sup>17</sup>	NA	608/4668	694/4672	RR 0.88 (0.79, 0.97)	18 fewer per 1000 (31 fewer to 4 fewer)	moderate
<b>3-point mace at end of follow up (hazard ratio) Mean follow-up: 45.6 month(s)</b>											
1 (marso 2016a)	RCT	not serious	not serious	NA <sup>2</sup>	serious <sup>17</sup>	NA	466	4672	HR 0.87 (0.78, 0.97)	Not estimable	moderate
<b>non-fatal stroke at end of follow up Mean follow-up: 28.8 month(s)</b>											
2	RCT	not serious	not serious	serious <sup>16</sup>	serious <sup>17</sup>	NA	159/4952	178/	RR 0.89	4 fewer per 1000 (10	low

			ious					48 14	(0.72, 1.10)	fewer to 4 more)	
<b>non-fatal stroke at end of follow up (hazard ratio) Mean follow-up: 45.6 month(s)</b>											
1 (marso 2016a)	R C T	not seri ous	not seri ous	NA <sup>2</sup>	seri ous <sup>17</sup>	NA	466 8	46 72	HR 0.89 (0.72, 1.10)	Not estimable	m od er at e
<b>non-fatal myocardial infarction at end of follow up Mean follow-up: 28.8 month(s)</b>											
2	R C T	not seri ous	not seri ous	seri ous <sup>16</sup>	seri ous <sup>17</sup>	NA	282 /49 52	31 7/ 48 14	RR 0.89 (0.76, 1.04)	7 fewer per 1000 (16 fewer to 2 more)	lo w
<b>non-fatal myocardial infarction at end of follow up (hazard ratio) Mean follow-up: 45.6 month(s)</b>											
1 (marso 2016a)	R C T	not seri ous	not seri ous	NA <sup>2</sup>	seri ous <sup>17</sup>	NA	466 8	46 72	HR 0.88 (0.75, 1.03)	Not estimable	m od er at e
<b>unstable angina at end of follow up Mean follow-up: 28.8 month(s)</b>											
2	R C T	not seri ous	not seri ous	seri ous <sup>16</sup>	ver y seri ous <sup>18</sup>	NA	122 /49 52	12 4/ 48 14	RD - 0.00 (- 0.01, 0.01)	0 fewer per 1000 (7 fewer to 6 more)	ve ry lo w
<b>unstable angina at end of follow up (hazard ratio) Mean follow-up: 45.6 month(s)</b>											
1 (marso 2016a)	R C T	not seri ous	not seri ous	NA <sup>2</sup>	ver y seri ous <sup>19</sup>	NA	466 8	46 72	HR 0.98 (0.76, 1.26)	Not estimable	lo w

<b>hospitalisation for heart failure at end of follow up Mean follow-up: 45.6 month(s)</b>											
1 (marso 2016a)	R C T	not seri ous	not seri ous	NA <sup>2</sup>	seri ous <sup>17</sup>	NA	218 /46 68	24 8/ 46 72	RR 0.88 (0.74, 1.05)	6 fewer per 1000 (14 fewer to 3 more)	m od er at e
<b>hospitalisation for heart failure at end of follow up (hazard ratio) Mean follow-up: 45.6 month(s)</b>											
1 (marso 2016a)	R C T	not seri ous	not seri ous	NA <sup>2</sup>	seri ous <sup>17</sup>	NA	466 8	46 72	HR 0.87 (0.73, 1.04)	Not estimable	m od er at e
<b>acute kidney injury at end of follow up Mean follow-up: 21.2 month(s)</b>											
3	R C T	not seri ous	not seri ous	seri ous <sup>16</sup>	seri ous <sup>17</sup>	NA	112 /51 54	10 0/ 49 14	RR 1.11 (0.85, 1.44)	2 more per 1000 (3 fewer to 9 more)	lo w
<b>persistent signs of worsening kidney disease at end of follow up Mean follow-up: 25.6 month(s)</b>											
2	R C T	not seri ous	not seri ous	seri ous <sup>16</sup>	seri ous <sup>17</sup>	NA	269 /47 21	33 7/ 46 99	RR 0.80 (0.68, 0.93)	15 fewer per 1000 (23 fewer to 5 fewer)	lo w
<b>persistent signs of worsening kidney disease at end of follow up (hazard ratio) Mean follow-up: 45.6 month(s)</b>											
1 (marso 2016a)	R C T	not seri ous	not seri ous	NA <sup>2</sup>	seri ous <sup>17</sup>	NA	466 8	46 72	HR 0.78 (0.67, 0.91)	Not estimable	m od er at e
<b>development of end stage kidney disease at end of follow up Mean follow-up: 29.2 month(s)</b>											

2	RCT	not serious	not serious	serious <sup>16</sup>	very serious <sup>19</sup>	NA	57/530	64/488	RR 0.88 (0.62, 1.25)	2 fewer per 1000 (5 fewer to 3 more)	very low
<b>development of end stage kidney disease at end of follow up (hazard ratio) Mean follow-up: 45.6 month(s)</b>											
1 (marso 2016a)	RCT	not serious	not serious	NA <sup>2</sup>	serious <sup>17</sup>	NA	4668	4672	HR 0.87 (0.61, 1.24)	Not estimable	moderate
<b>death from renal causes at end of follow up Mean follow-up: 34.8 month(s)</b>											
2	RCT	very serious <sup>1</sup>	not serious	serious <sup>16</sup>	very serious <sup>19</sup>	NA	9/5392	5/4793	PETOR 1.63 (0.56, 4.74)	1 more per 1000 (1 fewer to 2 more)	very low
<b>death from renal causes at end of follow up (hazard ratio) Mean follow-up: 45.6 month(s)</b>											
1 (marso 2016a)	RCT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>19</sup>	NA	4668	4672	HR 1.59 (0.52, 4.86)	Not estimable	very low
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 12.1 month(s)</b>											
13	RCT	not serious	not serious	serious <sup>20</sup>	serious <sup>17</sup>	NA	2527/762	24/6183	RR 1.18 (1.02, 1.36)	69 more per 1000 (6 more to 142 more)	low
<b>at night hypoglycaemic episodes at end of follow up Mean follow-up: 7.2 month(s)</b>											

2	R C T	not seri ous	not seri ous	seri ous 16	seri ous 21	NA	6/3 57	11 /2 44	RD - 0.02 (- 0.10, 0.06)	16 fewer per 1000 (95 fewer to 63 more)	lo w
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 12.1 month(s)</b>											
13	R C T	not seri ous	not seri ous	seri ous 16	not seri ous	NA	129 /81 33	15 7/ 60 51	RD - 0.01 (- 0.01, - 0.00)	5 fewer per 1000 (10 fewer to 0 more)	m od er at e
<b>hba1c change (mmol/mol, lower values are better, change score) at end of follow up Mean follow-up: 6 month(s)</b>											
1 (bizino 2019)	R C T	ver y seri ous 1	not seri ous	NA <sup>2</sup>	seri ous 22	NA	23	26	MD - 2.90 (- 8.09, 2.29)	MD 2.90 lower (8.09 lower to 2.29 higher)	ve ry lo w
<b>hba1c change (% , lower values are better, change scores and final values) at end of follow up Mean follow-up: 9.9 month(s)</b>											
19	R C T	ver y seri ous 1	not seri ous	ver y seri ous 23	not seri ous	NA	795 0	58 70	MD - 0.88 (- 1.03, - 0.72)	MD 0.88 lower (1.03 lower to 0.72 lower)	ve ry lo w
<b>weight change (kg, lower values are better, change scores and final values) at end of follow up Mean follow-up: 8.8 month(s)</b>											
19	R C T	seri ous 3	not seri ous	ver y seri ous 23	seri ous 24	NA	727 6	54 96	MD - 2.02 (- 2.85, - 1.20)	MD 2.02 lower (2.85 lower to 1.20 lower)	ve ry lo w
<b>bmi change (kg/m2, lower values are better, change scores and final values) at end of follow up Mean follow-up: 7.4 month(s)</b>											

9	R C T	not seri ous	not seri ous	seri ous <sup>20</sup>	seri ous <sup>25</sup>	NA	147 1	28 29	MD - 1.08 (- 1.37, - 0.79)	MD 1.08 lower (1.37 lower to 0.79 lower)	lo w
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1. >33.3% of the studies in the meta-analysis were at high risk of bias
2. Only one study so no inconsistency
3. >33.3% of the studies in the meta-analysis were at moderate risk of bias
4. 95% confidence intervals cross both ends of the defined MIDs (-2.00, 2.00)
5. 95% confidence intervals cross one end of the defined MIDs (-0.38, 0.38)
6. 95% confidence intervals cross one end of the defined MIDs (-0.55, 0.55)
7. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
8. 95% confidence intervals cross both ends of the defined MIDs (-4.00, 4.00)
9. 95% confidence intervals cross one end of the defined MIDs (-2.00, 2.00)
10. 95% confidence intervals cross one end of the defined MIDs (-0.40, 0.40)
11. 95% confidence intervals cross one end of the defined MIDs (-0.33, 0.33)
12. 95% confidence intervals cross both ends of the defined MIDs (-3.00, 3.00)
13. 95% confidence intervals cross one end of the defined MIDs (-0.35, 0.35)
14. 95% confidence intervals cross one end of the defined MIDs (-0.42, 0.42)
15. 95% confidence intervals cross one end of the defined MIDs (-0.53, 0.53)
16. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
17. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)

18. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.07 (0.8-0.9 = serious, <0.8 = very serious).

19. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

20. I2 between 50% and 75%

21. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.81 (0.8-0.9 = serious, <0.8 = very serious).

22. 95% confidence intervals cross one end of the defined MIDs (-5.50, 5.50)

23. I2 > 75%

24. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

25. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

#### L.1.3.10 Adding liraglutide compared to adding insulin

**Table 23: Adding liraglutide compared to adding insulin**

No of studies	De sig n	Risk of bias	Indir ectn ess	Incon sisten cy	Impr ecisio n	Other consider ations	Interv entio n N	Con trol N	Relative effect (95% CI)	Absolute effect	Cer tain ty
health-related quality of life - subscale mental component (SF-36, higher values are better, change score) at end of follow-up Mean follow-up: 15 month(s)											
2	R CT	very serio us <sup>1</sup>	not serio us	not serio us	not serio us	NA	1277	127 0	MD 0.04 (-0.10, 0.18)	MD 0.04 higher (0.10 lower to 0.18 higher)	low
health-related quality of life -subscale physical component (SF-36, higher values are better, change score) at end of follow-up											

<b>Mean follow-up: 9 month(s)</b>											
2	R CT	very serious <sup>1</sup>	not serious	very serious <sup>2</sup>	not serious	NA	1277	127 0	MD 0.48 (-0.29, 1.24)	MD 0.48 higher (0.29 lower to 1.24 higher)	ver y low
<b>all-cause mortality at end of follow up Mean follow-up: 18 month(s)</b>											
5	R CT	serious <sup>3</sup>	not serious	serious <sup>4</sup>	very serious <sup>5</sup>	NA	29/20 23	43/2 022	RD -0.00 (-0.01, 0.01)	2 fewer per 1000 (12 fewer to 8 more)	ver y low
<b>all-cause mortality at end of follow-up (hazard ratio) Mean follow-up: 60 month(s)</b>											
1 (group 2022)	R CT	serious <sup>3</sup>	not serious	NA <sup>6</sup>	serious <sup>7</sup>	NA	1262	126 3	HR 0.65 (0.40, 1.05)	Not estimable	low
<b>cardiovascular mortality at end of follow up Mean follow-up: 21 month(s)</b>											
4	R CT	serious <sup>3</sup>	not serious	serious <sup>4</sup>	serious <sup>8</sup>	NA	9/187 6	21/1 879	RD -0.00 (-0.01, 0.01)	3 fewer per 1000 (12 fewer to 6 more)	ver y low
<b>cardiovascular mortality at end of follow-up (hazard ratio) Mean follow-up: 60 month(s)</b>											
1 (group 2022)	R CT	serious <sup>3</sup>	not serious	NA <sup>6</sup>	serious <sup>7</sup>	NA	1251	125 7	HR 0.43 (0.20, 0.95)	Not estimable	low
<b>3-point mace at end of follow up Mean follow-up: 36 month(s)</b>											
2	R CT	serious <sup>3</sup>	not serious	not serious	serious <sup>7</sup>	NA	49/16 65	66/1 670	RR 0.75 (0.52, 1.07)	10 fewer per 1000 (19 fewer to 3 more)	low
<b>3-point mace at end of follow up (hazard ratio)</b>											

<b>Mean follow-up: 60 month(s)</b>											
1 (group 2022)	R CT	serious <sup>3</sup>	not serious	NA <sup>6</sup>	serious <sup>7</sup>	NA	1251	125 7	HR 0.74 (0.51, 1.07)	Not estimable	low
<b>4-point mace at end of follow up Mean follow-up: 60 month(s)</b>											
1 (group 2022)	R CT	very serious <sup>1</sup>	not serious	NA <sup>6</sup>	serious <sup>7</sup>	NA	54/12 62	71/1 263	RR 0.76 (0.54, 1.07)	13 fewer per 1000 (26 fewer to 4 more)	very low
<b>non-fatal myocardial infarction at end of follow up Mean follow-up: 12 month(s)</b>											
1 (gough 2014)	R CT	not serious	not serious	NA <sup>6</sup>	very serious <sup>9</sup>	NA	1/414	1/41 3	PETO OR 1.00 (0.06, 15.98)	0 fewer per 1000 (7 fewer to 7 more)	low
<b>unstable angina at end of follow up Mean follow-up: 33 month(s)</b>											
2	R CT	very serious <sup>1</sup>	not serious	serious <sup>4</sup>	very serious <sup>9</sup>	NA	7/144 2	10/1 442	PETO OR 0.70 (0.27, 1.82)	2 fewer per 1000 (8 fewer to 4 more)	very low
<b>non-fatal stroke at end of follow up Mean follow-up: 5.8 month(s)</b>											
2	R CT	serious <sup>3</sup>	not serious	serious <sup>4</sup>	very serious <sup>9</sup>	NA	4/661	1/66 3	PETO OR 3.34 (0.57, 19.37)	5 more per 1000 (2 fewer to 11 more)	very low
<b>hospitalisation for heart failure at end of follow up Mean follow-up: 60 month(s)</b>											
1 (group 2022)	R CT	serious <sup>3</sup>	not serious	NA <sup>6</sup>	serious <sup>7</sup>	NA	14/12 51	26/1 257	RR 0.54 (0.28, 1.03)	9 fewer per 1000 (15 fewer to 1 more)	low
<b>hospitalisation for heart failure at end of follow-up (hazard ratio)</b>											

Mean follow-up: 60 month(s)											
1 (group 2022)	R CT	serious <sup>3</sup>	not serious	NA <sup>6</sup>	serious <sup>7</sup>	NA	1251	125 7	HR 0.54 (0.28, 1.04)	Not estimable	low
acute kidney injury at end of follow up Mean follow-up: 6 month(s)											
1 (pasquel 2021)	R CT	very serious <sup>1</sup>	serious <sup>10</sup>	NA <sup>6</sup>	very serious <sup>9</sup>	NA	1/136	3/13 7	RR 0.34 (0.04, 3.19)	15 fewer per 1000 (21 fewer to 48 more)	very low
hypoglycaemia episodes at end of follow up Mean follow-up: 11.9 month(s)											
9	R CT	not serious	not serious	very serious <sup>2</sup>	not serious	NA	527/2 781	100 0/27 99	RR 0.46 (0.31, 0.68)	193 fewer per 1000 (246 fewer to 115 fewer)	low
hypoglycaemia episodes at end of follow-up (hazard ratio) Mean follow-up: 60 month(s)											
1 (group 2022)	R CT	very serious <sup>1</sup>	not serious	NA <sup>6</sup>	not serious	NA	1233	124 5	HR 0.61 (0.53, 0.70)	Not estimable	low
at night hypoglycaemic episodes at end of follow up Mean follow-up: 5.8 month(s)											
3	R CT	not serious	not serious	serious <sup>4</sup>	not serious	NA	15/89 1	93/8 95	RD -0.06 (-0.23, 0.12)	57 fewer per 1000 (234 fewer to 121 more)	moderate
severe hypoglycaemic episodes at end of follow up Mean follow-up: 13.6 month(s)											
7	R CT	very serious <sup>1</sup>	not serious	serious <sup>4</sup>	very serious <sup>11</sup>	NA	22/26 08	23/2 615	RD -0.00 (-0.01, 0.00)	0 fewer per 1000	very low

										(6 fewer to 5 more)	
<b>hba1c change (% , lower values are better, change scores and final values) at end of follow up Mean follow-up: 12.6 month(s)</b>											
9	R CT	not serious	not serious	serious <sup>12</sup>	not serious	NA	1697	1804	MD -0.10 (-0.29, 0.09)	MD 0.10 lower (0.29 lower to 0.09 higher)	moderate
<b>weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 6.7 month(s)</b>											
8	R CT	not serious	not serious	serious <sup>12</sup>	not serious	NA	1352	1376	MD -4.13 (-4.81, -3.45)	MD 4.13 lower (4.81 lower to 3.45 lower)	moderate
<b>bmi change (kg/m2, lower values are better, change scores and final values) at end of follow up Mean follow-up: 8 month(s)</b>											
3	R CT	serious <sup>3</sup>	not serious	not serious	serious <sup>13</sup>	NA	95	94	MD -1.18 (-1.73, -0.63)	MD 1.18 lower (1.73 lower to 0.63 lower)	low

1. >33.3% of the studies in the meta-analysis were at high risk of bias

2. I<sup>2</sup> > 75%

3. >33.3% of the studies in the meta-analysis were at moderate risk of bias

4. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

5. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.65 (0.8-0.9 = serious, <0.8 = very serious).

6. Only one study so no inconsistency
7. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
8. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.87 (0.8-0.9 = serious, <0.8 = very serious).
9. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
10. Largest proportion of studies in the meta-analysis came from partially direct studies
11. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.04 (0.8-0.9 = serious, <0.8 = very serious).
12. I2 between 50% and 75%
13. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

#### L.1.3.11 Adding liraglutide compared to adding dulaglutide

**Table 24: Adding liraglutide compared to adding dulaglutide**

No of studies	De sig n	Risk of bias	Indir ectn ess	Incon sisten cy	Impr ecisi on	Other consider ations	Interv entio n N	Con trol N	Relative effect (95% CI)	Absolute effect	Cer tain ty
<b>all-cause mortality at end of follow up Mean follow-up: 6 month(s)</b>											
1 (dungan 2014)	R CT	not serio us	not serio us	NA <sup>1</sup>	not serio us	NA	0/299	0/3 00	RD 0.00 (- 0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	high
<b>cardiovascular mortality at end of follow up Mean follow-up: 6 month(s)</b>											
1 (dungan 2014)	R CT	not serio us	not serio us	NA <sup>1</sup>	not serio us	NA	0/299	0/3 00	RD 0.00 (- 0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	high

<b>falls requiring hospitalisation at end of follow up Mean follow-up: 6 month(s)</b>											
1 (dungan 2014)	R CT	not serio us	not serio us	NA <sup>1</sup>	very serio us <sup>2</sup>	NA	1/299	0/3 00	PETO OR 7.41 (0.15, 373.63)	3 more per 1000 (3 fewer to 10 more)	low
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 6 month(s)</b>											
1 (dungan 2014)	R CT	not serio us	not serio us	NA <sup>1</sup>	serio us <sup>3</sup>	NA	26/29 9	17/ 300	RR 1.53 (0.85, 2.77)	30 more per 1000 (8 fewer to 100 more)	mo der ate
<b>at night hypoglycaemic episodes at end of follow up Mean follow-up: 6 month(s)</b>											
1 (dungan 2014)	R CT	not serio us	not serio us	NA <sup>1</sup>	very serio us <sup>2</sup>	NA	4/299	6/3 00	RR 0.67 (0.19, 2.35)	7 fewer per 1000 (16 fewer to 27 more)	low
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 6 month(s)</b>											
1 (dungan 2014)	R CT	not serio us	not serio us	NA <sup>1</sup>	not serio us	NA	0/299	0/3 00	RD 0.00 (- 0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	high
<b>hba1c change (% , lower values are better, change score) at end of follow up Mean follow-up: 6 month(s)</b>											
1 (dungan 2014)	R CT	not serio us	not serio us	NA <sup>1</sup>	not serio us	NA	299	300	MD -0.06 (- 0.20, 0.08)	MD 0.06 lower (0.20 lower to 0.08 higher)	high
<b>weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)</b>											
1 (dungan 2014)	R CT	not serio us	not serio us	NA <sup>1</sup>	not serio us	NA	299	300	MD 0.71 (0.16, 1.26)	MD 0.71 higher (0.16 higher to 1.26 higher)	high

1. Only one study so no inconsistency

2. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

3. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)

### L.1.3.12 Adding liraglutide compared to adding saxagliptin

**Table 25: Clinical evidence profile: Adding liraglutide compared to adding saxagliptin**

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerat ions	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>hypoglycaemia episodes at the end of follow-up</b>											
<b>Mean follow-up: 5.5 month(s)</b>											
1 (li 2014a)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>3</sup>	NA	4/61	3/60	RR 1.31 (0.31, 5.61)	16 more per 1000 (35 fewer to 231 more)	very low
<b>severe hypoglycaemic episodes at the end of follow-up</b>											
<b>Mean follow-up: 5.5 month(s)</b>											
1 (li 2014a)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	seriou s <sup>4</sup>	NA	0/61	0/60	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (32 fewer to 32 more)	very low
<b>hba1c change (% , lower values are better, final values) at the end of follow-up</b>											
<b>Mean follow-up: 5.5 month(s)</b>											
1 (li 2014a)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	not seriou s	NA	61	60	MD -0.27 (-0.47, - 0.07)	MD 0.27 lower (0.47 lower to 0.07 lower)	low

<b>weight change (kg, lower values are better, change scores) at end of follow-up Mean follow-up: 5.5 month(s)</b>											
1 (li 2014a)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	61	60	MD -5.10 (-6.01, -4.19)	MD 5.10 lower (6.01 lower to 4.19 lower)	low
<b>bmi change (kg/m2, lower values are better, change scores) at end of follow-up Mean follow-up: 5.5 month(s)</b>											
1 (li 2014a)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	61	60	MD -1.80 (-2.11, -1.49)	MD 1.80 lower (2.11 lower to 1.49 lower)	low

1. >33.3% of the studies in the meta-analysis were at high risk of bias
2. Only one study so no inconsistency
3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
4. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.

L.1.3.13 Adding liraglutide compared to adding sitagliptin

Table 22: Clinical evidence profile: Adding liraglutide compared to adding sitagliptin (adding therapy)

No of studies	De sig n	Risk of bias	Indire ctness	Incons istenc y	Impre cision	Other considerat ions	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>health-related quality of life - subscale mental component (SF-36, higher values are better, change scores) at end of follow up</b>											
<b>Mean follow-up: 24 month(s)</b>											
1 (group 2022)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	1218	1236	MD -0.27 (-0.85, 0.31)	MD 0.27 lower (0.85 lower to 0.31 higher)	low
<b>health-related quality of life - subscale physical component (SF-36, higher values are better, change scores) at end of follow up</b>											
<b>Mean follow-up: 12 month(s)</b>											
1 (group 2022)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	1218	1236	MD 0.66 (0.11, 1.21)	MD 0.66 higher (0.11 higher to 1.21 higher)	low
<b>all-cause mortality at the end of follow-up</b>											
<b>Mean follow-up: 21 month(s)</b>											
4	RC T	serious <sup>3</sup>	not serious	serious <sup>4</sup>	not serious	NA	28/220 8	44/1 996	RD -0.01	8 fewer per 1000	low

										(-0.02, -0.00)	(16 fewer to 0 more)	
<p><b>all-cause mortality at the end of follow-up</b>  <b>Mean follow-up: 60 month(s)</b></p>												
1 (group 2022)	RC T	serious <sup>3</sup>	not serious	NA <sup>2</sup>	serious <sup>5</sup>	NA	1262	1267	HR 0.66 (0.41, 1.07)	Not estimable	low	
<p><b>cardiovascular mortality at the end of follow-up</b>  <b>Mean follow-up: 26 month(s)</b></p>												
3	RC T	serious <sup>3</sup>	not serious	serious <sup>4</sup>	not serious	NA	9/1873	23/1667	RD -0.01 (-0.01, 0.00)	6 fewer per 1000 (13 fewer to 1 more)	low	
<p><b>cardiovascular mortality at the end of follow-up</b>  <b>Mean follow-up: 60 month(s)</b></p>												
1 (group 2022)	RC T	serious <sup>3</sup>	not serious	NA <sup>2</sup>	serious <sup>5</sup>	NA	1251	1264	HR 0.44 (0.20, 0.95)	Not estimable	low	
<p><b>3-point mace at end of follow-up</b>  <b>Mean follow-up: 60 month(s)</b></p>												
1 (group 2022)	RC T	serious <sup>3</sup>	not serious	NA <sup>2</sup>	serious <sup>5</sup>	NA	48/1251	69/1264	RR 0.70 (0.49, 1.01)	16 fewer per 1000 (28 fewer to 0 more)	low	

<b>3-point mace at the end of follow-up</b>											
<b>Mean follow-up: 60 month(s)</b>											
1 (group 2022)	RC T	serious <sup>3</sup>	not serious	NA <sup>2</sup>	serious <sup>5</sup>	NA	1251	1264	HR 0.70 (0.48, 1.02)	Not estimable	low
<b>4-point mace at end of follow-up</b>											
<b>Mean follow-up: 60 month(s)</b>											
1 (group 2022)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>5</sup>	NA	54/126 2	78/1 268	RR 0.70 (0.50, 0.98)	19 fewer per 1000 (31 fewer to 2 fewer)	very low
<b>non-fatal stroke at the end of follow-up</b>											
<b>Mean follow-up: 6 month(s)</b>											
1 (zang 2016)	RC T	not serious	not serious	NA <sup>2</sup>	very serious <sup>6</sup>	NA	0/183	1/18 4	PETO OR 0.14 (0.00, 6.86)	5 fewer per 1000 (16 fewer to 5 more)	low
<b>non-fatal myocardial infarction at the end of follow-up</b>											
<b>Mean follow-up: 6 month(s)</b>											
1 (webb 2020)	RC T	not serious	not serious	NA <sup>2</sup>	very serious <sup>6</sup>	NA	0/38	1/38	PETO OR 0.14 (0.00, 6.82)	26 fewer per 1000 (77 fewer to 25 more)	low

<p><b>unstable angina at end of follow-up</b>  <b>Mean follow-up: 60 month(s)</b></p>											
1 (group 2022)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>5</sup>	NA	7/1262	15/1 268	RR 0.47 (0.19, 1.15)	6 fewer per 1000 (10 fewer to 2 more)	very low
<p><b>hospitalisation for heart failure at the end of follow-up</b>  <b>Mean follow-up: 60 month(s)</b></p>											
1 (group 2022)	RC T	serious <sup>3</sup>	not serious	NA <sup>2</sup>	serious <sup>5</sup>	NA	14/125 1	30/1 264	RR 0.47 (0.25, 0.88)	13 fewer per 1000 (18 fewer to 3 fewer)	low
<p><b>hospitalisation for heart failure at the end of follow-up</b>  <b>Mean follow-up: 60 month(s)</b></p>											
1 (group 2022)	RC T	serious <sup>3</sup>	not serious	NA <sup>2</sup>	serious <sup>5</sup>	NA	1262	1267	HR 0.47 (0.25, 0.88)	Not estimable	low
<p><b>cardiac arrhythmia at the end of follow-up</b>  <b>Mean follow-up: 6 month(s)</b></p>											
1 (zang 2016)	RC T	not serious	not serious	NA <sup>2</sup>	very serious <sup>6</sup>	NA	0/183	1/18 4	PETO OR 0.14 (0.00, 6.86)	5 fewer per 1000 (16 fewer to 5 more)	low

<b>diabetic ketoacidosis at the end of follow-up</b>											
<b>Mean follow-up: 6 month(s)</b>											
1 (zang 2016)	RC T	not serious	not serious	NA <sup>2</sup>	very serious <sup>6</sup>	NA	1/183	0/184	PETO OR 7.43 (0.15, 374.43)	5 more per 1000 (5 fewer to 16 more)	low
<b>hypoglycaemia episodes at the end of follow-up</b>											
<b>Mean follow-up: 14.5 month(s)</b>											
7	RC T	very serious <sup>1</sup>	not serious	serious <sup>7</sup>	very serious <sup>6</sup>	NA	361/2291	387/ 2096	RR 0.84 (0.50, 1.39)	30 fewer per 1000 (92 fewer to 72 more)	very low
<b>hypoglycaemia episodes at end of follow up</b>											
<b>Mean follow-up: 60 month(s)</b>											
1 (group 2022)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	1233	1253	HR 0.97 (0.84, 1.12)	Not estimable	low
<b>at night hypoglycaemic episodes at the end of follow-up</b>											
<b>Mean follow-up: 6 month(s)</b>											
1 (zang 2016)	RC T	not serious	not serious	NA <sup>2</sup>	not serious	NA	0/183	0/184	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (11 fewer to 11 more)	high

<b>severe hypoglycaemic episodes at the end of follow-up</b>											
<b>Mean follow-up: 15.9 month(s)</b>											
6	RC T	very serious <sup>1</sup>	not serious	serious <sup>4</sup>	very serious <sup>8</sup>	NA	14/229 6	10/2 084	RD 0.00 (-0.00, 0.01)	2 more per 1000 (3 fewer to 6 more)	very low
<b>hba1c change (% , lower values are better, final values) at the end of follow-up</b>											
<b>Mean follow-up: 13.4 month(s)</b>											
8	RC T	serious <sup>3</sup>	not serious	serious <sup>9</sup>	serious <sup>10</sup>	NA	1335	1084	MD -0.33 (-0.56, - 0.10)	MD 0.33 lower (0.56 lower to 0.10 lower)	very low
<b>weight change (kg, lower values are better, change scores) at end of follow-up</b>											
<b>Mean follow-up: 6.8 month(s)</b>											
6	RC T	serious <sup>3</sup>	not serious	serious <sup>7</sup>	serious <sup>11</sup>	NA	975	786	MD -2.10 (-2.65, - 1.55)	MD 2.10 lower (2.65 lower to 1.55 lower)	very low
<b>bmi change (kg/m2, lower values are better, change scores) at end of follow-up</b>											
<b>Mean follow-up: 5.8 month(s)</b>											



## L.1.3.14 Adding liraglutide compared to adding vildagliptin

Table 23: Clinical evidence profile: Adding liraglutide compared to adding vildagliptin

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerat ions	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>hypoglycaemia episodes at the end of follow-up</b> Mean follow-up: 5.5 month(s)											
1 (li 2014a)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>3</sup>	NA	4/61	5/57	RR 0.75 (0.21, 2.65)	22 fewer per 1000 (69 fewer to 144 more)	very low
<b>severe hypoglycaemic episodes at the end of follow-up</b> Mean follow-up: 5.5 month(s)											
1 (li 2014a)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	seriou s <sup>4</sup>	NA	0/61	0/57	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (33 fewer to 33 more)	very low
<b>hba1c change (% , lower values are better, final values) at the end of follow-up</b> Mean follow-up: 5.5 month(s)											
1 (li 2014a)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	not seriou s	NA	61	57	MD -0.25 (-0.45, - 0.05)	MD 0.25 lower (0.45 lower to 0.05 lower)	low
<b>weight change (kg, lower values are better, change scores) at end of follow-up</b> Mean follow-up: 5.5 month(s)											

1 (li 2014a)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	not seriou s	NA	61	57	MD -5.20 (-6.08, - 4.32)	MD 5.20 lower (6.08 lower to 4.32 lower)	low
<b>bmi change (kg/m2, lower values are better, change scores) at end of follow-up</b> <b>Mean follow-up: 5.5 month(s)</b>											
1 (li 2014a)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	not seriou s	NA	61	57	MD -1.80 (-2.09, - 1.51)	MD 1.80 lower (2.09 lower to 1.51 lower)	low

- >33.3% of the studies in the meta-analysis were at high risk of bias
- Only one study so no inconsistency
- 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.

#### L.1.3.15 Adding lixisenatide compared to adding placebo

**Table 26: Clinical evidence profile: Adding lixisenatide compared to adding placebo**

No of studies	De sig n	Risk of bias	Indir ectn ess	Incon siste ncy	Impr ecisi on	Other consider ations	Interv entio n N	Con trol N	Relative effect (95% CI)	Absolute effect	Cer tain ty
health-related quality of life - subscale physical component (sf-12 scores, higher values are better, mean difference) at end of follow-up											

<b>Mean follow-up: 5.3 month(s)</b>											
1 (meneilly 2017)	R C T	not serio us	not serio us	NA <sup>1</sup>	serio us <sup>2</sup>	NA	175	173	MD 1.73 (0.01, 3.45)	MD 1.73 higher (0.01 higher to 3.45 higher)	mo der ate
<b>health-related quality of life - subscale mental component (sf-12 scores, higher values are better, mean difference) at end of follow-up Mean follow-up: 5.3 month(s)</b>											
1 (meneilly 2017)	R C T	not serio us	not serio us	NA <sup>1</sup>	not serio us	NA	175	173	MD 0.33 (-1.57, 2.23)	MD 0.33 higher (1.57 lower to 2.23 higher)	hig h
<b>all-cause mortality at end of follow-up Mean follow-up: 6.7 month(s)</b>											
10	R C T	not serio us	not serio us	serio us <sup>3</sup>	very serio us <sup>4</sup>	NA	5/303 0	8/1 914	RD -0.00 (-0.01, 0.00)	3 fewer per 1000 (7 fewer to 1 more)	ver y low
<b>cardiovascular mortality at end of follow-up Mean follow-up: 5.5 month(s)</b>											
9	R C T	not serio us	not serio us	serio us <sup>3</sup>	very serio us <sup>5</sup>	NA	2/270 8	2/1 754	RD -0.00 (-0.00, 0.00)	0 fewer per 1000 (4 fewer to 3 more)	ver y low
<b>non-fatal stroke at end of follow-up Mean follow-up: 5.5 month(s)</b>											
2	R C T	not serio us	not serio us	not serio us	very serio us <sup>6</sup>	NA	3/350	0/3 51	PETO OR 7.49 (0.78, 72.21)	9 more per 1000 (1 fewer to 18 more)	low
<b>non-fatal myocardial infarction at end of follow-up Mean follow-up: 5.5 month(s)</b>											

1 (pan 2014)	R C T	not serio us	not serio us	NA <sup>1</sup>	very serio us <sup>6</sup>	NA	1/196	0/1 94	PETO OR 7.31 (0.15, 368.62)	5 more per 1000 (5 fewer to 15 more)	low
<b>hypoglycaemia episodes at end of follow-up</b> <b>Mean follow-up: 6.7 month(s)</b>											
10	R C T	not serio us	not serio us	not serio us	serio us <sup>7</sup>	NA	396/3 030	191 /19 14	RR 1.44 (1.18, 1.76)	44 more per 1000 (18 more to 76 more)	mo der ate
<b>severe hypoglycaemic episodes at end of outcome</b> <b>Mean follow-up: 6.7 month(s)</b>											
10	R C T	not serio us	not serio us	serio us <sup>3</sup>	not serio us	NA	7/303 0	0/1 914	RD 0.00 (-0.00, 0.01)	2 more per 1000 (1 fewer to 6 more)	mo der ate
<b>hba1c change (% , lower values are better, mean difference) at end of follow-up</b> <b>Mean follow-up: 6.7 month(s)</b>											
10	R C T	not serio us	not serio us	serio us <sup>8</sup>	serio us <sup>9</sup>	NA	2977	188 9	MD -0.51 (-0.63, - 0.40)	MD 0.51 lower (0.63 lower to 0.40 lower)	low
<b>weight change (kg, lower values are better, mean difference) at end of follow-up</b> <b>Mean follow-up: 6.7 month(s)</b>											
10	R C T	not serio us	not serio us	not serio us	not serio us	NA	3012	189 8	MD -0.74 (-1.02, - 0.46)	MD 0.74 lower (1.02 lower to 0.46 lower)	hig h

1. Only one study so no inconsistency

2. 95% confidence intervals cross one end of the defined MIDs (-2.00, 2.00)

3. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
4. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.65 (0.8-0.9 = serious, <0.8 = very serious).
5. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.09 (0.8-0.9 = serious, <0.8 = very serious).
6. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
7. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
8. I2 between 50% and 75%
9. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

#### L.1.3.16 Adding lixisenatide compared to adding insulin

**Table 27: Clinical evidence profile: Adding lixisenatide compared to adding insulin**

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>all-cause mortality at end of follow up Mean follow-up: 6.2 month(s)</b>											
3	RC T	serio us <sup>1</sup>	not seriou s	serious <sup>2</sup>	very seriou s <sup>3</sup>	NA	2/707	5/14 11	RD -0.00 (-0.01, 0.00)	1 fewer per 1000 (6 fewer to 5 more)	very low
<b>cardiovascular mortality at end of follow up Mean follow-up: 6.2 month(s)</b>											
3	RC T	serio us <sup>1</sup>	not seriou s	serious <sup>2</sup>	very seriou s <sup>4</sup>	NA	1/707	3/14 11	RD -0.00 (-0.01, 0.00)	1 fewer per 1000 (6 fewer to 4 more)	very low

<b>non-fatal stroke at end of follow up</b> <b>Mean follow-up: 7 month(s)</b>											
1 (rosenstock 2016b)	RC T	serious <sup>1</sup>	not serious	NA <sup>5</sup>	very serious <sup>6</sup>	NA	1/233	1/46 7	RR 2.00 (0.13, 31.90)	2 more per 1000 (2 fewer to 66 more)	very low
<b>unstable angina at end of follow up</b> <b>Mean follow-up: 7 month(s)</b>											
1 (rosenstock 2016b)	RC T	serious <sup>1</sup>	not serious	NA <sup>5</sup>	very serious <sup>6</sup>	NA	0/233	1/46 7	PETO OR 0.22 (0.00, 14.30)	2 fewer per 1000 (6 fewer to 2 more)	very low
<b>hospitalisation for heart failure at end of follow up</b> <b>Mean follow-up: 7 month(s)</b>											
1 (rosenstock 2016b)	RC T	serious <sup>1</sup>	not serious	NA <sup>5</sup>	very serious <sup>6</sup>	NA	0/233	2/46 7	PETO OR 0.22 (0.01, 4.23)	4 fewer per 1000 (10 fewer to 2 more)	very low
<b>hypoglycaemia episodes at end of follow up</b> <b>Mean follow-up: 6.2 month(s)</b>											
3	RC T	serious <sup>1</sup>	not serious	very serious <sup>7</sup>	not serious	NA	125/70 7	618/ 1411	RR 0.29 (0.12, 0.71)	310 fewer per 1000 (386 fewer to 126 fewer)	very low
<b>severe hypoglycaemic episodes at end of follow up</b> <b>Mean follow-up: 6.2 month(s)</b>											
3	RC T	serious <sup>1</sup>	not serious	serious <sup>2</sup>	very serious <sup>6</sup>	NA	1/707	4/14 11	PETO OR 0.55 (0.09, 3.51)	1 fewer per 1000 (5 fewer to 2 more)	very low
<b>hba1c change (% , lower values are better, change scores) at end of follow up</b>											

Mean follow-up: 6.2 month(s)											
3	RC T	not serio us	not seriou s	serious <sup>8</sup>	seriou s <sup>9</sup>	NA	700	1402	MD 0.36 (0.17, 0.54)	MD 0.36 higher (0.17 higher to 0.54 higher)	low
<b>weight change (kg, lower values are better, change scores) at end of follow up</b> <b>Mean follow-up: 6.2 month(s)</b>											
3	RC T	not serio us	not seriou s	very serious <sup>7</sup>	seriou s <sup>10</sup>	NA	703	1402	MD -2.73 (-3.59, - 1.87)	MD 2.73 lower (3.59 lower to 1.87 lower)	very low

1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
3. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.06 (0.8-0.9 = serious, <0.8 = very serious).
4. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.08 (0.8-0.9 = serious, <0.8 = very serious).
5. Only one study so no inconsistency
6. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
7. I<sup>2</sup> > 75%
8. I<sup>2</sup> between 50% and 75%
9. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
10. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

## L.1.3.17 Adding lixisenatide compared to adding liraglutide

Table 28: Clinical evidence profile: Adding lixisenatide compared to adding liraglutide

No of studies	De sig n	Risk of bias	Indire ctness	Incons istency	Impre cision	Other considerat ions	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>cardiac arrhythmia at end of follow-up</b> <b>Mean follow-up: 6 month(s)</b>											
1 (nauck 2016b)	RC T	very seriou s <sup>3</sup>	not seriou s	NA <sup>1</sup>	very seriou s <sup>2</sup>	NA	1/202	0/202	PETO OR 7.39 (0.15, 372.38)	5 more per 1000 (5 fewer to 15 more)	very low
<b>hypoglycaemia episodes at end of follow-up</b> <b>Mean follow-up: 6 month(s)</b>											
1 (nauck 2016b)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	very seriou s <sup>2</sup>	NA	5/202	3/202	RR 1.67 (0.40, 6.88)	10 more per 1000 (9 fewer to 87 more)	low
<b>severe hypoglycaemic episodes at end of follow-up</b> <b>Mean follow-up: 6 month(s)</b>											
1 (nauck 2016b)	RC T	very seriou s <sup>3</sup>	not seriou s	NA <sup>1</sup>	not seriou s	NA	0/202	0/202	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (10 fewer to 10 more)	low
<b>hba1c change (% , lower values are better, mean difference) at end of follow-up</b> <b>Mean follow-up: 6 month(s)</b>											
1 (nauck 2016b)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	seriou s <sup>4</sup>	NA	202	202	MD 0.60 (0.40, 0.80)	MD 0.60 higher (0.40 higher to 0.80 higher)	mod erat e

weight change (kg, lower values are better, mean difference) at end of follow-up Mean follow-up: 6 month(s)											
1 (nauck 2016b)	RC T	not serious	not serious	NA <sup>1</sup>	not serious	NA	0	0	MD 0.60 (-0.18, 1.38)	MD 0.60 higher (0.18 lower to 1.38 higher)	high

1. Only one study so no inconsistency
2. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
3. >33.3% of the studies in the meta-analysis were at high risk of bias
4. 95% confidence intervals cross both ends of the defined MIDs (-0.50, 0.50)

#### L.1.3.18 Adding lixisenatide compared to adding exenatide

**Table 29: Clinical evidence profile: Adding lixisenatide compared to adding exenatide**

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
<b>all-cause mortality at end of follow up Mean follow-up: 5.5 month(s)</b>											
1 (rosenstock 2013)	RC T	not serious	not serious	NA <sup>1</sup>	very serious <sup>2</sup>	NA	1/318	1/316	PETO OR 0.99 (0.06, 15.92)	0 fewer per 1000 (9 fewer to 9 more)	low
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 5.5 month(s)</b>											

1 (rosenstock 2013)	RC T	not serio us	not seriou s	NA <sup>1</sup>	not seriou s	NA	8/318	25/3 16	RD -0.05 (-0.09, -0.02)	54 fewer per 1000 (88 fewer to 20 fewer)	high
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 5.5 month(s)</b>											
1 (rosenstock 2013)	RC T	not serio us	not seriou s	NA <sup>1</sup>	not seriou s	NA	0/318	0/31 6	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	high
<b>hba1c change (% , lower values are better, change score) at end of follow- up Mean follow-up: 5.5 month(s)</b>											
1 (rosenstock 2013)	RC T	not serio us	not seriou s	NA <sup>1</sup>	not seriou s	NA	315	315	MD 0.17 (0.03, 0.31)	MD 0.17 higher (0.03 higher to 0.31 higher)	high
<b>weight change (kg, lower vaues are better, change score) at end of follow- up Mean follow-up: 5.5 month(s)</b>											
1 (rosenstock 2013)	RC T	not serio us	not seriou s	NA <sup>1</sup>	not seriou s	NA	315	315	MD 1.02 (0.46, 1.58)	MD 1.02 higher (0.46 higher to 1.58 higher)	high

1. Only one study so no inconsistency
2. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

## L.1.3.19 Adding lixisenatide compared to adding sitagliptin

Table 30: Clinical evidence profile: Adding lixisenatide compared to adding sitagliptin

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerat ions	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>all-cause mortality at end of follow-up</b> Mean follow-up: 5.5 month(s)											
1 (van gaal 2014)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	seriou s <sup>3</sup>	NA	0/158	0/16 1	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	very low
<b>cardiovascular mortality at end of follow-up</b> Mean follow-up: 5.5 month(s)											
1 (van gaal 2014)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	seriou s <sup>3</sup>	NA	0/158	0/16 1	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	very low
<b>hypoglycaemia episodes at end of follow-up</b> Mean follow-up: 5.5 month(s)											
1 (van gaal 2014)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>4</sup>	NA	1/158	3/16 1	RR 0.34 (0.04, 3.23)	12 fewer per 1000 (18 fewer to 42 more)	very low
<b>severe hypoglycaemic episodes at end of follow-up</b> Mean follow-up: 5.5 month(s)											
1 (van gaal 2014)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	seriou s <sup>3</sup>	NA	0/158	0/16 1	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	very low
<b>hba1c change (% , lower values are better, change score) at end of follow-up</b>											

Mean follow-up: 5.5 month(s)											
1 (van gaal 2014)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	not seriou s	NA	158	161	MD 0.00 (-0.28, 0.28)	MD 0.00 lower (0.28 lower to 0.28 higher)	low
<b>weight change (kg, lower values are better, mean difference) at end of follow-up</b> <b>Mean follow-up: 5.5 month(s)</b>											
1 (van gaal 2014)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	not seriou s	NA	152	160	MD -1.30 (-2.10, -0.50)	MD 1.30 lower (2.10 lower to 0.50 lower)	low

1. >33.3% of the studies in the meta-analysis were at high risk of bias
2. Only one study so no inconsistency
3. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision
4. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

#### L.1.3.20 Adding semaglutide compared to adding placebo

**Table 31: Clinical evidence profile: Adding semaglutide compared to adding placebo**

No of studies	D es ig n	Risk of bias	Indi rect nes s	Inco nsist ency	Impr ecisi on	Other consid eration s	Inter venti on N	Co ntr ol N	Relative effect (95% CI)	Absolute effect	Cer tai nty
health-related quality of life - subscale mental component (sf-36, 0-100, higher values are better, change scores) at end of follow-up ~ Mean follow-up: 12.7 month(s)											

5	rc t	not seri ous	not seri ous	not serio us	not serio us	NA	3286	24 29	MD 0.75~(0.2 8, 1.22)	MD 0.75 higher~(0.28 higher to 1.22 higher)	high
<b>health-related quality of life - subscale physical component (sf-36, 0-100, higher values are better, change scores) at end of follow-up ~ Mean follow-up: 12.7 month(s)</b>											
5	R C T	not seri ous	not seri ous	not serio us	not serio us	NA	3286	24 29	MD 0.55~(0.1 7, 0.93)	MD 0.55 higher~(0.17 higher to 0.93 higher)	high
<b>all-cause mortality at end of follow up ~ Mean follow-up: 14.6 month(s)</b>											
11	R C T	not seri ous	not seri ous	serio us <sup>1</sup>	not serio us	NA	622/ 1074 6	68 4/9 20 7	RD - 0.01~(- 0.01, 0.00)	7 fewer per 1000~(14 fewer to 0 more)	moderate
<b>all-cause mortality at end of follow up ~ Mean follow-up: 29.5 month(s)</b>											
3	R C T	not seri ous	not seri ous	serio us <sup>2</sup>	serio us <sup>3</sup>	NA	8064	80 66	HR 0.84~(0.6 2, 1.14)	Not estimable	low
<b>cardiovascular mortality at end of follow up ~ Mean follow-up: 15.8 month(s)</b>											
8	R C T	not seri ous	not seri ous	serio us <sup>1</sup>	not serio us	NA	361/ 9365	39 6/8 59 1	RD - 0.00~(- 0.01, 0.00)	4 fewer per 1000~(10 fewer to 2 more)	moderate
<b>cardiovascular mortality at end of follow up ~ Mean follow-up: 29.5 month(s)</b>											
3	R C T	not seri ous	not seri ous	serio us <sup>2</sup>	serio us <sup>3</sup>	NA	8064	80 66	HR 0.84~(0.6 2, 1.14)	Not estimable	low
<b>3-point mace at end of follow up ~ Mean follow-up: 29.5 month(s)</b>											

3	R C T	not seri ous	not seri ous	not serio us	serio us <sup>3</sup>	NA	748/ 8064	89 0/8 06 6	RR 0.84~(0.7 7, 0.92)	18 fewer per 1000~(26 fewer to 9 fewer)	mo der ate
<b>3-point mace at end of follow up ~ Mean follow-up: 29.5 month(s)</b>											
3	R C T	not seri ous	not seri ous	not serio us	serio us <sup>3</sup>	NA	8064	80 66	HR 0.83~(0.7 6, 0.92)	Not estimable	mo der ate
<b>5-point mace at end of follow up ~ Mean follow-up: 20.4 month(s)</b>											
2	R C T	not seri ous	not seri ous	not serio us	serio us <sup>3</sup>	NA	282/ 3239	36 4/3 24 1	RR 0.78~(0.6 7, 0.90)	25 fewer per 1000~(37 fewer to 12 fewer)	mo der ate
<b>5-point mace at end of follow up ~ Mean follow-up: 20.4 month(s)</b>											
2	R C T	not seri ous	not seri ous	not serio us	serio us <sup>3</sup>	NA	3239	32 41	HR 0.76~(0.6 5, 0.88)	Not estimable	mo der ate
<b>non-fatal stroke at end of follow up ~ Mean follow-up: 17.9 month(s)</b>											
7	R C T	not seri ous	not seri ous	serio us <sup>1</sup>	serio us <sup>3</sup>	NA	191/ 9717	22 6/8 59 6	PETO OR 0.82~(0.6 7, 0.99)	7 fewer per 1000~(11 fewer to 2 fewer)	low
<b>non-fatal stroke at end of follow up ~ Mean follow-up: 29.5 month(s)</b>											
3	R C T	not seri ous	not seri ous	not serio us	serio us <sup>3</sup>	NA	8064	80 66	HR 0.81~(0.6 7, 0.99)	Not estimable	mo der ate
<b>non-fatal myocardial infarction at end of follow up ~ Mean follow-up: 19.7 month(s)</b>											
6	R C T	not seri ous	not seri ous	serio us <sup>1</sup>	not serio us	NA	282/ 9454	35 1/8	RD - 0.01~(-	9 fewer per 1000~(14 fewer to 3 fewer)	mo der ate

								46 3	0.01, - 0.00)		
<b>non-fatal myocardial infarction at end of follow up ~ Mean follow-up: 29.5 month(s)</b>											
3	R C T	not seri ous	not seri ous	not serio us	serio us <sup>3</sup>	NA	8064	80 66	HR 0.81~(0.6 4, 1.03)	Not estimable	mo der ate
<b>unstable angina at end of follow up ~ Mean follow-up: 25.1 month(s)</b>											
4	R C T	not seri ous	not seri ous	serio us <sup>1</sup>	serio us <sup>3</sup>	NA	108/ 8349	11 4/8 20 8	PETO OR 0.94~(0.7 2, 1.23)	1 fewer per 1000~(4 fewer to 3 more)	low
<b>unstable angina at end of follow up ~ Mean follow-up: 29.5 month(s)</b>											
3	R C T	not seri ous	not seri ous	not serio us	serio us <sup>3</sup>	NA	8064	80 66	HR 0.93~(0.7 2, 1.22)	Not estimable	mo der ate
<b>hospitalisation for heart failure at end of follow up ~ Mean follow-up: 21.5 month(s)</b>											
5	R C T	not seri ous	not seri ous	not serio us	serio us <sup>3</sup>	NA	229/ 8873	24 6/8 38 3	RR 0.92~(0.7 7, 1.10)	2 fewer per 1000~(7 fewer to 3 more)	mo der ate
<b>hospitalisation for heart failure at end of follow up ~ Mean follow-up: 29.5 month(s)</b>											
3	R C T	not seri ous	not seri ous	not serio us	serio us <sup>3</sup>	NA	8064	80 66	HR 0.91~(0.7 6, 1.09)	Not estimable	mo der ate
<b>acute kidney injury at end of follow up ~ Mean follow-up: 14.6 month(s)</b>											
6	R C T	not seri ous	not seri ous	serio us <sup>1</sup>	very serio us <sup>4</sup>	NA	107/ 5024	10 8/4 12 0	RD - 0.00~(- 0.01, 0.01)	1 fewer per 1000~(8 fewer to 5 more)	ver y low

<b>persistent signs of worsening kidney disease at end of follow up ~ Mean follow-up: 25.2 month(s)</b>												
1 (marso 2016b)	R C T	not seri ous	not seri ous	NA <sup>5</sup>	serio us <sup>3</sup>	NA	62/1 648	10 0/1 64 9	RR 0.62~(0.4 6, 0.85)	23 fewer per 1000~(33 fewer to 9 fewer)	mo der ate	
<b>persistent signs of worsening kidney disease at end of follow up ~ Mean follow-up: 25.2 month(s)</b>												
1 (marso 2016b)	R C T	not seri ous	not seri ous	NA <sup>5</sup>	serio us <sup>3</sup>	NA	1648	16 49	HR 0.64~(0.4 6, 0.89)	Not estimable	mo der ate	
<b>cardiac arrhythmia at end of follow up ~ Mean follow-up: 25.2 month(s)</b>												
1 (marso 2016b)	R C T	not seri ous	not seri ous	NA <sup>5</sup>	very serio us <sup>6</sup>	NA	50/1 648	58/ 16 49	RR 0.86~(0.5 9, 1.25)	5 fewer per 1000~(14 fewer to 9 more)	low	
<b>hypoglycaemia episodes at end of follow up ~ Mean follow-up: 9.3 month(s)</b>												
7	R C T	not seri ous	not seri ous	serio us <sup>2</sup>	very serio us <sup>6</sup>	NA	288/ 2418	82/ 10 08	RR 1.31~(0.7 7, 2.25)	26 more per 1000~(19 fewer to 102 more)	ver y low	
<b>severe hypoglycaemic episodes at end of follow up ~ Mean follow-up: 15.9 month(s)</b>												
8	R C T	not seri ous	not seri ous	serio us <sup>1</sup>	very serio us <sup>7</sup>	NA	507/ 9626	45/ 5/8 63 3	RD 0.00~(- 0.00, 0.01)	4 more per 1000~(2 fewer to 10 more)	ver y low	
<b>hba1c change (% , lower values are better, change scores) at end of follow up ~ Mean follow-up: 15.5 month(s)</b>												
8	R C T	not seri ous	not seri ous	very serio us <sup>8</sup>	not serio us	NA	9028	75 21	MD - 1.00~(- 1.22, - 0.78)	MD 1.00 lower~(1.22 lower to 0.78 lower)	low	
<b>hba1c change (mmol/mol, lower values are better, change scores) at end of follow up ~ Mean follow-up: 6.2 month(s)</b>												

2	R C T	serious <sup>9</sup>	not serious	very serious <sup>8</sup>	serious <sup>10</sup>	NA	71	50	MD -14.67~(-27.41, -1.94)	MD 14.67 lower~(27.41 lower to 1.94 lower)	very low
<b>weight change (kg, lower values are better, change scores) at end of follow up ~ Mean follow-up: 13.8 month(s)</b>											
10	R C T	not serious	not serious	very serious <sup>8</sup>	not serious	NA	9100	75 72	MD -3.52~(-4.06, -2.98)	MD 3.52 lower~(4.06 lower to 2.98 lower)	low
<b>bmi change (kg/m2, lower values are better, change scores) at end of follow up ~ Mean follow-up: 11.8 month(s)</b>											
4	R C T	not serious	not serious	very serious <sup>8</sup>	not serious	NA	1741	84 4	MD -1.26~(-1.60, -0.91)	MD 1.26 lower~(1.60 lower to 0.91 lower)	low

1. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
2. I2 between 50% and 75%
3. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
4. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.59 (0.8-0.9 = serious, <0.8 = very serious).
5. Only one study so no inconsistency
6. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
7. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.03 (0.8-0.9 = serious, <0.8 = very serious).
8. I2 > 75%
9. Largest proportion of studies in the meta-analysis were at moderate risk of bias
10. 95% confidence intervals cross one end of the defined MIDs (-5.50, 5.50)

## L.1.3.21 Adding semaglutide compared to adding insulin

Table 32: Clinical evidence profile: Adding semaglutide compared to adding insulin

No of studies	De sig n	Risk of bias	Indir ectn ess	Incon siste ncy	Impr ecisi on	Other consider ations	Interv entio n N	Con trol N	Relative effect (95% CI)	Absolute effect	Cer tain ty
<b>health-related quality of life - subscale mental component (sf-36 v2, higher values are better, change scores) at end of follow-up Mean follow-up: 12 month(s)</b>											
1 (kellerer 2022)	R C T	very serio us <sup>1</sup>	not serio us	NA <sup>2</sup>	not serio us	NA	874	874	MD 0.59 (-0.14, 1.32)	MD 0.59 higher (0.14 lower to 1.32 higher)	low
<b>health-related quality of life - subscale physical component (sf-36 v2, higher values are better, change scores) at end of follow-up Mean follow-up: 12 month(s)</b>											
1 (kellerer 2022)	R C T	very serio us <sup>1</sup>	not serio us	NA <sup>2</sup>	not serio us	NA	874	874	MD 0.95 (0.37, 1.53)	MD 0.95 higher (0.37 higher to 1.53 higher)	low
<b>all-cause mortality at end of follow up Mean follow-up: 9.5 month(s)</b>											
2	R C T	serio us <sup>3</sup>	not serio us	serio us <sup>4</sup>	not serio us	NA	16/15 96	3/1 224	PETO OR 3.32 (1.32, 8.31)	8 more per 1000 (2 more to 13 more)	low
<b>cardiovascular mortality at end of follow up Mean follow-up: 7 month(s)</b>											

1 (aroda 2017)	R C T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>5</sup>	NA	3/722	2/3 60	PETO OR 0.74 (0.11, 4.76)	1 fewer per 1000 (10 fewer to 8 more)	ver y low
<b>unstable angina at end of follow up Mean follow-up: 12 month(s)</b>											
1 (kellerer 2022)	R C T	serious <sup>3</sup>	not serious	NA <sup>2</sup>	very serious <sup>5</sup>	NA	1/874	1/8 64	PETO OR 0.99 (0.06, 15.82)	0 fewer per 1000 (3 fewer to 3 more)	ver y low
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 12 month(s)</b>											
1 (kellerer 2022)	R C T	serious <sup>3</sup>	not serious	NA <sup>2</sup>	not serious	NA	328/8 74	527 /86 4	RR 0.62 (0.56, 0.68)	235 fewer per 1000 (271 fewer to 195 fewer)	mo de rate
<b>at night hypoglycaemic episodes at end of follow up Mean follow-up: 7 month(s)</b>											
1 (aroda 2017)	R C T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>6</sup>	NA	7/722	8/3 60	RR 0.44 (0.16, 1.19)	13 fewer per 1000 (19 fewer to 4 more)	ver y low
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 9.5 month(s)</b>											
2	R C T	very serious <sup>1</sup>	not serious	not serious	not serious	NA	40/15 96	45/ 122 4	RR 0.48 (0.32, 0.73)	19 fewer per 1000 (25 fewer to 10 fewer)	low
<b>hba1c change (% , lower values are better, change scores) at end of follow up Mean follow-up: 8.7 month(s)</b>											
2	R C T	very serious <sup>1</sup>	not serious	very serious <sup>7</sup>	serious <sup>8</sup>	NA	1596	123 4	MD -0.49 (-0.79, - 0.19)	MD 0.49 lower	ver y low

										(0.79 lower to 0.19 lower)	
<b>weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 8.7 month(s)</b>											
2	R C T	very serious <sup>1</sup>	not serious	very serious <sup>7</sup>	not serious	NA	1596	1234	MD -6.69 (-8.73, -4.65)	MD 6.69 lower (8.73 lower to 4.65 lower)	very low
<b>bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)</b>											
1 (kellerer 2022)	R C T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	874	874	MD -2.54 (-2.69, -2.39)	MD 2.54 lower (2.69 lower to 2.39 lower)	low

1. >33.3% of the studies in the meta-analysis were at high risk of bias
2. Only one study so no inconsistency
3. >33.3% of the studies in the meta-analysis were at moderate risk of bias
4. I2 between 50% and 75%
5. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
6. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
7. I2 > 75%
8. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

## L.1.3.22 Adding semaglutide compared to adding dulaglutide

Table 33: Clinical evidence profile: Adding semaglutide compared to adding dulaglutide

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
<b>health-related quality of life - subscale mental component (sf-36-v2, higher values are better, change scores) at end of follow-up Mean follow-up: 12 month(s)</b>											
1 (yabe 2020)	RCT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	393	65	MD 0.26 (-0.86, 1.38)	MD 0.26 higher (0.86 lower to 1.38 higher)	low
<b>health-related quality of life - subscale physical component (sf-36-v2, higher values are better, change scores) at end of follow-up Mean follow-up: 12 month(s)</b>											
1 (yabe 2020)	RCT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	393	65	MD -0.12 (-0.88, 0.64)	MD 0.12 lower (0.88 lower to 0.64 higher)	low
<b>all-cause mortality at end of follow up Mean follow-up: 11.2 month(s)</b>											
2	RCT	not serious	not serious	serious <sup>3</sup>	very serious <sup>4</sup>	NA	2/994	4/63	RD -0.00 (-0.01, 0.00)	3 fewer per 1000 (10 fewer to 5 more)	very low
<b>cardiovascular mortality at end of follow up Mean follow-up: 11.2 month(s)</b>											
2	RCT	not serious	not serious	serious <sup>3</sup>	very serious <sup>5</sup>	NA	1/994	2/63	RD -0.00 (-0.01, 0.00)	1 fewer per 1000	very low

										(7 fewer to 4 more)	
<b>acute kidney injury at end of follow up</b>											
<b>Mean follow-up: 12 month(s)</b>											
1 (yabe 2020)	R C T	not serious	not serious	NA <sup>2</sup>	not serious	NA	0/393	0/65	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (21 fewer to 21 more)	high
<b>death from renal causes at end of follow up</b>											
<b>Mean follow-up: 12 month(s)</b>											
1 (yabe 2020)	R C T	not serious	not serious	NA <sup>2</sup>	not serious	NA	0/393	0/65	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (21 fewer to 21 more)	high
<b>hypoglycaemia episodes at end of follow up</b>											
<b>Mean follow-up: 9 month(s)</b>											
2	R C T	not serious	not serious	serious <sup>3</sup>	very serious <sup>6</sup>	NA	67/409	13/81	RD -0.03 (-0.12, 0.07)	26 fewer per 1000 (118 fewer to 67 more)	very low
<b>severe hypoglycaemic episodes at end of follow up</b>											
<b>Mean follow-up: 11.2 month(s)</b>											
2	R C T	not serious	not serious	serious <sup>3</sup>	very serious <sup>7</sup>	NA	7/994	8/63	PETO OR 0.87 (0.31, 2.41)	5 fewer per 1000 (15 fewer to 5 more)	very low
<b>hba1c change (% , lower values are better, change scores) at end of follow up</b>											
<b>Mean follow-up: 9.1 month(s)</b>											
3	R C T	serious <sup>8</sup>	not serious	very serious <sup>9</sup>	serious <sup>10</sup>	NA	1010	679	MD -0.25 (-0.56, 0.06)	MD 0.25 lower	very low

										(0.56 lower to 0.06 higher)	
<b>weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 9.1 month(s)</b>											
3	R C T	not serious	not serious	serious <sup>11</sup>	serious <sup>12</sup>	NA	1010	679	MD -2.45 (-3.26, -1.64)	MD 2.45 lower (3.26 lower to 1.64 lower)	low
<b>bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 11.3 month(s)</b>											
2	R C T	serious <sup>8</sup>	not serious	very serious <sup>9</sup>	serious <sup>13</sup>	NA	994	663	MD -0.74 (-1.05, -0.43)	MD 0.74 lower (1.05 lower to 0.43 lower)	very low

1. >33.3% of the studies in the meta-analysis were at high risk of bias

2. Only one study so no inconsistency

3. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

4. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.45 (0.8-0.9 = serious, <0.8 = very serious).

5. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.25 (0.8-0.9 = serious, <0.8 = very serious).

6. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.03 (0.8-0.9 = serious, <0.8 = very serious).

7. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.32 (0.8-0.9 = serious, <0.8 = very serious).

8. >33.3% of the studies in the meta-analysis were at moderate risk of bias
9. I2 > 75%
10. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
11. I2 between 50% and 75%
12. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)
13. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

### L.1.3.23 Adding semaglutide compared to adding exenatide

**Table 34: Clinical evidence profile: Adding semaglutide compared to adding exenatide**

No of studies	De sig n	Risk of bias	Indir ectn ess	Incon sisten cy	Impr ecisi on	Other consider ations	Interv entio n N	Con trol N	Relative effect (95% CI)	Absolute effect	Cer tain ty
<b>health-related quality of life - subscale mental component (sf-36, higher values are better, change scores) at end of follow-up Mean follow-up: 12 month(s)</b>											
1 (ahmann 2018)	R CT	very serio us <sup>1</sup>	not serio us	NA <sup>2</sup>	not serio us	NA	404	405	MD 0.16 (-1.14, 1.46)	MD 0.16 higher (1.14 lower to 1.46 higher)	low
<b>health-related quality of life - subscale physical component (sf-36, higher values are better, change scores) at end of follow-up Mean follow-up: 12 month(s)</b>											
1 (ahmann 2018)	R CT	very serio us <sup>1</sup>	not serio us	NA <sup>2</sup>	not serio us	NA	404	405	MD 0.46 (-0.64, 1.56)	MD 0.46 higher	low

										(0.64 lower to 1.56 higher)	
<b>all-cause mortality at end of follow up</b>											
<b>Mean follow-up: 12 month(s)</b>											
1 (ahmann 2018)	R CT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	0/405	2/404	PETO OR 0.13 (0.01, 2.16)	5 fewer per 1000 (12 fewer to 2 more)	very low
<b>severe hypoglycaemic episodes at end of follow up</b>											
<b>Mean follow-up: 12 month(s)</b>											
1 (ahmann 2018)	R CT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	33/404	33/405	RR 1.00 (0.63, 1.59)	0 more per 1000 (30 fewer to 48 more)	very low
<b>hba1c change (% , lower values are better, change scores) at end of follow up</b>											
<b>Mean follow-up: 12 month(s)</b>											
1 (ahmann 2018)	R CT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>4</sup>	NA	404	405	MD -0.60 (-0.77, -0.43)	MD 0.60 lower (0.77 lower to 0.43 lower)	very low
<b>weight change (kg, lower values are better, change scores) at end of follow up</b>											
<b>Mean follow-up: 12 month(s)</b>											
1 (ahmann 2018)	R CT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	404	405	MD -3.70 (-4.50, -2.90)	MD 3.70 lower (4.50 lower to 2.90 lower)	low
<b>bmi change (kg/m2, lower values are better, change scores) at end of follow up</b>											
<b>Mean follow-up: 12 month(s)</b>											

1 (ahmann 2018)	R CT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	404	405	MD -1.40 (-1.68, - 1.12)	MD 1.40 lower (1.68 lower to 1.12 lower)	low
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- >33.3% of the studies in the meta-analysis were at high risk of bias
- Only one study so no inconsistency
- 95% confidence intervals cross both ends of the defined MID (0.80, 1.25)
- 95% confidence intervals cross one end of the defined MID (-0.50, 0.50)

#### L.1.3.24 Adding semaglutide compared to adding liraglutide

**Table 35: Clinical evidence profile: Adding semaglutide compared to adding liraglutide**

No of studies	De sig n	Risk of bias	Indir ectn ess	Incon sisten cy	Impr ecisi on	Other consider ations	Interv entio n N	Con trol N	Relative effect (95% CI)	Absolute effect	Cer tain ty
health-related quality of life - subscale mental component (sf-36 v2, higher values are better, change scores) at end of follow-up Mean follow-up: 7 month(s)											
1 (capehorn 2020)	R C T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	290	287	MD 1.00 (-0.11, 2.11)	MD 1.00 higher (0.11 lower to 2.11 higher)	low
health-related quality of life - subscale physical component (sf-36 v2, higher values are better, change scores) at end of follow-up Mean follow-up: 7 month(s)											

1 (capehorn 2020)	R C T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	290	287	MD 0.70 (-0.41, 1.81)	MD 0.70 higher (0.41 lower to 1.81 higher)	low
<b>all-cause mortality at end of follow up Mean follow-up: 9.5 month(s)</b>											
2	R C T	very serious <sup>1</sup>	not serious	serious <sup>3</sup>	very serious <sup>4</sup>	NA	3/575	4/5 71	RD -0.00 (-0.01, 0.01)	2 fewer per 1000 (11 fewer to 8 more)	very low
<b>cardiovascular mortality at end of follow up Mean follow-up: 9.5 month(s)</b>											
2	R C T	very serious <sup>1</sup>	not serious	serious <sup>3</sup>	very serious <sup>5</sup>	NA	1/575	2/5 71	RD -0.00 (-0.01, 0.01)	2 fewer per 1000 (9 fewer to 5 more)	very low
<b>non-fatal stroke at end of follow up Mean follow-up: 12 month(s)</b>											
1 (pratley 2019)	R C T	not serious	not serious	NA <sup>2</sup>	very serious <sup>6</sup>	NA	2/285	0/2 84	PETO OR 7.39 (0.46, 118.42)	7 more per 1000 (3 fewer to 17 more)	low
<b>non-fatal myocardial infarction at end of follow up Mean follow-up: 12 month(s)</b>											
1 (pratley 2019)	R C T	not serious	not serious	NA <sup>2</sup>	very serious <sup>6</sup>	NA	0/285	1/2 84	PETO OR 0.13 (0.00, 6.80)	4 fewer per 1000 (10 fewer to 3 more)	low
<b>unstable angina at end of follow up Mean follow-up: 12 month(s)</b>											
1 (pratley 2019)	R C T	not serious	not serious	NA <sup>2</sup>	very serious <sup>6</sup>	NA	1/285	0/2 84	PETO OR 7.36 (0.15, 371.08)	4 more per 1000 (3 fewer to 10 more)	low
<b>acute kidney injury at end of follow up</b>											

<b>Mean follow-up: 12 month(s)</b>											
1 (pratley 2019)	R C T	not serio us	not serio us	NA <sup>2</sup>	very serio us <sup>6</sup>	NA	0/285	1/2 84	PETO OR 0.13 (0.00, 6.80)	4 fewer per 1000 (10 fewer to 3 more)	low
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 9.5 month(s)</b>											
2	R C T	very serio us <sup>1</sup>	not serio us	not serio us	serio us <sup>7</sup>	NA	7/575	14/ 571	RR 0.50 (0.20, 1.22)	12 fewer per 1000 (20 fewer to 5 more)	ver y low
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 7 month(s)</b>											
1 (capehorn 2020)	R C T	very serio us <sup>1</sup>	not serio us	NA <sup>2</sup>	not serio us	NA	0/290	0/2 87	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	low
<b>hba1c change (% , lower values are better, change scores) at end of follow up Mean follow-up: 6.5 month(s)</b>											
2	R C T	very serio us <sup>1</sup>	not serio us	very serio us <sup>8</sup>	serio us <sup>9</sup>	NA	568	559	MD -0.41 (-0.99, 0.17)	MD 0.41 lower (0.99 lower to 0.17 higher)	ver y low
<b>weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 6.5 month(s)</b>											
2	R C T	not serio us	not serio us	very serio us <sup>8</sup>	serio us <sup>10</sup>	NA	568	558	MD -2.55 (-5.03, - 0.07)	MD 2.55 lower (5.03 lower to 0.07 lower)	ver y low
<b>bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 9.5 month(s)</b>											

2	R C T	very serious <sup>1</sup>	not serious	very serious <sup>8</sup>	serious <sup>11</sup>	NA	565	556	MD -0.90 (-1.68, - 0.12)	MD 0.90 lower (1.68 lower to 0.12 lower)	very low
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1. >33.3% of the studies in the meta-analysis were at high risk of bias
2. Only one study so no inconsistency
3. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
4. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.08 (0.8-0.9 = serious, <0.8 = very serious).
5. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.13 (0.8-0.9 = serious, <0.8 = very serious).
6. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
7. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
8. I<sup>2</sup> > 75%
9. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
10. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)
11. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

## L.1.3.25 Semaglutide compared to adding sitagliptin

Table 36: Clinical evidence profile - Semaglutide v sitagliptin

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
<b>health-related quality of life - subscale mental component (sf36 v2, higher values are better, change scores) at end of follow-up Mean follow-up: 16.5 month(s)</b>											
2	RCT	not serious	not serious	not serious	not serious	NA	1649	718	MD 0.05 (-0.52, 0.63)	MD 0.05 higher (0.52 lower to 0.63 higher)	high
<b>health-related quality of life - subscale physical component (sf36 v2, higher values are better, change scores) at end of follow-up Mean follow-up: 16.5 month(s)</b>											
2	RCT	not serious	not serious	not serious	not serious	NA	1649	718	MD 0.09 (-0.33, 0.52)	MD 0.09 higher (0.33 lower to 0.52 higher)	high
<b>all-cause mortality at end of follow up Mean follow-up: 12.5 month(s)</b>											
4	RCT	not serious	not serious	serious <sup>1</sup>	very serious <sup>2</sup>	NA	14/3044	8/1413	PETO OR 0.74 (0.30, 1.87)	1 fewer per 1000 (6 fewer to 4 more)	very low
<b>cardiovascular mortality at end of follow up Mean follow-up: 12.5 month(s)</b>											
4	RCT	not serious	not serious	serious <sup>1</sup>	very serious <sup>2</sup>	NA	7/3044	4/1413	PETO OR 0.90	1 fewer per 1000	very low

									(0.25, 3.19)	(4 fewer to 3 more)	
<b>non-fatal stroke at end of follow up</b>											
<b>Mean follow-up: 18 month(s)</b>											
1 (rosenstock 2019c)	R CT	not serious	not serious	NA <sup>3</sup>	very serious <sup>2</sup>	NA	9/139 5	1/4 66	PETO OR 2.24 (0.53, 9.39)	4 more per 1000 (2 fewer to 10 more)	low
<b>non-fatal myocardial infarction at end of follow up</b>											
<b>Mean follow-up: 18 month(s)</b>											
1 (rosenstock 2019c)	R CT	not serious	not serious	NA <sup>3</sup>	very serious <sup>2</sup>	NA	4/139 5	2/4 66	PETO OR 0.64 (0.10, 4.08)	1 fewer per 1000 (8 fewer to 5 more)	low
<b>unstable angina at end of follow up</b>											
<b>Mean follow-up: 18 month(s)</b>											
1 (rosenstock 2019c)	R CT	not serious	not serious	NA <sup>3</sup>	very serious <sup>2</sup>	NA	6/139 5	1/4 66	PETO OR 1.78 (0.32, 9.85)	2 more per 1000 (3 fewer to 8 more)	low
<b>hospitalisation for heart failure at end of follow up</b>											
<b>Mean follow-up: 15 month(s)</b>											
2	R CT	not serious	not serious	serious <sup>1</sup>	very serious <sup>2</sup>	NA	5/164 8	4/7 16	PETO OR 0.42 (0.10, 1.87)	3 fewer per 1000 (9 fewer to 4 more)	very low
<b>acute kidney injury at end of follow up</b>											
<b>Mean follow-up: 15 month(s)</b>											
2	R CT	not serious	not serious	serious <sup>1</sup>	very serious <sup>2</sup>	NA	11/16 48	3/7 16	PETO OR 1.32 (0.40, 4.39)	2 more per 1000 (4 fewer to 9 more)	very low
<b>death from renal causes at end of follow up</b>											
<b>Mean follow-up: 18 month(s)</b>											

1 (rosenstock 2019c)	R CT	not serious	not serious	NA <sup>3</sup>	very serious <sup>2</sup>	NA	1/139 5	0/4 66	PETO OR 3.80 (0.04, 350.01)	1 more per 1000 (1 fewer to 2 more)	low
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 12.7 month(s)</b>											
3	R CT	not serious	not serious	not serious	not serious	NA	358/2 791	124 /11 63	RR 0.99 (0.83, 1.19)	1 fewer per 1000 (18 fewer to 20 more)	high
<b>at night hypoglycaemic episodes at end of follow up Mean follow-up: 15 month(s)</b>											
2	R CT	not serious	not serious	not serious	very serious <sup>2</sup>	NA	20/16 48	7/7 16	RR 1.21 (0.51, 2.87)	2 more per 1000 (5 fewer to 18 more)	low
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 14 month(s)</b>											
3	R CT	not serious	not serious	serious <sup>1</sup>	not serious	NA	1/246 6	6/1 123	RD -0.01 (-0.01, - 0.00)	5 fewer per 1000 (11 fewer to 0 more)	moderate
<b>hba1c change (% , lower values are better, change scores) at end of follow up Mean follow-up: 13.1 month(s)</b>											
4	R CT	not serious	not serious	very serious <sup>4</sup>	serious <sup>5</sup>	NA	3045	141 5	MD -0.39 (-0.61, - 0.17)	MD 0.39 lower (0.61 lower to 0.17 lower)	very low
<b>weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 13.1 month(s)</b>											

4	R CT	not serious	not serious	very serious <sup>4</sup>	serious <sup>6</sup>	NA	3045	141 5	MD -2.03 (-2.77, - 1.30)	MD 2.03 lower (2.77 lower to 1.30 lower)	ver y low
<b>bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 13.1 month(s)</b>											
4	R CT	not serious	not serious	very serious <sup>4</sup>	serious <sup>7</sup>	NA	3045	141 5	MD -0.75 (-1.02, - 0.49)	MD 0.75 lower (1.02 lower to 0.49 lower)	ver y low

1. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
2. 95% confidence intervals cross both ends of the defined MIDd (0.80, 1.25)
3. Only one study so no inconsistency
4. I<sup>2</sup> > 75%
5. 95% confidence intervals cross one end of the defined MIDd (-0.50, 0.50)
6. 95% confidence intervals cross one end of the defined MIDd (-2.40, 2.40)
7. 95% confidence intervals cross one end of the defined MIDd (-0.80, 0.80)

#### L.1.3.26 Adding SC semaglutide compared to adding oral semaglutide

**Table 37: Clinical evidence profile: Adding SC semaglutide compared to adding oral semaglutide**

No of studies	De sig n	Risk of bias	Indir ectn ess	Incon sisten cy	Impr ecisio n	Other consider ations	Interv ention N	Con trol N	Relative effect (95% CI)	Absolute effect	Cer tain ty
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<b>health-related quality of life - subscale mental component (sf-36, higher values are better, change scores) at follow-up</b> <b>Mean follow-up: 6 month(s)</b>											
1 (davies 2017)	R CT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	69	490	MD -0.43 (-2.63, 1.77)	MD 0.43 lower (2.63 lower to 1.77 higher)	low
<b>health-related quality of life - subscale physical component (sf-36, higher values are better, change scores) at follow-up</b> <b>Mean follow-up: 6 month(s)</b>											
1 (davies 2017)	R CT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	69	490	MD 0.22 (-1.30, 1.74)	MD 0.22 higher (1.30 lower to 1.74 higher)	low
<b>all-cause mortality at end of follow up</b> <b>Mean follow-up: 6 month(s)</b>											
1 (davies 2017)	R CT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	0/69	0/490	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	low
<b>cardiovascular mortality at end of follow up</b> <b>Mean follow-up: 6 month(s)</b>											
1 (davies 2017)	R CT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	0/69	0/490	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	low
<b>non-fatal stroke at end of follow up</b> <b>Mean follow-up: 6 month(s)</b>											
1 (davies 2017)	R CT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	0/69	0/490	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	low

<b>non-fatal myocardial infarction at end of follow up</b> <b>Mean follow-up: 6 month(s)</b>											
1 (davies 2017)	R CT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	0/69	2/49 0	PETO OR 0.32 (0.00, 21.63)	4 fewer per 1000 (10 fewer to 2 more)	very low
<b>hypoglycaemia episodes at end of follow up</b> <b>Mean follow-up: 6 month(s)</b>											
1 (davies 2017)	R CT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	12/69	63/4 90	RR 1.35 (0.77, 2.38)	45 more per 1000 (30 fewer to 177 more)	very low
<b>severe hypoglycaemic episodes at end of follow up</b> <b>Mean follow-up: 6 month(s)</b>											
1 (davies 2017)	R CT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	1/69	1/49 0	PETO OR 32.67 (0.48, 2216.41)	12 more per 1000 (16 fewer to 41 more)	very low
<b>hba1c change (% , lower values are better, change scores) at end of follow up</b> <b>Mean follow-up: 6 month(s)</b>											
1 (davies 2017)	R CT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>4</sup>	NA	69	490	MD -0.41 (-0.62, - 0.20)	MD 0.41 lower (0.62 lower to 0.20 lower)	very low
<b>weight change (kg, lower values are better, change scores) at end of follow up</b> <b>Mean follow-up: 6 month(s)</b>											
1 (davies 2017)	R CT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	69	490	MD -1.12 (-2.29, 0.05)	MD 1.12 lower (2.29 lower to 0.05 higher)	low

1. >33.3% of the studies in the meta-analysis were at high risk of bias

2. Only one study so no inconsistency
3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
4. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

## L.1.4 Dual GIP/GLP-1 receptor co-agonists

### L.1.4.1 Adding tirzepatide compared to adding placebo

**Table 38: Clinical evidence profile: Adding tirzepatide compared to adding placebo**

No of studies	D e s i g n	Ri s k o f b i a s	I n d i r e c t n e s s	I n c o n s i s t e n c y	I m p r e c i s i o n	O t h e r c o n s i d e r a t i o n s	I n t e r v e n t i o n N	C o n t r o l N	Relative effect (95% CI)	Absolute effect	Ce r t a i n t y
<b>health-related quality of life - subscale physical functioning (sf-36 physical function scores, higher values are better) at end of follow-up Mean follow-up: 18 month(s)</b>											
1 (garvey 2023)	R C T	not seri ous	not seri ous	NA <sup>1</sup>	not serio us	NA	623	31 5	MD 2.00 (1.04, 2.96)	MD 2.00 higher (1.04 higher to 2.96 higher)	hig h
<b>all-cause mortality at end of follow-up Mean follow-up: 10.4 month(s)</b>											
4	R C T	not seri ous	not seri ous	serio us <sup>2</sup>	very serio us <sup>3</sup>	NA	2/12 34	1/5 10	RD -0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 7 more)	ver y low
<b>cardiovascular mortality at end of follow-up Mean follow-up: 8.8 month(s)</b>											
2	R C T	not seri ous	not seri ous	not serio us	not serio us	NA	0/40 0	0/1 48	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	hig h
<b>4-point mace at end of follow-up Mean follow-up: 11 month(s)</b>											

1 (dahl 2022)	R C T	not seri ous	not seri ous	NA <sup>1</sup>	very serio us <sup>4</sup>	NA	2/35 5	1/1 20	RR 0.68 (0.06, 7.39)	3 fewer per 1000 (8 fewer to 53 more)	low
<b>cardiac arrhythmia at end of follow-up Mean follow-up: 18 month(s)</b>											
1 (garvey 2023)	R C T	not seri ous	not seri ous	NA <sup>1</sup>	very serio us <sup>4</sup>	NA	5/62 3	1/3 15	RR 2.53 (0.30, 21.55)	5 more per 1000 (2 fewer to 65 more)	low
<b>persistent signs of worsening kidney disease at end of follow-up Mean follow-up: 18 month(s)</b>											
1 (garvey 2023)	R C T	not seri ous	not seri ous	NA <sup>1</sup>	very serio us <sup>4</sup>	NA	3/62 3	1/3 15	RR 1.52 (0.16, 14.52)	2 more per 1000 (3 fewer to 43 more)	low
<b>progression of liver disease at end of follow-up Mean follow-up: 18 month(s)</b>											
1 (garvey 2023)	R C T	not seri ous	not seri ous	NA <sup>1</sup>	very serio us <sup>4</sup>	NA	2/62 3	0/3 15	PETO OR 4.51 (0.24, 85.06)	3 more per 1000 (1 fewer to 8 more)	low
<b>hypoglycaemia episodes at end of follow-up Mean follow-up: 10.4 month(s)</b>											
4	R C T	not seri ous	not seri ous	serio us <sup>5</sup>	very serio us <sup>4</sup>	NA	318/ 1234	94/ 51 4	RR 1.74 (0.75, 4.04)	136 more per 1000 (45 fewer to 556 more)	ver y low
<b>severe hypoglycaemic episodes at end of follow-up Mean follow-up: 10.4 month(s)</b>											
4	R C T	not seri ous	not seri ous	serio us <sup>2</sup>	very serio us <sup>6</sup>	NA	3/12 34	0/5 14	RD 0.00 (-0.00, 0.01)	2 more per 1000 (4 fewer to 9 more)	ver y low
<b>hba1c change (% , lower values are better, change scores) at end of follow-up Mean follow-up: 11.3 month(s)</b>											
3	R C T	not seri ous	not seri ous	not serio us	not serio us	NA	1189	48 6	MD -1.53 (-1.65, - 1.42)	MD 1.53 lower (1.65 lower to 1.42 lower)	hig h
<b>hba1c change (mmol/mol, lower values are better, change scores) at end of follow-up Mean follow-up: 6.5 month(s)</b>											

1 (heise 2022)	R C T	seri ous <sup>7</sup>	not seri ous	NA <sup>1</sup>	not serio us	NA	41	24	MD - 25.50 (- 26.02, - 24.98)	MD 25.50 lower (26.02 lower to 24.98 lower)	mo der ate
<b>weight change (kg, lower values are better, change scores) at end of follow-up Mean follow-up: 10.1 month(s)</b>											
4	R C T	not seri ous	not seri ous	very serio us <sup>8</sup>	serio us <sup>9</sup>	NA	1070	67 0	MD -6.55 (-12.94, - 0.16)	MD 6.55 lower (12.94 lower to 0.16 lower)	ver y low
<b>bmi change (kg/m2, lower values are better, change scores) at end of follow-up Mean follow-up: 12 month(s)</b>											
2	R C T	not seri ous	not seri ous	very serio us <sup>8</sup>	very serio us <sup>10</sup>	NA	674	52 6	MD -0.83 (-6.76, 5.10)	MD 0.83 lower (6.76 lower to 5.10 higher)	ver y low

1. Only one study so no inconsistency
2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
3. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.04 (0.8-0.9 = serious, <0.8 = very serious).
4. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
5. I2 between 50% and 75%
6. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.54 (0.8-0.9 = serious, <0.8 = very serious).
7. >33.3% of the studies in the meta-analysis were at moderate risk of bias
8. I2 > 75%
9. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)
10. 95% confidence intervals cross both ends of the defined MIDs (-0.80, 0.80)

## L.1.4.2 Adding tirzepatide compared to adding insulin

Table 39: Clinical evidence profile: Adding tirzepatide compared to adding insulin

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>all-cause mortality at end of follow-up</b> Mean follow-up: 11 month(s)											
3	RC T	serious <sup>1</sup>	not serious	not serious	serious <sup>2</sup>	NA	12/248	15/1 288	RR 0.55 (0.26, 1.18)	5 fewer per 1000 (9 fewer to 2 more)	low
<b>cardiovascular mortality at end of follow-up</b> Mean follow-up: 10.5 month(s)											
2	RC T	serious <sup>1</sup>	not serious	serious <sup>3</sup>	very serious <sup>4</sup>	NA	2/1764	2/58 0	PETO OR 0.25 (0.03, 2.45)	2 fewer per 1000 (7 fewer to 3 more)	very low
<b>4-point mace at end of follow-up</b> Mean follow-up: 10.5 month(s)											
2	RC T	not serious	not serious	not serious	very serious <sup>4</sup>	NA	15/176 4	4/58 0	RR 1.11 (0.36, 3.44)	1 more per 1000 (4 fewer to 17 more)	low
<b>non-fatal stroke at end of follow-up</b> Mean follow-up: 9 month(s)											
1 (gao 2023)	RC T	serious <sup>1</sup>	not serious	NA <sup>5</sup>	very serious <sup>4</sup>	NA	10/687	2/22 0	RR 1.60 (0.35, 7.25)	5 more per 1000 (6 fewer to 57 more)	very low
<b>non-fatal myocardial infaRcTion at end of follow-up</b> Mean follow-up: 9 month(s)											

1 (gao 2023)	RC T	serious <sup>1</sup>	not serious	NA <sup>5</sup>	very serious <sup>4</sup>	NA	1/687	0/220	PETO OR 3.74 (0.04, 362.44)	1 more per 1000 (1 fewer to 4 more)	very low
<b>cardiac arrhythmia at end of follow-up</b> <b>Mean follow-up: 9 month(s)</b>											
1 (gao 2023)	RC T	serious <sup>1</sup>	not serious	NA <sup>5</sup>	very serious <sup>4</sup>	NA	0/687	1/220	PETO OR 0.02 (0.00, 1.57)	5 fewer per 1000 (13 fewer to 4 more)	very low
<b>hospitalisation for heart failure at end of follow-up</b> <b>Mean follow-up: 9 month(s)</b>											
1 (gao 2023)	RC T	serious <sup>1</sup>	not serious	NA <sup>5</sup>	very serious <sup>4</sup>	NA	1/687	0/220	PETO OR 3.74 (0.04, 362.44)	1 more per 1000 (1 fewer to 4 more)	very low
<b>acute kidney injury</b> <b>Mean follow-up: 12 month(s)</b>											
1 (rosenstock 2023)	RC T	serious <sup>1</sup>	not serious	NA <sup>5</sup>	very serious <sup>4</sup>	NA	1/717	0/708	PETO OR 7.30 (0.14, 367.77)	1 more per 1000 (1 fewer to 4 more)	very low
<b>hypoglycaemia episodes at end of follow-up</b> <b>Mean follow-up: 11 month(s)</b>											
3	RC T	serious <sup>1</sup>	not serious	very serious <sup>6</sup>	not serious	NA	413/2481	607/1288	RR 0.34 (0.16, 0.70)	312 fewer per 1000 (394 fewer to 141 fewer)	very low
<b>severe hypoglycaemic episodes at end of follow-up</b> <b>Mean follow-up: 11 month(s)</b>											
3	RC T	serious <sup>1</sup>	not serious	serious <sup>3</sup>	not serious	NA	4/2481	30/1288	RD -0.02 (-0.02, -0.01)	17 fewer per 1000	low

										(24 fewer to 10 fewer)	
<b>hba1c change (% , lower values are better, change scores) at end of follow-up</b>											
<b>Mean follow-up: 11 month(s)</b>											
3	RC T	serious <sup>1</sup>	not serious	very serious <sup>6</sup>	not serious	NA	2479	1287	MD -1.08 (-1.46, -0.70)	MD 1.08 lower (1.46 lower to 0.70 lower)	very low
<b>weight change (kg, lower values are better, change scores) at end of follow-up</b>											
<b>Mean follow-up: 11 month(s)</b>											
3	RC T	serious <sup>1</sup>	not serious	very serious <sup>6</sup>	not serious	NA	2479	1287	MD -10.90 (-14.29, -7.52)	MD 10.90 lower (14.29 lower to 7.52 lower)	very low

1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
2. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
3. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
4. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
5. Only one study so no inconsistency
6. I<sup>2</sup> > 75%

## L.1.4.3 Adding tirzepatide compared to adding dulaglutide

Table 40: Clinical evidence profile: Adding tirzepatide compared to adding dulaglutide

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>all-cause mortality at end of follow up Mean follow-up: 6 month(s)</b>											
1 (frias 2018)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	seriou s <sup>2</sup>	NA	0/211	0/54	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (26 fewer to 26 more)	mod erat e
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 6 month(s)</b>											
1 (frias 2018)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	very seriou s <sup>3</sup>	NA	14/211	2/54	RR 1.79 (0.42, 7.65)	29 more per 1000 (21 fewer to 246 more)	low
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 6 month(s)</b>											
1 (frias 2018)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	seriou s <sup>2</sup>	NA	0/211	0/54	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (26 fewer to 26 more)	mod erat e
<b>hba1c change (% , lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)</b>											
1 (frias 2018)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	seriou s <sup>4</sup>	NA	211	54	MD -0.68 (-0.86, - 0.50)	MD 0.68 lower (0.86 lower to 0.50 lower)	mod erat e

<b>weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)</b>											
1 (frias 2018)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	seriou s <sup>5</sup>	NA	211	54	MD -2.07 (-3.96, - 0.18)	MD 2.07 lower (3.96 lower to 0.18 lower)	mod erat e
<b>bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)</b>											
1 (frias 2018)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	seriou s <sup>6</sup>	NA	211	54	MD -1.30 (-1.93, - 0.67)	MD 1.30 lower (1.93 lower to 0.67 lower)	mod erat e

1. Only one study so no inconsistency
2. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
4. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
5. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)
6. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

#### L.1.4.4 Adding tirzepatide compared to adding semaglutide

**Table 41: Clinical evidence profile: Adding tirzepatide compared to adding semaglutide**

No of studies	De sig n	Risk of bias	Indir ectn ess	Incon siste ncy	Impr ecisi on	Other consider ations	Interv entio n N	Con trol N	Relative effect (95% CI)	Absolute effect	Cer tain ty
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<b>all-cause mortality at end of follow up Mean follow-up: 7.8 month(s)</b>												
2	R C T	serious <sup>1</sup>	not serious	serious <sup>2</sup>	very serious <sup>3</sup>	NA	12/14 54	1/5 13	RD 0.01 (- 0.00, 0.01)	6 more per 1000 (1 fewer to 13 more)	very low	
<b>cardiovascular mortality at end of follow up Mean follow-up: 7.8 month(s)</b>												
2	R C T	serious <sup>1</sup>	not serious	serious <sup>2</sup>	very serious <sup>4</sup>	NA	5/145 5	0/5 13	RD 0.00 (- 0.00, 0.01)	3 more per 1000 (2 fewer to 8 more)	very low	
<b>non-fatal myocardial infarction at end of follow up Mean follow-up: 9 month(s)</b>												
1 (frias 2021)	R C T	serious <sup>1</sup>	not serious	NA <sup>5</sup>	very serious <sup>6</sup>	NA	3/140 9	0/4 69	PETO OR 3.80 (0.28, 51.93)	2 more per 1000 (0 more to 5 more)	very low	
<b>cardiac arrhythmia at end of follow up Mean follow-up: 9 month(s)</b>												
1 (frias 2021)	R C T	serious <sup>1</sup>	not serious	not serious	very serious <sup>6</sup>	NA	2/140 9	0/4 69	PETO OR 3.79 (0.15, 93.33)	1 more per 1000 (1 fewer to 3 more)	very low	
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 6.5 month(s)</b>												
2	R C T	serious <sup>1</sup>	not serious	not serious	very serious <sup>6</sup>	NA	15/14 54	3/5 13	PETO OR 2.00 (0.71, 5.64)	4 more per 1000 (4 fewer to 13 more)	very low	
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 7.8 month(s)</b>												
2	R C T	serious <sup>1</sup>	not serious	serious <sup>2</sup>	very serious <sup>7</sup>	NA	2/145 4	0/5 13	RD 0.00 (- 0.00, 0.01)	1 more per 1000 (3 fewer to 6 more)	very low	
<b>hba1c change (% , lower values are better, mean difference) at end of follow up Mean follow-up: 9 month(s)</b>												
1 (frias 2021)	R C T	serious <sup>1</sup>	not serious	NA <sup>5</sup>	serious <sup>8</sup>	NA	1408	468	MD -0.33 (- 0.51, -0.16)	MD 0.33 lower (0.51 lower to 0.16 lower)	low	

<b>hba1c change (mmol/mol, lower values are better, change scores) at end of follow up Mean follow-up: 6.5 month(s)</b>											
1 (heise 2022)	R C T	serious <sup>1</sup>	not serious	NA <sup>5</sup>	serious <sup>9</sup>	NA	41	43	MD -4.50 (-6.99, -2.01)	MD 4.50 lower (6.99 lower to 2.01 lower)	low
<b>weight change (kg, lower values are better, mean difference) at end of follow up Mean follow-up: 8.4 month(s)</b>											
2	R C T	serious <sup>1</sup>	not serious	very serious <sup>10</sup>	not serious	NA	1449	511	MD -3.82 (-5.24, -2.41)	MD 3.82 lower (5.24 lower to 2.41 lower)	very low

1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
3. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.79 (0.8-0.9 = serious, <0.8 = very serious).
4. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.74 (0.8-0.9 = serious, <0.8 = very serious).
5. Only one study so no inconsistency
6. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
7. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.38 (0.8-0.9 = serious, <0.8 = very serious).
8. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
9. 95% confidence intervals cross one end of the defined MIDs (-5.50, 5.50)
10. I<sup>2</sup> > 75%

**L.1.5 SGLT2 inhibitors**

**L.1.5.1 Adding canagliflozin compared to adding placebo**

**Table 42: Clinical evidence profile: Adding canagliflozin compared to adding placebo**

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Imprec ision	Other considerat ions	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>all-cause mortality at end of follow up Mean follow-up: 9.9 month(s)</b>											
6	RC T	very serious <sup>1</sup>	not serious	serious <sup>2</sup>	very serious <sup>3</sup>	NA	3/1930	0/86 7	RD 0.00 (-0.00, 0.01)	2 more per 1000 (3 fewer to 6 more)	very low
<b>all-cause mortality at end of follow up Mean follow-up: 43 month(s)</b>											
1 (mahaffey 2018)	RC T	not serious	not serious	NA <sup>4</sup>	serious <sup>5</sup>	NA	5795	4347	HR 0.87 (0.75, 1.01)	Not estimable	mod erat e
<b>cardiovascular mortality at end of follow up Mean follow-up: 10.7 month(s)</b>											
5	RC T	very serious <sup>1</sup>	not serious	serious <sup>2</sup>	very serious <sup>6</sup>	NA	2/1195	0/68 4	RD 0.00 (-0.00, 0.01)	2 more per 1000 (4 fewer to 7 more)	very low
<b>cardiovascular mortality at end of follow up Mean follow-up: 43 month(s)</b>											
1 (mahaffey 2018)	RC T	not serious	not serious	NA <sup>4</sup>	serious <sup>5</sup>	NA	5795	4347	HR 0.87 (0.71, 1.06)	Not estimable	mod erat e
<b>3-point mace at end of follow up Mean follow-up: 43 month(s)</b>											

1 (mahaffey 2018)	RC T	not seriou s	not seriou s	NA <sup>4</sup>	serious <sup>5</sup>	NA	5795	4347	HR 0.85 (0.75, 0.97)	Not estimable	mod erat e
<b>non-fatal stroke at end of follow up Mean follow-up: 43 month(s)</b>											
1 (mahaffey 2018)	RC T	not seriou s	not seriou s	NA <sup>4</sup>	serious <sup>5</sup>	NA	5795	4347	HR 0.90 (0.71, 1.15)	Not estimable	mod erat e
<b>non-fatal myocardial infarction at end of follow up Mean follow-up: 43 month(s)</b>											
1 (mahaffey 2018)	RC T	not seriou s	not seriou s	NA <sup>4</sup>	serious <sup>5</sup>	NA	5795	4347	HR 0.85 (0.69, 1.05)	Not estimable	mod erat e
<b>hospitalisation for heart failure at end of follow up Mean follow-up: 43 month(s)</b>											
1 (mahaffey 2018)	RC T	not seriou s	not seriou s	NA <sup>4</sup>	serious <sup>5</sup>	NA	5795	4347	HR 0.67 (0.52, 0.87)	Not estimable	mod erat e
<b>persistent signs of worsening kidney disease at end of follow up Mean follow-up: 43 month(s)</b>											
1 (mahaffey 2018)	RC T	not seriou s	not seriou s	NA <sup>4</sup>	not serious	NA	5795	4347	HR 0.73 (0.67, 0.79)	Not estimable	high
<b>development of end stage kidney disease at end of follow up Mean follow-up: 43 month(s)</b>											
1 (mahaffey 2018)	RC T	not seriou s	not seriou s	NA <sup>4</sup>	very serious <sup>7</sup>	NA	5795	4347	HR 0.77 (0.30, 1.97)	Not estimable	low
<b>cardiac arrhythmia at end of follow up Mean follow-up: 43 month(s)</b>											

1 (mahaffey 2018)	RC T	not seriou s	not seriou s	NA <sup>4</sup>	serious <sup>5</sup>	NA	125/57 95	84/4 347	RR 1.12 (0.85, 1.47)	2 more per 1000 (3 fewer to 9 more)	mod erat e
<b>cardiac arrhythmia at end of follow up Mean follow-up: 43 month(s)</b>											
1 (mahaffey 2018)	RC T	not seriou s	not seriou s	NA <sup>4</sup>	serious <sup>5</sup>	NA	5795	4347	HR 0.84 (0.64, 1.12)	Not estimable	mod erat e
<b>diabetic ketoacidosis at end of follow up Mean follow-up: 5.8 month(s)</b>											
2	RC T	very seriou s <sup>1</sup>	not seriou s	not serious	not serious	NA	0/178	0/17 6	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (16 fewer to 16 more)	low
<b>diabetic ketoacidosis at end of follow up Mean follow-up: 43 month(s)</b>											
1 (mahaffey 2018)	RC T	not seriou s	not seriou s	NA <sup>4</sup>	very serious <sup>7</sup>	NA	1447	2039	HR 1.57 (0.40, 6.16)	Not estimable	low
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 11.9 month(s)</b>											
4	RC T	very seriou s <sup>1</sup>	not seriou s	serious <sup>2</sup>	not serious	NA	205/96 8	73/5 69	RD 0.04 (-0.03, 0.12)	45 more per 1000 (32 fewer to 121 more)	very low
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 43 month(s)</b>											
1 (mahaffey 2018)	RC T	not seriou s	not seriou s	NA <sup>4</sup>	very serious <sup>7</sup>	NA	1447	2039	HR 1.04 (0.78, 1.39)	Not estimable	low
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 14 month(s)</b>											

3	RC T	serious <sup>8</sup>	serious <sup>9</sup>	serious <sup>2</sup>	very serious <sup>10</sup>	NA	13/898	9/50 1	RD -0.01 (-0.02, 0.01)	5 fewer per 1000 (20 fewer to 9 more)	very low
<b>hba1c change (% , lower values are better, change scores) at end of follow up Mean follow-up: 12.7 month(s)</b>											
8	RC T	very serious <sup>1</sup>	not serious	very serious <sup>11</sup>	not serious	NA	7672	5152	MD -0.71 (-0.87, - 0.54)	MD 0.71 lower (0.87 lower to 0.54 lower)	very low
<b>weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 12.1 month(s)</b>											
7	RC T	very serious <sup>1</sup>	not serious	very serious <sup>11</sup>	serious <sup>12</sup>	NA	7253	4991	MD -2.16 (-2.67, - 1.65)	MD 2.16 lower (2.67 lower to 1.65 lower)	very low
<b>weight change (% , lower values are better, change scores) Mean follow-up: 24 month(s)</b>											
1 (bode 2013)	RC T	serious <sup>8</sup>	not serious	NA <sup>4</sup>	serious <sup>13</sup>	NA	425	170	MD -2.93 (-3.89, - 1.97)	MD 2.93 lower (3.89 lower to 1.97 lower)	low

1. >33.3% of the studies in the meta-analysis were at high risk of bias
2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
3. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.55 (0.8-0.9 = serious, <0.8 = very serious).

4. Only one study so no inconsistency
5. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
6. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.43 (0.8-0.9 = serious, <0.8 = very serious).
7. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
8. >33.3% of the studies in the meta-analysis were at moderate risk of bias
9. Largest proportion of studies in the meta-analysis came from partially direct studies
10. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.11 (0.8-0.9 = serious, <0.8 = very serious).
11.  $I^2 > 75\%$
12. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)
13. 95% confidence intervals cross one end of the defined MIDs (-3.00, 3.00)

#### L.1.5.2 Adding canagliflozin compared to adding sitagliptin

**Table 43: Clinical evidence profile: Adding canagliflozin compared to adding sitagliptin**

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
<b>all-cause mortality at end of follow up Mean follow-up: 12 month(s)</b>											
2	RCT	very serious <sup>1</sup>	not serious	serious <sup>2</sup>	very serious <sup>3</sup>	NA	3/1112	1/744	PETO OR 2.03	1 more per 1000 (3 fewer to 5 more)	very low

									(0.27, 15.26)		
<b>cardiovascular mortality at end of follow up</b> <b>Mean follow-up: 12 month(s)</b>											
1 (schernthaler 2013)	RCT	very serious <sup>1</sup>	not serious	NA <sup>4</sup>	very serious <sup>3</sup>	NA	2/377	0/378	PETO OR 2.03 (0.27, 15.26)	5 more per 1000 (2 fewer to 13 more)	very low
<b>hypoglycaemia episodes at end of follow up</b> <b>Mean follow-up: 12 month(s)</b>											
2	RCT	very serious <sup>1</sup>	not serious	serious <sup>5</sup>	serious <sup>6</sup>	NA	213/112	169/744	RR 1.22 (0.81, 1.86)	51 more per 1000 (44 fewer to 196 more)	very low
<b>severe hypoglycaemic episodes at end of follow up</b> <b>Mean follow-up: 12 month(s)</b>											
2	RCT	very serious <sup>1</sup>	not serious	not serious	very serious <sup>3</sup>	NA	16/112	14/744	RR 1.10 (0.54, 2.21)	2 more per 1000 (9 fewer to 23 more)	very low
<b>hba1c change (% , lower values are better, change scores) at end of follow up</b> <b>Mean follow-up: 12 month(s)</b>											
2	RCT	very serious <sup>1</sup>	not serious	very serious <sup>7</sup>	serious <sup>8</sup>	NA	1102	732	MD -0.22 (-0.51, 0.07)	MD 0.22 lower (0.51 lower to 0.07 higher)	very low
<b>weight change (kg, lower values are better, change scores) at end of follow up</b> <b>Mean follow-up: 12 month(s)</b>											
2	RCT	not serious	not serious	not serious	serious <sup>9</sup>	NA	1102	733	MD -2.31 (-2.77, -1.86)	MD 2.31 lower (2.77 lower to 1.86 lower)	moderate

1. >33.3% of the studies in the meta-analysis were at high risk of bias
2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

4. Only one study so no inconsistency
5. I2 between 50% and 75%
6. 95% confidence intervals cross one end of the defined MID (0.80, 1.25)
7. I2 > 75%
8. 95% confidence intervals cross one end of the defined MID (-0.50, 0.50)
9. 95% confidence intervals cross one end of the defined MID (-2.40, 2.40)

#### L.1.5.3 Adding canagliflozin compared to adding semaglutide

**Table 44: Clinical evidence profile: Adding canagliflozin compared to adding semaglutide**

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert ainty
<b>all-cause mortality at end of follow up Mean follow-up: 12 month(s)</b>											
1 (lingvay 2019)	RC T	not serio us	not seriou s	NA <sup>1</sup>	very seriou s <sup>2</sup>	NA	0/394	1/39 2	PETO OR 0.13 (0.00, 6.79)	3 fewer per 1000 (8 fewer to 2 more)	low
<b>cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)</b>											
1 (lingvay 2019)	RC T	not serio us	not seriou s	NA <sup>1</sup>	very seriou s <sup>2</sup>	NA	0/394	1/39 2	PETO OR 0.13 (0.00, 6.79)	3 fewer per 1000 (8 fewer to 2 more)	low
<b>acute kidney injury at end of follow up Mean follow-up: 12 month(s)</b>											
1 (lingvay 2019)	RC T	not serio us	not seriou s	NA <sup>1</sup>	seriou s <sup>3</sup>	NA	0/394	4/39 2	PETO OR 0.13 (0.02, 0.95)	10 fewer per 1000	mod erat e

										(20 fewer to 0 more)	
<b>hypoglycaemia episodes at end of follow up</b> <b>Mean follow-up: 12 month(s)</b>											
1 (lingvay 2019)	RC T	not serious	not serious	NA <sup>1</sup>	serious <sup>3</sup>	NA	32/394	53/392	RR 0.60 (0.40, 0.91)	54 fewer per 1000 (82 fewer to 12 fewer)	moderate
<b>severe hypoglycaemic episodes at end of follow up</b> <b>Mean follow-up: 12 month(s)</b>											
1 (lingvay 2019)	RC T	not serious	not serious	NA <sup>1</sup>	very serious <sup>2</sup>	NA	0/394	1/392	PETO OR 0.13 (0.00, 6.79)	3 fewer per 1000 (8 fewer to 2 more)	low
<b>hba1c change (% , lower values are better, change scores) at end of follow up</b> <b>Mean follow-up: 12 month(s)</b>											
1 (lingvay 2019)	RC T	not serious	not serious	NA <sup>1</sup>	serious <sup>4</sup>	NA	394	394	MD 0.50 (0.38, 0.62)	MD 0.50 higher (0.38 higher to 0.62 higher)	moderate
<b>weight change (kg, lower values are better, change scores) at end of follow up</b> <b>Mean follow-up: 12 month(s)</b>											
1 (lingvay 2019)	RC T	not serious	not serious	NA <sup>1</sup>	not serious	NA	394	394	MD 1.10 (0.41, 1.79)	MD 1.10 higher (0.41 higher to 1.79 higher)	high

1. Only one study so no inconsistency

2. 95% confidence intervals cross both ends of the defined MID (0.80, 1.25)
3. 95% confidence intervals cross one end of the defined MID (0.80, 1.25)
4. 95% confidence intervals cross one end of the defined MID (-0.50, 0.50)

#### L.1.5.4 Adding dapagliflozin compared to adding placebo

**Table 45: Clinical evidence profile: Adding dapagliflozin compared to adding placebo**

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
<b>health-related quality of life - overall (eq-5d, -0.59-1.0, higher values are better, change scores) at end of follow up</b> Mean follow-up: 17.8 month(s)											
2	RCT	serious <sup>1</sup>	not serious	not serious	very serious <sup>2</sup>	NA	176	178	MD 0.00 (-0.03, 0.04)	MD 0.00 higher (0.03 lower to 0.04 higher)	very low
<b>all-cause mortality at end of follow up</b> Mean follow-up: 17.2 month(s)											
11	RCT	serious <sup>1</sup>	not serious	serious <sup>3</sup>	not serious	NA	540/1353	572/10061	RD -0.00 (-0.01, 0.00)	4 fewer per 1000 (10 fewer to 3 more)	low
<b>all-cause mortality at end of follow up</b> Mean follow-up: 50.4 month(s)											
1 (wiviott 2019)	RCT	serious <sup>1</sup>	not serious	NA <sup>4</sup>	not serious	NA	8582	8578	HR 0.98 (0.82, 1.17)	Not estimable	moderate
<b>cardiovascular mortality at end of follow up</b> Mean follow-up: 18.9 month(s)											

7	R CT	serious <sup>1</sup>	not serious	serious <sup>3</sup>	very serious <sup>5</sup>	NA	252/1 0596	251/ 944 5	RD -0.00 (-0.00, 0.00)	0 fewer per 1000 (5 fewer to 4 more)	very low
<b>cardiovascular mortality at end of follow up</b>											
<b>Mean follow-up: 50.4 month(s)</b>											
1 (wiviott 2019)	R CT	serious <sup>1</sup>	not serious	NA <sup>4</sup>	not serious	NA	8582	857 8	HR 0.92 (0.82, 1.04)	Not estimable	mo der ate
<b>3-point mace at end of follow up</b>											
<b>Mean follow-up: 50.4 month(s)</b>											
1 (wiviott 2019)	R CT	serious <sup>1</sup>	not serious	NA <sup>4</sup>	not serious	NA	756/8 582	803/ 857 8	RR 0.94 (0.86, 1.03)	6 fewer per 1000 (13 fewer to 3 more)	mo der ate
<b>3-point mace at end of follow up</b>											
<b>Mean follow-up: 50.4 month(s)</b>											
1 (wiviott 2019)	R CT	serious <sup>1</sup>	not serious	NA <sup>4</sup>	not serious	NA	8582	857 8	HR 0.93 (0.84, 1.03)	Not estimable	mo der ate
<b>non-fatal stroke at end of follow up</b>											
<b>Mean follow-up: 30.8 month(s)</b>											
2	R CT	serious <sup>1</sup>	not serious	serious <sup>3</sup>	not serious	NA	236/9 032	231/ 872 4	PETO OR 1.02 (0.85, 1.23)	0 fewer per 1000 (5 fewer to 4 more)	low
<b>non-fatal stroke at end of follow up</b>											
<b>Mean follow-up: 50.4 month(s)</b>											
1 (wiviott 2019)	R CT	serious <sup>1</sup>	not serious	NA <sup>4</sup>	not serious	NA	8582	857 8	HR 1.01 (0.84, 1.21)	Not estimable	mo der ate
<b>non-fatal myocardial infarction at end of follow up</b>											
<b>Mean follow-up: 50.4 month(s)</b>											
1 (wiviott 2019)	R CT	serious <sup>1</sup>	not serious	NA <sup>4</sup>	serious <sup>6</sup>	NA	393/8 582	441/ 857 8	RR 0.89 (0.78, 1.02)	6 fewer per 1000	low

										(11 fewer to 1 more)	
<b>non-fatal myocardial infarction at end of follow up</b>											
<b>Mean follow-up: 50.4 month(s)</b>											
1 (wiviott 2019)	R CT	serious <sup>1</sup>	not serious	NA <sup>4</sup>	serious <sup>6</sup>	NA	8582	857 8	HR 0.89 (0.77, 1.02)	Not estimable	low
<b>unstable angina at end of follow up</b>											
<b>Mean follow-up: 50.4 month(s)</b>											
1 (wiviott 2019)	R CT	serious <sup>1</sup>	not serious	NA <sup>4</sup>	not serious	NA	243/8 582	238/ 857 8	RR 1.02 (0.86, 1.22)	1 more per 1000 (4 fewer to 6 more)	moderate
<b>hospitalisation for heart failure at end of follow up</b>											
<b>Mean follow-up: 50.4 month(s)</b>											
1 (wiviott 2019)	R CT	serious <sup>1</sup>	not serious	NA <sup>4</sup>	serious <sup>6</sup>	NA	212/8 582	286/ 857 8	RR 0.74 (0.62, 0.88)	9 fewer per 1000 (13 fewer to 4 fewer)	low
<b>hospitalisation for heart failure at end of follow up</b>											
<b>Mean follow-up: 50.4 month(s)</b>											
1 (wiviott 2019)	R CT	serious <sup>1</sup>	not serious	NA <sup>4</sup>	serious <sup>6</sup>	NA	8582	857 8	HR 0.73 (0.61, 0.88)	Not estimable	low
<b>acute kidney injury at end of follow up</b>											
<b>Mean follow-up: 50.4 month(s)</b>											
1 (wiviott 2019)	R CT	serious <sup>1</sup>	not serious	NA <sup>4</sup>	serious <sup>6</sup>	NA	125/8 582	175/ 857 8	RR 0.71 (0.57, 0.90)	6 fewer per 1000 (9 fewer to 2 fewer)	low
<b>acute kidney injury at end of follow up</b>											
<b>Mean follow-up: 50.4 month(s)</b>											
1 (wiviott 2019)	R CT	serious <sup>1</sup>	not serious	NA <sup>4</sup>	serious <sup>6</sup>	NA	8582	857 8	HR 0.69 (0.55, 0.87)	Not estimable	low

<b>persistent signs of worsening kidney disease at end of follow up</b>											
<b>Mean follow-up: 27.2 month(s)</b>											
4	RCT	serious <sup>1</sup>	not serious	not serious	not serious	NA	149/10051	230/9058	RR 0.57 (0.46, 0.71)	11 fewer per 1000 (14 fewer to 7 fewer)	moderate
<b>persistent signs of worsening kidney disease at end of follow up</b>											
<b>Mean follow-up: 50.4 month(s)</b>											
1 (wiviott 2019)	RCT	serious <sup>1</sup>	not serious	NA <sup>4</sup>	not serious	NA	8582	8578	HR 0.54 (0.43, 0.67)	Not estimable	moderate
<b>development of end stage kidney disease at end of follow up</b>											
<b>Mean follow-up: 20.5 month(s)</b>											
3	RCT	serious <sup>1</sup>	not serious	serious <sup>3</sup>	not serious	NA	7/9018	20/8856	RD -0.00 (-0.00, -0.00)	1 fewer per 1000 (3 fewer to 0 more)	low
<b>development of end stage kidney disease at end of follow up</b>											
<b>Mean follow-up: 50.4 month(s)</b>											
1 (wiviott 2019)	RCT	serious <sup>1</sup>	not serious	NA <sup>4</sup>	not serious	NA	8582	8578	HR 0.31 (0.13, 0.78)	Not estimable	moderate
<b>death from renal causes at end of follow up</b>											
<b>Mean follow-up: 50.4 month(s)</b>											
1 (wiviott 2019)	RCT	serious <sup>1</sup>	not serious	NA <sup>4</sup>	very serious <sup>7</sup>	NA	10/8582	6/8578	PETO OR 1.65 (0.62, 4.39)	0 more per 1000 (0 more to 1 more)	very low
<b>death from renal causes at end of follow up</b>											
<b>Mean follow-up: 50.4 month(s)</b>											

1 (wiviott 2019)	R CT	serious <sup>1</sup>	not serious	NA <sup>4</sup>	very serious <sup>7</sup>	NA	8582	857 8	HR 0.60 (0.22, 1.65)	Not estimable	very low
<b>cardiac arrhythmia at end of follow up</b>											
<b>Mean follow-up: 50.4 month(s)</b>											
1 (wiviott 2019)	R CT	serious <sup>1</sup>	not serious	NA <sup>4</sup>	serious <sup>6</sup>	NA	94/85 82	121/ 857 8	RR 0.78 (0.59, 1.01)	3 fewer per 1000 (6 fewer to 0 more)	low
<b>diabetic ketoacidosis at end of follow up</b>											
<b>Mean follow-up: 22.6 month(s)</b>											
3	R CT	serious <sup>1</sup>	not serious	serious <sup>3</sup>	not serious	NA	27/87 53	12/8 745	RD 0.00 (0.00, 0.00)	2 more per 1000 (0 more to 3 more)	low
<b>diabetic ketoacidosis at end of follow up</b>											
<b>Mean follow-up: 50.4 month(s)</b>											
1 (wiviott 2019)	R CT	serious <sup>1</sup>	not serious	NA <sup>4</sup>	serious <sup>6</sup>	NA	8582	857 8	HR 2.18 (1.10, 4.30)	Not estimable	low
<b>progression of liver disease at end of follow up</b>											
<b>Mean follow-up: 50.4 month(s)</b>											
1 (wiviott 2019)	R CT	serious <sup>1</sup>	not serious	NA <sup>4</sup>	very serious <sup>7</sup>	NA	82/85 82	87/8 578	PETO OR 0.94 (0.70, 1.27)	1 fewer per 1000 (4 fewer to 2 more)	very low
<b>progression of liver disease at end of follow up</b>											
<b>Mean follow-up: 50.4 month(s)</b>											
1 (wiviott 2019)	R CT	serious <sup>1</sup>	not serious	NA <sup>4</sup>	serious <sup>6</sup>	NA	8582	857 8	HR 0.92 (0.68, 1.25)	Not estimable	low
<b>hypoglycaemia episodes at end of follow up</b>											
<b>Mean follow-up: 13.7 month(s)</b>											
11	R CT	serious <sup>1</sup>	not serious	serious <sup>3</sup>	not serious	NA	501/2 803	181/ 151 7	RD 0.01 (-0.01, 0.03)	13 more per 1000	low

											(8 fewer to 34 more)	
<b>severe hypoglycaemic episodes at end of follow up</b>												
<b>Mean follow-up: 17.2 month(s)</b>												
11	R CT	serious <sup>1</sup>	not serious	serious <sup>3</sup>	not serious	NA	62/11 353	84/1 006 1	RD -0.00 (-0.00, 0.00)	2 fewer per 1000 (5 fewer to 0 more)	low	
<b>hba1c change (% , lower values are better, change scores) at end of follow up</b>												
<b>Mean follow-up: 15.8 month(s)</b>												
12	R CT	serious <sup>1</sup>	not serious	very serious <sup>8</sup>	serious <sup>9</sup>	NA	10903	981 1	MD -0.54 (-0.62, -0.45)	MD 0.54 lower (0.62 lower to 0.45 lower)	very low	
<b>hba1c change (mmol/mol, lower values are better, change scores) at end of follow up</b>												
<b>Mean follow-up: 12 month(s)</b>												
1 (brown 2020)	R CT	not serious	not serious	NA <sup>4</sup>	serious <sup>10</sup>	NA	32	34	MD -5.49 (-10.13, -0.85)	MD 5.49 lower (10.13 lower to 0.85 lower)	moderate	
<b>weight change (kg, lower values are better, change scores) at end of follow up</b>												
<b>Mean follow-up: 14.5 month(s)</b>												
13	R CT	very serious <sup>11</sup>	not serious	serious <sup>12</sup>	not serious	NA	10679	986 7	MD -1.80 (-2.12, -1.49)	MD 1.80 lower (2.12 lower to 1.49 lower)	very low	
<b>bmi change (kg/m2, lower values are better, change scores) at end of follow up</b>												
<b>Mean follow-up: 8.8 month(s)</b>												

2	RCT	not serious	not serious	serious <sup>12</sup>	very serious <sup>13</sup>	NA	82	84	MD -0.45 (-2.85, 1.94)	MD 0.45 lower (2.85 lower to 1.94 higher)	very low
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1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
2. 95% confidence intervals cross both ends of the defined MIDs (-0.03, 0.03)
3. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
4. Only one study so no inconsistency
5. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.43 (0.8-0.9 = serious, <0.8 = very serious).
6. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
7. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
8. I<sup>2</sup> > 75%
9. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
10. 95% confidence intervals cross one end of the defined MIDs (-5.50, 5.50)
11. >33.3% of the studies in the meta-analysis were at high risk of bias
12. I<sup>2</sup> between 50% and 75%
13. 95% confidence intervals cross both ends of the defined MIDs (-0.80, 0.80)

## L.1.5.5 Adding dapagliflozin compared to adding exenatide

Table 46: Clinical evidence profile: Adding dapagliflozin compared to adding exenatide

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerat ions	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>all-cause mortality at end of follow up Mean follow-up: 24 month(s)</b>											
1 (frias 2016)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>3</sup>	NA	2/233	1/23 0	PETO OR 1.93 (0.20, 18.63)	4 more per 1000 (10 fewer to 19 more)	very low
<b>cardiovascular mortality at end of follow up Mean follow-up: 24 month(s)</b>											
1 (frias 2016)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>3</sup>	NA	1/233	1/23 0	PETO OR 0.99 (0.06, 15.83)	0 fewer per 1000 (12 fewer to 12 more)	very low
<b>acute kidney injury at end of follow up Mean follow-up: 24 month(s)</b>											
1 (frias 2016)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>3</sup>	NA	3/233	2/23 0	RR 1.48 (0.25, 8.78)	4 more per 1000 (15 fewer to 23 more)	very low
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 24 month(s)</b>											
1 (frias 2016)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>3</sup>	NA	1/233	0/23 0	PETO OR 7.29 (0.14, 367.65)	4 more per 1000 (4 fewer to 13 more)	very low
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 24 month(s)</b>											

1 (frias 2016)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	0/233	0/23 0	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 8 more)	low
<b>hba1c change (% , lower values are better, change scores) at end of follow up Mean follow-up: 24 month(s)</b>											
1 (frias 2016)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>4</sup>	NA	230	227	MD 0.23 (-0.10, 0.56)	MD 0.23 higher (0.10 lower to 0.56 higher)	very low
<b>weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 24 month(s)</b>											
1 (frias 2016)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>5</sup>	NA	230	227	MD -2.22 (-3.55, - 0.89)	MD 2.22 lower (3.55 lower to 0.89 lower)	very low

1. >33.3% of the studies in the meta-analysis were at high risk of bias
2. Only one study so no inconsistency
3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
4. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
5. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

## L.1.5.6 Adding dapagliflozin compared to adding liraglutide

Table 47: Clinical evidence profile: Adding dapagliflozin compared to adding liraglutide

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerat ions	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>all-cause mortality at end of follow up</b> <b>Mean follow-up: 5.5 month(s)</b>											
1 (jiang 2021b)	RC T	very seriou s <sup>1</sup>	seriou s <sup>2</sup>	NA <sup>3</sup>	seriou s <sup>4</sup>	NA	0/79	0/77	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (25 fewer to 25 more)	very low
<b>cardiovascular mortality at end of follow up</b> <b>Mean follow-up: 5.5 month(s)</b>											
1 (jiang 2021b)	RC T	very seriou s <sup>1</sup>	seriou s <sup>2</sup>	NA <sup>3</sup>	seriou s <sup>4</sup>	NA	0/79	0/77	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (25 fewer to 25 more)	very low
<b>non-fatal myocardial infarction at end of follow up</b> <b>Mean follow-up: 5.5 month(s)</b>											
1 (hao 2022)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>3</sup>	seriou s <sup>4</sup>	NA	0/166	0/14 3	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (13 fewer to 13 more)	very low
<b>unstable angina at end of follow up</b> <b>Mean follow-up: 5.5 month(s)</b>											
1 (hao 2022)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>3</sup>	very seriou s <sup>5</sup>	NA	2/166	2/14 3	RR 0.86 (0.12, 6.04)	2 fewer per 1000 (12 fewer to 70 more)	very low
<b>hospitalisation for heart failure at end of follow up</b> <b>Mean follow-up: 5.5 month(s)</b>											

1 (hao 2022)	RC T	very serious <sup>1</sup>	not serious	NA <sup>3</sup>	serious <sup>4</sup>	NA	0/166	0/14 3	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (13 fewer to 13 more)	very low
<b>diabetic ketoacidosis at end of follow up</b> <b>Mean follow-up: 5.5 month(s)</b>											
1 (jiang 2021b)	RC T	very serious <sup>1</sup>	serious <sup>2</sup>	NA <sup>3</sup>	serious <sup>4</sup>	NA	0/79	0/77	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (25 fewer to 25 more)	very low
<b>hypoglycaemia episodes at end of follow up</b> <b>Mean follow-up: 5.5 month(s)</b>											
1 (hao 2022)	RC T	very serious <sup>1</sup>	not serious	NA <sup>3</sup>	very serious <sup>5</sup>	NA	29/166	21/1 43	RR 1.19 (0.71, 1.99)	28 more per 1000 (42 fewer to 146 more)	very low
<b>severe hypoglycaemic episodes at end of follow up</b> <b>Mean follow-up: 5.5 month(s)</b>											
2	RC T	very serious <sup>1</sup>	not serious	not serious	not serious	NA	0/245	0/22 0	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	low
<b>hba1c change (% , lower values are better, change scores) at end of follow up</b> <b>Mean follow-up: 5.5 month(s)</b>											
1 (hao 2022)	RC T	very serious <sup>1</sup>	not serious	NA <sup>3</sup>	serious <sup>6</sup>	NA	166	143	MD 0.36 (-0.01, 0.73)	MD 0.36 higher (0.01 lower to 0.73 higher)	very low
<b>weight change (kg, lower values are better, change scores) at end of follow up</b> <b>Mean follow-up: 5.5 month(s)</b>											

2	RC T	very serious <sup>1</sup>	not serious	not serious	not serious	NA	245	220	MD -0.24 (-1.92, 1.43)	MD 0.24 lower (1.92 lower to 1.43 higher)	low
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- >33.3% of the studies in the meta-analysis were at high risk of bias
- Largest proportion of studies in the meta-analysis came from partially direct studies
- Only one study so no inconsistency
- Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
- 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

#### L.1.5.7 Adding dapagliflozin compared to adding saxagliptin

**Table 48: Clinical evidence profile: Adding dapagliflozin compared to adding saxagliptin**

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>all-cause mortality at end of follow up Mean follow-up: 5.5 month(s)</b>											
2	RC T	not serious	not serious	serious <sup>1</sup>	very serious <sup>2</sup>	NA	2/472	0/47 1	RD 0.00 (-0.00, 0.01)	4 more per 1000 (4 fewer to 13 more)	very low
<b>cardiovascular mortality at end of follow up Mean follow-up: 5.5 month(s)</b>											
2	RC T	not serious	not serious	serious <sup>1</sup>	very serious <sup>2</sup>	NA	2/472	0/47 1	RD 0.00 (-0.00, 0.01)	4 more per 1000 (4 fewer to 13 more)	very low

<b>persistent signs of worsening kidney disease at end of follow up Mean follow-up: 5.5 month(s)</b>												
1 (rosenstock 2015a)	RC T	serious <sup>3</sup>	not serious	NA <sup>4</sup>	not serious	NA	0/179	0/176	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (11 fewer to 11 more)	moderate	
<b>diabetic ketoacidosis at end of follow up Mean follow-up: 5.5 month(s)</b>												
1 (rosenstock 2019d)	RC T	not serious	not serious	NA <sup>4</sup>	not serious	NA	0/293	0/295	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	high	
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 5.5 month(s)</b>												
2	RC T	not serious	not serious	not serious	very serious <sup>5</sup>	NA	2/472	5/471	PETO OR 0.42 (0.10, 1.87)	6 fewer per 1000 (17 fewer to 5 more)	low	
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 5.5 month(s)</b>												
2	RC T	not serious	not serious	serious <sup>1</sup>	very serious <sup>6</sup>	NA	0/472	1/471	RD -0.00 (-0.01, 0.01)	2 fewer per 1000 (9 fewer to 5 more)	very low	
<b>hba1c change (% , lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)</b>												
2	RC T	not serious	not serious	very serious <sup>7</sup>	not serious	NA	431	431	MD -0.12 (-0.50, 0.25)	MD 0.12 lower (0.50 lower to 0.25 higher)	low	

weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)											
1 (rosenstock 2015a)	RC T	serious <sup>3</sup>	not serious	NA <sup>4</sup>	serious <sup>8</sup>	NA	152	145	MD -2.40 (-3.10, -1.70)	MD 2.40 lower (3.10 lower to 1.70 lower)	low

1. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
2. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.52 (0.8-0.9 = serious, <0.8 = very serious).
3. >33.3% of the studies in the meta-analysis were at moderate risk of bias
4. Only one study so no inconsistency
5. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
6. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.29 (0.8-0.9 = serious, <0.8 = very serious).
7. I2 > 75%
8. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

**L.1.5.8 Adding dapagliflozin compared to adding sitagliptin**

**Table 49: Clinical evidence profile: Adding dapagliflozin compared to adding sitagliptin**

No of studies	De sig n	Risk of bias	Indire ctnes s	Incons istenc y	Impre cision	Other considerat ions	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
all-cause mortality at end of follow up Mean follow-up: 5.5 month(s)											

1 (scott 2018)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	not seriou s	NA	0/306	0/30 7	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	high
<b>cardiovascular mortality at end of follow up Mean follow-up: 5.5 month(s)</b>											
1 (scott 2018)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	not seriou s	NA	0/306	0/30 7	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	high
<b>hospitalisation for heart failure at end of follow up Mean follow-up: 24 month(s)</b>											
1 (hong 2023)	RC T	seriou s <sup>2</sup>	not seriou s	NA <sup>1</sup>	very seriou s <sup>3</sup>	NA	0/26	0/26	RD 0.00 (-0.07, 0.07)	0 fewer per 1000 (72 fewer to 72 more)	very low
<b>diabetic ketoacidosis at end of follow up Mean follow-up: 5.5 month(s)</b>											
1 (lee 2022)	RC T	very seriou s <sup>4</sup>	not seriou s	NA <sup>1</sup>	very seriou s <sup>3</sup>	NA	0/30	0/30	RD 0.00 (-0.06, 0.06)	0 fewer per 1000 (63 fewer to 63 more)	very low
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 14.8 month(s)</b>											
2	RC T	not seriou s	not seriou s	not seriou s	very seriou s <sup>5</sup>	NA	20/332	21/3 33	RR 0.95 (0.53, 1.72)	3 fewer per 1000 (30 fewer to 46 more)	low
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 14.8 month(s)</b>											
2	RC T	not seriou s	not seriou s	not seriou s	very seriou s <sup>5</sup>	NA	3/332	2/33 3	PETO OR 1.50 (0.26, 8.74)	3 more per 1000	low

										(10 fewer to 16 more)	
<b>hba1c change (% , lower values are better, change and final scores) at end of follow up Mean follow-up: 11.7 month(s)</b>											
3	RC T	not seriou s	not seriou s	not seriou s	not seriou s	NA	361	362	MD 0.05 (-0.21, - 0.31)	MD 0.05 higher (0.21 lower to 0.31 higher)	high
<b>weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)</b>											
1 (lee 2022)	RC T	very seriou s <sup>4</sup>	not seriou s	NA <sup>1</sup>	seriou s <sup>6</sup>	NA	30	30	MD -1.59 (-2.70, - 0.48)	MD 1.59 lower (2.70 lower to 0.48 lower)	very low
<b>weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)</b>											
1 (lee 2022)	RC T	very seriou s <sup>4</sup>	not seriou s	NA <sup>1</sup>	seriou s <sup>7</sup>	NA	30	30	MD -1.59 (-2.70, - 0.48)	MD 1.59 lower (2.70 lower to 0.48 lower)	very low

1. Only one study so no inconsistency
2. >33.3% of the studies in the meta-analysis were at moderate risk of bias
3. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
4. >33.3% of the studies in the meta-analysis were at high risk of bias
5. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

6. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

7. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

### L.1.5.9 Adding empagliflozin compared to adding placebo

**Table 50: Clinical evidence profile: Adding empagliflozin compared to adding placebo**

No of studies	De sig n	Risk of bias	Indir ectne ss	Incon sisten cy	Impre cision	Other considera tions	Interv ention N	Con trol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>health-related quality of life - overall (eq-5d-5l, higher values are better, change scores) at end of follow up</b>											
<b>Mean follow-up: 12 month(s)</b>											
1 (yabe 2023)	R CT	not serio us	not serio us	NA <sup>1</sup>	seriou s <sup>2</sup>	NA	65	64	MD 0.05 (0.01, 0.09)	MD 0.05 higher (0.01 higher to 0.09 higher)	mod erat e
<b>all-cause mortality at end of follow up</b>											
<b>Mean follow-up: 13.1 month(s)</b>											
9	R CT	very serio us <sup>3</sup>	not serio us	seriou s <sup>4</sup>	very seriou s <sup>5</sup>	NA	7/2447	3/12 95	RD 0.00 (-0.00, 0.01)	1 more per 1000 (4 fewer to 5 more)	very low
<b>cardiovascular mortality at end of follow up</b>											
<b>Mean follow-up: 11.6 month(s)</b>											
5	R CT	very serio us <sup>3</sup>	not serio us	seriou s <sup>4</sup>	very seriou s <sup>6</sup>	NA	2/1356	0/71 1	RD 0.00 (-0.00, 0.01)	1 more per 1000 (4 fewer to 7 more)	very low
<b>non-fatal stroke at end of follow up</b>											
<b>Mean follow-up: 12 month(s)</b>											

1 (kawamori 2018)	R CT	not serio us	not serio us	NA <sup>1</sup>	very seriou s <sup>7</sup>	NA	0/182	1/93	PETO OR 0.05 (0.00, 3.27)	11 fewer per 1000 (32 fewer to 10 more)	low
<b>unstable angina at end of follow up</b>											
<b>Mean follow-up: 12 month(s)</b>											
1 (sone 2019)	R CT	not serio us	not serio us	NA <sup>1</sup>	very seriou s <sup>7</sup>	NA	0/176	1/90	PETO OR 0.05 (0.00, 3.28)	11 fewer per 1000 (33 fewer to 11 more)	low
<b>hospitalisation for heart failure at end of follow up</b>											
<b>Mean follow-up: 12 month(s)</b>											
1 (kawamori 2018)	R CT	not serio us	not serio us	NA <sup>1</sup>	seriou s <sup>8</sup>	NA	0/182	0/93	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (17 fewer to 17 more)	mod erat e
<b>acute kidney injury at end of follow up</b>											
<b>Mean follow-up: 8.8 month(s)</b>											
2	R CT	not serio us	not serio us	seriou s <sup>4</sup>	very seriou s <sup>9</sup>	NA	3/328	0/16 6	RD 0.01 (-0.01, 0.03)	9 more per 1000 (8 fewer to 26 more)	very low
<b>persistent signs of worsening kidney disease at end of follow up</b>											
<b>Mean follow-up: 8.9 month(s)</b>											
2	R CT	not serio us	not serio us	not seriou s	seriou s <sup>8</sup>	NA	0/145	0/14 1	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (19 fewer to 19 more)	mod erat e
<b>diabetic ketoacidosis at end of follow up</b>											
<b>Mean follow-up: 10.1 month(s)</b>											
7	R CT	not serio us	not serio us	seriou s <sup>4</sup>	very seriou s <sup>10</sup>	NA	0/1195	1/67 7	RD -0.00 (-0.01, 0.01)	2 fewer per 1000 (9 fewer to 5 more)	very low

<b>progression of liver disease at end of follow up</b> <b>Mean follow-up: 12 month(s)</b>												
1 (yabe 2023)	R CT	not serio us	not serio us	NA <sup>1</sup>	very seriou s <sup>7</sup>	NA	2/65	0/64	PETO OR 7.39 (0.46, 119.47)	31 more per 1000 (11 fewer to 73 more)	low	
<b>hypoglycaemia episodes at end of follow up</b> <b>Mean follow-up: 11.7 month(s)</b>												
12	R CT	not serio us	not serio us	seriou s <sup>4</sup>	not seriou s	NA	517/28 95	247/ 158 1	RR 1.08 (0.96, 1.22)	13 more per 1000 (7 fewer to 34 more)	mod erat e	
<b>severe hypoglycaemic episodes at end of follow up</b> <b>Mean follow-up: 11.8 month(s)</b>												
9	R CT	very serio us <sup>3</sup>	not serio us	seriou s <sup>4</sup>	very seriou s <sup>5</sup>	NA	9/2260	4/12 03	RD 0.00 (-0.00, 0.01)	0 more per 1000 (5 fewer to 6 more)	very low	
<b>hba1c change (% , lower values are better, change scores and final values) at end of follow up</b> <b>Mean follow-up: 11.3 month(s)</b>												
14	R CT	not serio us	not serio us	very seriou s <sup>11</sup>	seriou s <sup>12</sup>	NA	2471	131 4	MD -0.74 (-0.99, - 0.49)	MD 0.74 lower (0.99 lower to 0.49 lower)	very low	
<b>weight change (kg, lower values are better, change scores) at end of follow up</b> <b>Mean follow-up: 10.6 month(s)</b>												
14	R CT	not serio us	not serio us	very seriou s <sup>11</sup>	seriou s <sup>13</sup>	NA	2526	134 0	MD -2.22 (-2.62, - 1.81)	MD 2.22 lower (2.62 lower to 1.81 lower)	very low	

bmi change (kg/m2, lower values are better, change scores and final values) at end of follow up Mean follow-up: 8.8 month(s)											
2	RCT	not serious	not serious	not serious	serious <sup>14</sup>	NA	100	102	MD -0.58 (-0.92, -0.24)	MD 0.58 lower (0.92 lower to 0.24 lower)	moderate

1. Only one study so no inconsistency
2. 95% confidence intervals cross one end of the defined MIDs (-0.03, 0.03)
3. >33.3% of the studies in the meta-analysis were at high risk of bias
4. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
5. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.07 (0.8-0.9 = serious, <0.8 = very serious).
6. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.44 (0.8-0.9 = serious, <0.8 = very serious).
7. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
8. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
9. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.57 (0.8-0.9 = serious, <0.8 = very serious).
10. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.38 (0.8-0.9 = serious, <0.8 = very serious).
11. I<sup>2</sup> > 75%
12. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

13. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

14. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

#### L.1.5.10 Adding empagliflozin compared to adding insulin

**Table 51: Clinical evidence profile: Adding empagliflozin compared to adding insulin**

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>hba1c change (% , lower values are better, final scores) at end of follow up Mean follow-up: 12 month(s)</b>											
1 (ikonomidis 2020)	RC T	seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>3</sup>	NA	40	40	MD 0.00 (-0.50, 0.50)	MD 0.00 lower (0.50 lower to 0.50 higher)	very low
<b>weight change (kg, lower values are better, final scores) at end of follow up Mean follow-up: 12 month(s)</b>											
1 (ikonomidis 2020)	RC T	seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	seriou s <sup>4</sup>	NA	40	40	MD -2.90 (-7.07, 1.27)	MD 2.90 lower (7.07 lower to 1.27 higher)	low
<b>bmi change (kg/m2, lower values are better, final scores) at end of follow up Mean follow-up: 12 month(s)</b>											
1 (ikonomidis 2020)	RC T	seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	seriou s <sup>5</sup>	NA	40	40	MD -1.20 (-2.32, - 0.08)	MD 1.20 lower (2.32 lower to 0.08 lower)	low

1. >33.3% of the studies in the meta-analysis were at moderate risk of bias

2. Only one study so no inconsistency
3. 95% confidence intervals cross both ends of the defined MIDs (-0.50, 0.50)
4. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)
5. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

#### L.1.5.11 Adding empagliflozin compared to adding linagliptin

**Table 52: Clinical evidence profile: Adding empagliflozin compared to adding linagliptin**

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>all-cause mortality at end of follow up</b> Mean follow-up: 5.5 month(s)											
1 (liu 2021)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	seriou s <sup>2</sup>	NA	0/53	0/53	RD 0.00 (-0.04, 0.04)	0 fewer per 1000 (36 fewer to 36 more)	mod erat e
<b>cardiovascular mortality at end of follow up</b> Mean follow-up: 5.5 month(s)											
1 (liu 2021)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	seriou s <sup>2</sup>	NA	0/53	0/53	RD 0.00 (-0.04, 0.04)	0 fewer per 1000 (36 fewer to 36 more)	mod erat e
<b>diabetic ketoacidosis at end of follow up</b> Mean follow-up: 5.5 month(s)											
1 (liu 2021)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	very seriou s <sup>3</sup>	NA	1/53	0/53	PETO OR 7.39 (0.15, 372.38)	19 more per 1000 (18 fewer to 56 more)	low
<b>hypoglycaemia episodes at end of follow up</b>											

Mean follow-up: 5.5 month(s)											
1 (liu 2021)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	very seriou s <sup>3</sup>	NA	5/53	5/53	RR 1.00 (0.31, 3.25)	0 fewer per 1000 (65 fewer to 213 more)	low
<b>severe hypoglycaemic episodes at end of follow up</b>											
<b>Mean follow-up: 5.5 month(s)</b>											
1 (liu 2021)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	seriou s <sup>2</sup>	NA	0/53	0/53	RD 0.00 (-0.04, 0.04)	0 fewer per 1000 (36 fewer to 36 more)	mod erat e
<b>hba1c change (% , lower values are better, change scores) at end of follow up</b>											
<b>Mean follow-up: 5.5 month(s)</b>											
1 (liu 2021)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	seriou s <sup>4</sup>	NA	51	53	MD -0.95 (-1.41, - 0.49)	MD 0.95 lower (1.41 lower to 0.49 lower)	mod erat e
<b>weight change (kg, lower values are better, change scores) at end of follow up</b>											
<b>Mean follow-up: 5.5 month(s)</b>											
1 (liu 2021)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	seriou s <sup>5</sup>	NA	51	53	MD -1.70 (-2.58, - 0.82)	MD 1.70 lower (2.58 lower to 0.82 lower)	mod erat e

1. Only one study so no inconsistency
2. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
4. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

5. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

#### L.1.5.12 Adding empagliflozin compared to adding liraglutide

**Table 53: Clinical evidence profile: Adding empagliflozin compared to adding liraglutide**

	De sig n	Risk of bias	Indire ctnes s	Incons istenc y	Impre cision	Other considerat ions	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>No of studies</b>											
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 5.5 month(s)</b>											
1 (nakaguchi 2020)	RC T	not serio us	not seriou s	NA <sup>1</sup>	very seriou s <sup>2</sup>	NA	0/31	0/30	RD 0.00 (-0.06, 0.06)	0 fewer per 1000 (62 fewer to 62 more)	low
<b>hba1c change (% , lower values are better, change and final scores) at end of follow up Mean follow-up: 8.8 month(s)</b>											
2	RC T	not serio us	not seriou s	very seriou s <sup>3</sup>	seriou s <sup>4</sup>	NA	71	70	MD 0.46 (-0.41, 1.33)	MD 0.46 higher (0.41 lower to 1.33 higher)	very low
<b>weight change (kg, lower values are better, final scores) at end of follow up Mean follow-up: 8.8 month(s)</b>											
2	RC T	not serio us	not seriou s	not seriou s	not seriou s	NA	71	70	MD -0.34 (-1.30, 0.61)	MD 0.34 lower (1.30 lower to 0.61 higher)	high
<b>bmi change (kg/m2, lower values are better, final scores) at end of follow up Mean follow-up: 8.8 month(s)</b>											

2	RC T	not serio us	not seriou s	seriou s <sup>5</sup>	seriou s <sup>6</sup>	NA	71	70	MD -0.51 (-1.55, 0.53)	MD 0.51 lower (1.55 lower to 0.53 higher)	low
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1. Only one study so no inconsistency
2. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
3. I2 > 75%
4. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
5. I2 between 50% and 75%
6. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

**L.1.5.13 Adding empagliflozin compared to adding semaglutide**

**Table 54: Clinical evidence profile: Adding empagliflozin compared to adding semaglutide**

No of studies	De sig n	Risk of bias	Indir ectn ess	Incon sisten cy	Impr ecisi on	Other consider ations	Interv entio n N	Con trol N	Relative effect (95% CI)	Absolute effect	Cer tain ty
health-related quality of life - subscale mental component (sf36, higher values are better, change scores) at end of follow-up Mean follow-up: 12 month(s)											
1 (rodbard 2019)	R CT	serio us <sup>1</sup>	not serio us	NA <sup>2</sup>	not serio us	NA	409	409	MD -0.20 (-1.33, 0.93)	MD 0.20 lower (1.33 lower to 0.93 higher)	mo der ate
health-related quality of life - subscale physical component (sf-36, higher values are better, change scores) at end of follow-up											

Mean follow-up: 12 month(s)											
1 (rodbard 2019)	R CT	serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	410	409	MD 1.00 (0.12, 1.88)	MD 1.00 higher (0.12 higher to 1.88 higher)	moderate
all-cause mortality at end of follow up Mean follow-up: 12 month(s)											
1 (rodbard 2019)	R CT	not serious	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	1/409	0/4 10	PETO OR 7.41 (0.15, 373.30)	2 more per 1000 (2 fewer to 7 more)	low
cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)											
1 (rodbard 2019)	R CT	not serious	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	1/409	0/4 10	PETO OR 7.41 (0.15, 373.30)	2 more per 1000 (2 fewer to 7 more)	low
hospitalisation for heart failure at end of follow up Mean follow-up: 12 month(s)											
1 (rodbard 2019)	R CT	not serious	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	1/409	2/4 10	PETO OR 0.51 (0.05, 4.95)	2 fewer per 1000 (11 fewer to 6 more)	low
acute kidney injury at end of follow up Mean follow-up: 12 month(s)											
1 (rodbard 2019)	R CT	not serious	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	1/409	2/4 10	PETO OR 0.51 (0.05, 4.95)	2 fewer per 1000 (11 fewer to 6 more)	low
hypoglycaemia episodes at end of follow up Mean follow-up: 12 month(s)											
1 (rodbard 2019)	R CT	not serious	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	39/40 9	45/ 410	RR 0.87 (0.58, 1.30)	14 fewer per 1000	low

										(46 fewer to 33 more)	
<b>severe hypoglycaemic episodes at end of follow up</b> <b>Mean follow-up: 12 month(s)</b>											
1 (rodbard 2019)	R CT	not serious	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	1/409	1/4 10	RR 1.00 (0.06, 15.97)	0 more per 1000 (2 fewer to 37 more)	low
<b>hba1c change (% , lower values are better, change scores) at end of follow up</b> <b>Mean follow-up: 12 month(s)</b>											
1 (rodbard 2019)	R CT	not serious	not serious	NA <sup>2</sup>	not serious	NA	410	411	MD 0.40 (0.30, 0.50)	MD 0.40 higher (0.30 higher to 0.50 higher)	high
<b>weight change (kg, lower values are better, change scores) at end of follow up</b> <b>Mean follow-up: 12 month(s)</b>											
1 (rodbard 2019)	R CT	not serious	not serious	NA <sup>2</sup>	not serious	NA	410	411	MD 0.20 (-0.50, 0.90)	MD 0.20 higher (0.50 lower to 0.90 higher)	high
<b>bmi change (kg/m2, lower values are better, change scores) at end of follow up</b> <b>Mean follow-up: 12 month(s)</b>											
1 (rodbard 2019)	R CT	not serious	not serious	NA <sup>2</sup>	not serious	NA	410	411	MD 0.10 (-0.15, 0.35)	MD 0.10 higher (0.15 lower to 0.35 higher)	high

1. >33.3% of the studies in the meta-analysis were at moderate risk of bias

2. Only one study so no inconsistency

3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

#### L.1.5.14 Adding empagliflozin compared to adding sitagliptin

**Table 55: Clinical evidence profile: Adding empagliflozin compared to adding sitagliptin**

No of studies	De sig n	Risk of bias	Indire ctnes s	Incons istenc y	Impre cision	Other considerat ions	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>hba1c change (mmol/mol, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)</b>											
1 (nesti 2022)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	not seriou s	NA	22	22	MD -1.70 (-3.20, - 0.20)	MD 1.70 lower (3.20 lower to 0.20 lower)	low
<b>weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)</b>											
1 (nesti 2022)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>3</sup>	NA	22	22	MD 0.30 (-4.26, 4.86)	MD 0.30 higher (4.26 lower to 4.86 higher)	very low

1. Largest proportion of studies in the meta-analysis were at high risk of bias
2. Only one study so no inconsistency
3. 95% confidence intervals cross both ends of the defined MIDs (-2.40, 2.40)

## L.1.5.15 Adding empagliflozin compared to adding vildagliptin

Table 56: Clinical evidence profile: Adding empagliflozin compared to adding vildagliptin

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>hba1c change (% , lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)</b>											
1 (khan 2022)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	seriou s <sup>3</sup>	NA	53	54	MD -0.15 (-0.61, 0.31)	MD 0.15 lower (0.61 lower to 0.31 higher)	very low
<b>weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)</b>											
1 (khan 2022)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	not seriou s	NA	53	54	MD -0.12 (-1.44, 1.20)	MD 0.12 lower (1.44 lower to 1.20 higher)	low

- >33.3% of the studies in the meta-analysis were at high risk of bias
- Only one study so no inconsistency
- 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

## L.1.5.16 Adding ertugliflozin compared to adding placebo

Table 57: Clinical evidence profile: Adding ertugliflozin compared to adding placebo

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
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<b>all-cause mortality at end of follow up</b> <b>Mean follow-up: 8 month(s)</b>												
3	RC T	not seriou s	not seriou s	not serious	not seriou s	NA	0/1060	0/52 9	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (5 fewer to 5 more)	high	
<b>cardiovascular mortality at end of follow up</b> <b>Mean follow-up: 8 month(s)</b>												
3	RC T	not seriou s	not seriou s	not serious	not seriou s	NA	0/1060	0/52 9	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (5 fewer to 5 more)	high	
<b>diabetic ketoacidosis at end of follow up</b> <b>Mean follow-up: 12 month(s)</b>												
1 (dagogo-jack 2017)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	not seriou s	NA	0/309	0/15 3	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (10 fewer to 10 more)	high	
<b>hypoglycaemia episodes at end of follow up</b> <b>Mean follow-up: 8 month(s)</b>												
3	RC T	not seriou s	not seriou s	not serious	seriou s <sup>2</sup>	NA	66/106 0	20/5 29	RR 1.65 (1.01, 2.69)	25 more per 1000 (0 more to 64 more)	mod erat e	
<b>severe hypoglycaemic episodes at end of follow up</b> <b>Mean follow-up: 12 month(s)</b>												
1 (dagogo-jack 2017)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	very seriou s <sup>3</sup>	NA	0/309	1/15 3	PETO OR 0.05 (0.00, 3.14)	7 fewer per 1000 (19 fewer to 6 more)	low	
<b>hba1c change (% , lower values are better, change scores) at end of follow up</b> <b>Mean follow-up: 8 month(s)</b>												

3	RC T	not seriou s	not seriou s	not serious	not seriou s	NA	1060	529	MD -0.73 (-0.81, - 0.64)	MD 0.73 lower (0.81 lower to 0.64 lower)	high
<b>weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 8 month(s)</b>											
2	RC T	not seriou s	not seriou s	not serious	not seriou s	NA	648	320	MD -1.94 (-2.26, - 1.62)	MD 1.94 lower (2.26 lower to 1.62 lower)	high

1. Only one study so no inconsistency
2. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

#### L.1.5.17 Adding ertugliflozin compared to adding sitagliptin

**Table 58: Clinical evidence profile: Adding ertugliflozin compared to adding sitagliptin**

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerat ions	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>all-cause mortality at end of follow up Mean follow-up: 12 month(s)</b>											
1 (pratley 2018a)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	very seriou s <sup>2</sup>	NA	1/498	0/24 7	PETO OR 4.46 (0.07, 286.95)	2 more per 1000 (2 fewer to 6 more)	low
<b>cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)</b>											

1 (pratley 2018a)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	very seriou s <sup>2</sup>	NA	1/498	0/24 7	PETO OR 4.46 (0.07, 286.95)	2 more per 1000 (2 fewer to 6 more)	low
<b>diabetic ketoacidosis at end of follow up</b> <b>Mean follow-up: 12 month(s)</b>											
1 (pratley 2018a)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	not seriou s	NA	0/498	0/24 7	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	high
<b>hypoglycaemia episodes at end of follow up</b> <b>Mean follow-up: 12 month(s)</b>											
1 (pratley 2018a)	RC T	very seriou s <sup>3</sup>	not seriou s	NA <sup>1</sup>	very seriou s <sup>2</sup>	NA	15/498	7/24 7	RR 1.06 (0.44, 2.57)	2 more per 1000 (16 fewer to 45 more)	very low
<b>severe hypoglycaemic episodes at end of follow up</b> <b>Mean follow-up: 12 month(s)</b>											
1 (pratley 2018a)	RC T	very seriou s <sup>3</sup>	not seriou s	NA <sup>1</sup>	very seriou s <sup>2</sup>	NA	2/498	0/24 7	PETO OR 4.47 (0.24, 85.11)	4 more per 1000 (2 fewer to 10 more)	very low
<b>hba1c change (% , lower values are better, change scores) at end of follow up</b> <b>Mean follow-up: 12 month(s)</b>											
1 (pratley 2018a)	RC T	very seriou s <sup>3</sup>	not seriou s	NA <sup>1</sup>	not seriou s	NA	498	247	MD -0.10 (-0.28, 0.08)	MD 0.10 lower (0.28 lower to 0.08 higher)	low
<b>weight change (kg, lower values are better, change scores) at end of follow up</b> <b>Mean follow-up: 12 month(s)</b>											

1 (pratley 2018a)	RC T	very serious <sup>3</sup>	not serious	NA <sup>1</sup>	serious <sup>4</sup>	NA	498	247	MD -2.70 (-3.41, - 1.99)	MD 2.70 lower (3.41 lower to 1.99 lower)	very low
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1. Only one study so no inconsistency
2. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
3. >33.3% of the studies in the meta-analysis were at high risk of bias
4. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

## L.1.6 Sulfonylureas

### L.1.6.1 Adding gliclazide compared to adding vildagliptin

**Table 59: Clinical evidence profile: Adding gliclazide compared to adding vildagliptin**

No of studies	De sign	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerat ions	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert ainty
<b>all-cause mortality at end of follow up Mean follow-up: 12 month(s)</b>											
2	RC T	serious <sup>1</sup>	not serious	serious <sup>2</sup>	very serious <sup>3</sup>	NA	2/514	1/53 1	RR 1.70 (0.23, 12.67)	1 more per 1000 (1 fewer to 22 more)	very low
<b>cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)</b>											
1 (vianna 2018)	RC T	serious <sup>1</sup>	not serious	NA <sup>4</sup>	very serious <sup>3</sup>	NA	1/21	0/21	PETO OR 7.39 (0.15, 372.38)	48 more per 1000 (43 fewer to 139 more)	very low
<b>non-fatal stroke at end of follow up</b>											

<b>Mean follow-up: 12 month(s)</b>											
1 (vianna 2018)	RC T	serious <sup>1</sup>	not serious	NA <sup>4</sup>	very serious <sup>3</sup>	NA	0/21	1/21	PETO OR 0.14 (0.00, 6.82)	48 fewer per 1000 (139 fewer to 43 more)	very low
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)</b>											
1 (vianna 2018)	RC T	serious <sup>1</sup>	not serious	NA <sup>4</sup>	very serious <sup>5</sup>	NA	0/21	0/21	RD 0.00 (-0.09, 0.09)	0 fewer per 1000 (88 fewer to 88 more)	very low
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 12 month(s)</b>											
1 (vianna 2018)	RC T	serious <sup>1</sup>	not serious	NA <sup>4</sup>	serious <sup>5</sup>	NA	7/21	2/21	RR 3.50 (0.82, 14.93)	238 more per 1000 (17 fewer to 1326 more)	low
<b>hba1c change (% , lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)</b>											
2	RC T	very serious <sup>6</sup>	not serious	not serious	not serious	NA	414	407	MD -0.07 (-0.23, 0.09)	MD 0.07 lower (0.23 lower to 0.09 higher)	low
<b>weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 8.8 month(s)</b>											
2	RC T	very serious <sup>6</sup>	not serious	not serious	not serious	NA	512	532	MD 1.22 (0.47, 1.97)	MD 1.22 higher (0.47 higher to 1.97 higher)	low

1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
4. Only one study so no inconsistency
5. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
5. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
6. >33.3% of the studies in the meta-analysis were at high risk of bias

### L.1.6.2 Adding glimepiride compared to adding placebo

**Table 60: Clinical evidence profile: Adding glimepiride compared to adding placebo**

No of studies	D es ig n	Risk of bias	Indi rect ness	Inco nsist ency	Impr ecisi on	Other conside rations	Inter venti on N	Co ntr ol N	Relative effect (95% CI)	Absolute effect	Cer tai nty
<b>health-related quality of life - overall health utilities index mark 3 (higher values are better, change scores) at end of follow-up Mean follow-up: 6 month(s)</b>											
1 (roberts 2005)	R C T	very seri ous <sup>1</sup>	not seri ous	NA <sup>2</sup>	serio us <sup>3</sup>	NA	82	77	MD 0.03 (- 0.02, 0.08)	MD 0.03 higher (0.02 lower to 0.08 higher)	ver y low
<b>all-cause mortality at end of follow up Mean follow-up: 5.8 month(s)</b>											
2	R C T	very seri ous <sup>1</sup>	not seri ous	not serio us	serio us <sup>4</sup>	NA	0/15 4	0/1 46	RD 0.00 (- 0.02, 0.02)	0 fewer per 1000 (18 fewer to 18 more)	ver y low
<b>cardiovascular mortality at end of follow up Mean follow-up: 5.8 month(s)</b>											

2	R C T	very seri ous <sup>1</sup>	not seri ous	not serio us	serio us <sup>4</sup>	NA	0/15 4	0/1 46	RD 0.00 (- 0.02, 0.02)	0 fewer per 1000 (18 fewer to 18 more)	ver y low
<b>non-fatal stroke at end of follow up Mean follow-up: 5.5 month(s)</b>											
1 (riddle 1998)	R C T	very seri ous <sup>1</sup>	not seri ous	NA <sup>2</sup>	very serio us <sup>5</sup>	NA	1/70	0/6 2	PETO OR 6.59 (0.13, 334.58)	14 more per 1000 (13 fewer to 42 more)	ver y low
<b>non-fatal myocardial infarction at end of follow up Mean follow-up: 5.8 month(s)</b>											
2	R C T	very seri ous <sup>1</sup>	not seri ous	serio us <sup>6</sup>	very serio us <sup>5</sup>	NA	1/15 4	3/1 46	RR 0.41 (0.06, 2.72)	12 fewer per 1000 (19 fewer to 35 more)	ver y low
<b>death from renal causes at end of follow up Mean follow-up: 24 month(s)</b>											
1 (nauck 2009b)	R C T	very seri ous <sup>1</sup>	not seri ous	NA <sup>2</sup>	not serio us	NA	0/24 2	0/1 21	RD 0.00 (- 0.01, 0.01)	0 fewer per 1000 (13 fewer to 13 more)	low
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 14.9 month(s)</b>											
4	R C T	very seri ous <sup>1</sup>	not seri ous	very serio us <sup>7</sup>	serio us <sup>8</sup>	NA	164/ 703	23/ 36 8	RR 3.75 (1.25, 11.25)	172 more per 1000 (15 more to 641 more)	ver y low
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 14.9 month(s)</b>											
4	R C T	very seri ous <sup>1</sup>	not seri ous	serio us <sup>6</sup>	very serio us <sup>9</sup>	NA	1/70 3	1/5 69	RD -0.00 (-0.01, 0.01)	1 fewer per 1000 (9 fewer to 8 more)	ver y low
<b>hba1c change (% , lower values are better, change scores and final values) at end of follow up Mean follow-up: 10.6 month(s)</b>											
4	R C T	very seri ous <sup>1</sup>	not seri ous	very serio us <sup>7</sup>	serio us <sup>10</sup>	NA	419	27 5	MD -0.69 (-1.10, - 0.29)	MD 0.69 lower (1.10 lower to 0.29 lower)	ver y low

<b>weight change (kg, lower values are better, change scores and final values) at end of follow up Mean follow-up: 5.8 month(s)</b>											
2	R C T	very seri ous <sup>1</sup>	not seri ous	very serio us <sup>7</sup>	very serio us <sup>11</sup>	NA	152	13 9	MD -0.24 (-8.30, 7.81)	MD 0.24 lower (8.30 lower to 7.81 higher)	ver y low
<b>bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)</b>											
1 (roberts 2005)	R C T	very seri ous <sup>1</sup>	not seri ous	NA <sup>2</sup>	serio us <sup>12</sup>	NA	82	77	MD 1.09 (0.65, 1.53)	MD 1.09 higher (0.65 higher to 1.53 higher)	ver y low

1. >33.3% of the studies in the meta-analysis were at high risk of bias
2. Only one study so no inconsistency
3. 95% confidence intervals cross one end of the defined MIDs (-0.05, 0.05)
4. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
5. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
6. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
7. I<sup>2</sup> > 75%
8. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
9. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.04 (0.8-0.9 = serious, <0.8 = very serious).
10. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
11. 95% confidence intervals cross both ends of the defined MIDs (-2.40, 2.40)
12. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

## L.1.6.3 Adding glimepiride compared to adding metformin

Table 61: Clinical evidence profile: Adding glimepiride compared to adding metformin

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
<b>hypoglycaemia episodes at end of follow up</b> <b>Mean follow-up: 5.5 month(s)</b>											
1 (park 2014)	RCT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>3</sup>	NA	20/34	15/33	RR 1.29 (0.81, 2.07)	134 more per 1000 (86 fewer to 485 more)	very low
<b>at night hypoglycaemic episodes at end of follow up</b> <b>Mean follow-up: 5.5 month(s)</b>											
1 (park 2014)	RCT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>4</sup>	NA	6/34	3/33	RR 1.94 (0.53, 7.13)	86 more per 1000 (43 fewer to 557 more)	very low
<b>severe hypoglycaemic episodes at end of follow up</b> <b>Mean follow-up: 5.5 month(s)</b>											
1 (park 2014)	RCT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>5</sup>	NA	0/34	0/33	RD 0.00 (-0.06, 0.06)	0 fewer per 1000 (56 fewer to 56 more)	very low
<b>hba1c change (% , lower values are better, change scores) at end of follow up</b> <b>Mean follow-up: 5.5 month(s)</b>											
1 (park 2014)	RCT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>6</sup>	NA	32	32	MD 0.05 (-0.52, 0.62)	MD 0.05 higher (0.52 lower to 0.62 higher)	very low

1. >33.3% of the studies in the meta-analysis were at high risk of bias
2. Only one study so no inconsistency
3. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
4. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
5. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
6. 95% confidence intervals cross both ends of the defined MIDs (-0.50, 0.50)

#### L.1.6.4 Adding glimepiride compared to adding insulin

**Table 62: Clinical evidence profile: Adding glimepiride compared to adding insulin**

No of studies	De sig n	Risk of bias	Indir ectn ess	Incon sisten cy	Impr ecisi on	Other consider ations	Interv entio n N	Con trol N	Relative effect (95% CI)	Absolute effect	Cer tain ty
<b>health-related quality of life - subscale mental component (sf-36, higher values are better, change scores) at end of follow up Mean follow-up: 24 month(s)</b>											
1 (group 2022)	R CT	very serio us <sup>1</sup>	not serio us	NA <sup>2</sup>	not serio us	NA	1222	120 9	MD 0.18 (-0.42, 0.78)	MD 0.18 higher (0.42 lower to 0.78 higher)	low
<b>health-related quality of life - subscale physical component (sf-36, higher values are better, change scores) at end of follow up Mean follow-up: 12 month(s)</b>											
1 (group 2022)	R CT	very serio us <sup>1</sup>	not serio us	NA <sup>2</sup>	not serio us	NA	1222	120 9	MD 0.00 (-0.55, 0.55)	MD 0.00 lower	low

										(0.55 lower to 0.55 higher)	
<b>all-cause mortality at end of follow up</b>											
<b>Mean follow-up: 60 month(s)</b>											
1 (group 2022)	R CT	serious <sup>3</sup>	not serious	NA <sup>2</sup>	very serious <sup>4</sup>	NA	43/12 51	41/ 126 1	RR 1.06 (0.69, 1.61)	2 more per 1000 (10 fewer to 20 more)	very low
<b>all-cause mortality at end of follow up</b>											
<b>Mean follow-up: 60 month(s)</b>											
1 (group 2022)	R CT	serious <sup>3</sup>	not serious	NA <sup>2</sup>	very serious <sup>4</sup>	NA	1247	125 7	HR 1.04 (0.68, 1.58)	Not estimable	very low
<b>cardiovascular mortality at end of follow up</b>											
<b>Mean follow-up: 60 month(s)</b>											
1 (group 2022)	R CT	serious <sup>3</sup>	not serious	NA <sup>2</sup>	very serious <sup>4</sup>	NA	16/12 44	21/ 125 5	RR 0.77 (0.40, 1.47)	4 fewer per 1000 (10 fewer to 8 more)	very low
<b>cardiovascular mortality at end of follow-up</b>											
<b>Mean follow-up: 60 month(s)</b>											
1 (group 2022)	R CT	serious <sup>3</sup>	not serious	NA <sup>2</sup>	very serious <sup>4</sup>	NA	1247	125 7	HR 0.78 (0.40, 1.48)	Not estimable	very low
<b>3-point mace at end of follow up</b>											
<b>Mean follow-up: 60 month(s)</b>											
1 (group 2022)	R CT	serious <sup>3</sup>	not serious	NA <sup>2</sup>	very serious <sup>4</sup>	NA	59/12 44	65/ 125 5	RR 0.92 (0.65, 1.29)	4 fewer per 1000 (18 fewer to 15 more)	very low
<b>3-point mace at end of follow up</b>											
<b>Mean follow-up: 60 month(s)</b>											
1 (group 2022)	R CT	serious <sup>3</sup>	not serious	NA <sup>2</sup>	very serious <sup>4</sup>	NA	1247	125 7	HR 0.92 (0.65, 1.30)	Not estimable	very low

<b>4-point mace at end of follow up</b>											
<b>Mean follow-up: 60 month(s)</b>											
1 (group 2022)	R CT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>4</sup>	NA	67/12 54	71/ 126 3	RR 0.95 (0.69, 1.31)	3 fewer per 1000 (18 fewer to 18 more)	ver y low
<b>unstable angina at end of follow up</b>											
<b>Mean follow-up: 60 month(s)</b>											
1 (group 2022)	R CT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>4</sup>	NA	12/12 54	15/ 126 8	RR 0.81 (0.38, 1.72)	2 fewer per 1000 (7 fewer to 9 more)	ver y low
<b>hospitalisation for heart failure at end of follow up</b>											
<b>Mean follow-up: 60 month(s)</b>											
1 (group 2022)	R CT	serious <sup>3</sup>	not serious	NA <sup>2</sup>	very serious <sup>4</sup>	NA	30/12 44	26/ 125 5	RR 1.16 (0.69, 1.96)	3 more per 1000 (6 fewer to 20 more)	ver y low
<b>hospitalisation for heart failure at end of follow up</b>											
<b>Mean follow-up: 60 month(s)</b>											
1 (group 2022)	R CT	serious <sup>3</sup>	not serious	NA <sup>2</sup>	very serious <sup>4</sup>	NA	1247	126 4	HR 1.16 (0.69, 1.96)	Not estimable	ver y low
<b>hypoglycaemia episodes at end of follow up</b>											
<b>Mean follow-up: 54 month(s)</b>											
2	R CT	very serious <sup>1</sup>	not serious	not serious	not serious	NA	673/1 265	484 /12 83	RR 1.41 (1.29, 1.54)	155 more per 1000 (110 more to 203 more)	low
<b>hypoglycaemia episodes at end of follow up</b>											
<b>Mean follow-up: 60 month(s)</b>											
1 (group 2022)	R CT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	1231	124 5	HR 1.61 (1.43, 1.81)	Not estimable	low
<b>severe hypoglycaemic episodes at end of follow up</b>											

Mean follow-up: 54 month(s)											
2	R CT	very serious <sup>1</sup>	not serious	serious <sup>5</sup>	very serious <sup>6</sup>	NA	28/12 88	16/ 130 1	RD 0.01 (-0.00, 0.02)	9 more per 1000 (1 fewer to 19 more)	ver y low
hba1c change (% , lower values are better, change scores and final values) at end of follow up Mean follow-up: 35.5 month(s)											
2	R CT	very serious <sup>1</sup>	not serious	not serious	very serious <sup>7</sup>	NA	344	464	MD 0.00 (-0.56, 0.57)	MD 0.00 higher (0.56 lower to 0.57 higher)	ver y low
weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 11 month(s)											
1 (moon 2014)	R CT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>8</sup>	NA	34	38	MD -1.70 (-3.05, - 0.35)	MD 1.70 lower (3.05 lower to 0.35 lower)	ver y low

- >33.3% of the studies in the meta-analysis were at high risk of bias
- Only one study so no inconsistency
- >33.3% of the studies in the meta-analysis were at moderate risk of bias
- 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.75 (0.8-0.9 = serious, <0.8 = very serious).
- 95% confidence intervals cross both ends of the defined MIDs (-0.50, 0.50)

8. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

### L.1.6.5 Adding glimepiride compared to adding canagliflozin

**Table 63: Clinical evidence profile: Adding glimepiride compared to adding canagliflozin**

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerat ions	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>all-cause mortality at end of follow up</b> Mean follow-up: 24 month(s)											
1 (cevalu 2013)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	very seriou s <sup>2</sup>	NA	2/482	2/96 8	RR 2.01 (0.28, 14.21)	2 more per 1000 (1 fewer to 27 more)	low
<b>cardiovascular mortality at end of follow up</b> Mean follow-up: 24 month(s)											
1 (cevalu 2013)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	seriou s <sup>3</sup>	NA	2/482	0/96 8	PETO OR 20.30 (1.07, 385.05)	4 more per 1000 (2 fewer to 10 more)	mod erat e
<b>death from renal causes at end of follow up</b> Mean follow-up: 24 month(s)											
1 (cevalu 2013)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	very seriou s <sup>2</sup>	NA	0/482	1/96 8	PETO OR 0.22 (0.00, 14.33)	1 fewer per 1000 (3 fewer to 1 more)	low
<b>hypoglycaemia episodes at end of follow up</b> Mean follow-up: 24 month(s)											
1 (cevalu 2013)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	not seriou s	NA	197/48 2	71/9 68	RR 5.57 (4.35, 7.14)	335 more per 1000 (245 more to 451 more)	high

<b>severe hypoglycaemic episodes at end of follow up</b> <b>Mean follow-up: 24 month(s)</b>											
1 (cevalu 2013)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	not seriou s	NA	16/482	4/96 8	RR 8.03 (2.70, 23.90)	29 more per 1000 (7 more to 95 more)	high
<b>hba1c change (% , lower values are better, change scores) at end of follow up</b> <b>Mean follow-up: 24 month(s)</b>											
1 (cevalu 2013,cevalu 2013)	RC T	very seriou s <sup>4</sup>	not seriou s	NA <sup>1</sup>	not seriou s	NA	482	968	MD 0.14 (0.05, 0.22)	MD 0.14 higher (0.05 higher to 0.22 higher)	low
<b>weight change (kg, lower values are better, change scores) at end of follow up</b> <b>Mean follow-up: 24 month(s)</b>											
1 (cevalu 2013,cevalu 2013)	RC T	very seriou s <sup>4</sup>	not seriou s	NA <sup>1</sup>	not seriou s	NA	482	968	MD 5.15 (4.76, 5.54)	MD 5.15 higher (4.76 higher to 5.54 higher)	low

1. Only one study so no inconsistency
2. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
3. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
4. >33.3% of the studies in the meta-analysis were at high risk of bias

L.1.6.6 Adding glimepiride compared to adding dapagliflozin

**Table 64: Clinical evidence profile: Adding glimepiride compared to adding dapagliflozin**

No of studies	Des ign	Risk of bias	Indirec tness	Inconsis tency	Impreci sion	Other consideratio ns	Interven tion N	Contr ol N	Relative effect (95% CI)	Absolute effect	Certa nty
<b>all-cause mortality at end of follow up</b>											
<b>Mean follow-up: 12 month(s)</b>											
1 (park 2023)	RC T	not serious	not serious	NA <sup>1</sup>	serious <sup>2</sup>	NA	0/61	0/60	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (32 fewer to 32 more)	mode rate
<b>cardiovascular mortality at end of follow up</b>											
<b>Mean follow-up: 12 month(s)</b>											
1 (park 2023)	RC T	not serious	not serious	NA <sup>1</sup>	serious <sup>2</sup>	NA	0/61	0/60	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (32 fewer to 32 more)	mode rate
<b>hospitalisation for heart failure at end of follow up</b>											
<b>Mean follow-up: 12 month(s)</b>											
1 (muller-wieland 2018)	RC T	not serious	not serious	NA <sup>1</sup>	very serious <sup>3</sup>	NA	1/312	0/313	PETO OR 7.41 (0.15, 373.58)	3 more per 1000 (3 fewer to 9 more)	low
<b>hypoglycaemia episodes at end of follow up</b>											

	<b>Mean follow-up: 10.2 month(s)</b>											
3		RC T	not serious	not serious	serious <sup>4</sup>	not serious	NA	22/403	3/404	PETO OR 4.87 (2.18, 10.84)	47 more per 1000 (24 more to 71 more)	moderate
	<b>severe hypoglycaemic episodes at end of follow up</b>											
	<b>Mean follow-up: 12 month(s)</b>											
1 (muller-wieland 2018)		RC T	not serious	not serious	NA <sup>1</sup>	not serious	NA	0/312	0/313	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	high
	<b>hba1c change (% , lower values are better, change scores)</b>											
	<b>Mean follow-up: 10.2 month(s)</b>											
3		RC T	not serious	not serious	very serious <sup>5</sup>	serious <sup>6</sup>	NA	394	397	MD 0.14 (-0.29, 0.57)	MD 0.14 higher (0.29 lower to 0.57 higher)	very low
	<b>weight change (kg, lower values are better, change score) at end of follow up</b>											
	<b>Mean follow-up: 10.2 month(s)</b>											
3		RC T	not serious	not serious	very serious <sup>5</sup>	very serious <sup>7</sup>	NA	397	399	MD 1.59 (-4.00, 7.18)	MD 1.59 higher (4.00 lower to 7.18 higher)	very low

<b>bmi change (kg/m2, lower values are better, change scores) at end of follow up</b>											
<b>Mean follow-up: 12 month(s)</b>											
1 (park 2023)	RC T	not serious	not serious	NA <sup>1</sup>	not serious	NA	56	56	MD 1.37 (1.00, 1.74)	MD 1.37 higher (1.00 higher to 1.74 higher)	high

1. Only one study so no inconsistency
2. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
4. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
5. I2 > 75%
6. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
7. 95% confidence intervals cross both ends of the defined MIDs (-2.40, 2.40)

**L.1.6.7 Adding glimepiride compared to adding empagliflozin**

**Table 65: Clinical evidence profile: Adding glimepiride compared to adding empagliflozin**

No of studies	Des ign	Risk of bias	Indirec tness	Inconsis tency	Impreci sion	Other consideratio ns	Interven tion N	Contr ol N	Relative effect (95% CI)	Absolute effect	Certa inty
<b>all-cause mortality at end of follow up</b>											
<b>Mean follow-up: 48 month(s)</b>											

1 (ridderstrale 2014)	RC T	not serious	not serious	NA <sup>1</sup>	very serious <sup>2</sup>	NA	5/780	5/765	RR 0.98 (0.29, 3.37)	0 fewer per 1000 (5 fewer to 16 more)	low
<b>hypoglycaemia episodes at end of follow up</b> <b>Mean follow-up: 48 month(s)</b>											
1 (ridderstrale 2014)	RC T	not serious	not serious	NA <sup>1</sup>	not serious	NA	189/780	19/76 5	RR 9.76 (6.15, 15.47)	217 more per 1000 (128 more to 359 more)	high
<b>hba1c change (% , lower values are better, change scores) at end of follow up</b> <b>Mean follow-up: 48 month(s)</b>											
1 (ridderstrale 2014)	RC T	not serious	not serious	NA <sup>1</sup>	not serious	NA	780	765	MD 0.11 (0.03, 0.19)	MD 0.11 higher (0.03 higher to 0.19 higher)	high
<b>weight change (kg, lower values are better, change scores) at end of follow up</b> <b>Mean follow-up: 48 month(s)</b>											
1 (ridderstrale 2014)	RC T	not serious	not serious	NA <sup>1</sup>	not serious	NA	780	765	MD 4.61 (4.18, 5.04)	MD 4.61 higher (4.18 higher to 5.04 higher)	high

1. Only one study so no inconsistency

2. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

## L.1.6.8 Adding glimepiride compared to adding ertugliflozin

Table 66: Clinical evidence profile: Adding glimepiride compared to adding ertugliflozin

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerat ions	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>all-cause mortality at end of follow up Mean follow-up: 12 month(s)</b>											
1 (hollander 2018)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	seriou s <sup>3</sup>	NA	0/437	6/88 8	PETO OR 0.22 (0.04, 1.23)	7 fewer per 1000 (12 fewer to 1 fewer)	very low
<b>cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)</b>											
1 (hollander 2018)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>4</sup>	NA	0/435	1/88 0	PETO OR 0.22 (0.00, 14.46)	1 fewer per 1000 (3 fewer to 1 more)	very low
<b>acute kidney injury at end of follow up Mean follow-up: 12 month(s)</b>											
1 (hollander 2018)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>4</sup>	NA	0/437	1/88 8	RR 0.68 (0.03, 16.57)	0 fewer per 1000 (1 fewer to 18 more)	very low
<b>diabetic ketoacidosis at end of follow up Mean follow-up: 12 month(s)</b>											
1 (hollander 2018)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>4</sup>	NA	0/437	1/88 8	PETO OR 0.22 (0.00, 14.54)	1 fewer per 1000 (3 fewer to 1 more)	very low
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 12 month(s)</b>											

1 (hollander 2018)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	not seriou s	NA	84/437	37/8 88	RR 4.61 (3.19, 6.67)	151 more per 1000 (91 more to 236 more)	low
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)</b>											
1 (hollander 2018)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	not seriou s	NA	10/437	2/88 8	RR 10.16 (2.24, 46.17)	21 more per 1000 (3 more to 102 more)	low
<b>hba1c change (% , lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)</b>											
1 (hollander 2018)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	not seriou s	NA	437	888	MD -0.10 (-0.17, - 0.03)	MD 0.10 lower (0.17 lower to 0.03 lower)	low
<b>weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)</b>											
1 (hollander 2018)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	not seriou s	NA	437	888	MD 4.10 (3.67, 4.53)	MD 4.10 higher (3.67 higher to 4.53 higher)	low

1. >33.3% of the studies in the meta-analysis were at high risk of bias
2. Only one study so no inconsistency
3. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
4. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

## L.1.6.9 Adding glimepiride compared to adding exenatide

Table 67: Clinical evidence profile: Adding glimepiride compared to adding exenatide

	De sig n	Risk of bias	Indire ctnes s	Incons istenc y	Impre cision	Other considera tions	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>No of studies</b>											
<b>all-cause mortality at end of follow up</b> <b>Mean follow-up: 36 month(s)</b>											
1 (gallwitz 2012b)	RC T	not serio us	not seriou s	NA <sup>1</sup>	very seriou s <sup>2</sup>	NA	5/508	5/51 1	RR 1.01 (0.29, 3.45)	0 more per 1000 (7 fewer to 24 more)	low
<b>hypoglycaemia episodes at end of follow up</b> <b>Mean follow-up: 24 month(s)</b>											
2	RC T	not serio us	not seriou s	seriou s <sup>3</sup>	not seriou s	NA	341/56 2	186/ 568	RR 1.84 (1.62, 2.10)	276 more per 1000 (202 more to 360 more)	high
<b>at night hypoglycaemic episodes at end of</b> <b>follow up</b> <b>Mean follow-up: 36 month(s)</b>											
1 (gallwitz 2012b)	RC T	not serio us	not seriou s	NA <sup>1</sup>	seriou s <sup>4</sup>	NA	82/508	53/5 11	RR 1.56 (1.13, 2.15)	58 more per 1000 (13 more to 119 more)	mod erat e
<b>severe hypoglycaemic episodes at end of</b> <b>follow up</b> <b>Mean follow-up: 36 month(s)</b>											
1 (gallwitz 2012b)	RC T	not serio us	not seriou s	NA <sup>1</sup>	very seriou s <sup>2</sup>	NA	0/508	1/51 1	PETO OR 0.14 (0.00, 6.86)	2 fewer per 1000 (6 fewer to 2 more)	low

<b>hba1c change (% , lower values are better, change scores and final values) at end of follow up</b> <b>Mean follow-up: 24 month(s)</b>											
2	RC T	not serio us	not seriou s	very seriou s <sup>5</sup>	not seriou s	NA	246	234	MD 0.03 (-0.04, 0.10)	MD 0.03 higher (0.04 lower to 0.10 higher)	low
<b>weight change (kg, lower values are better, change scores and final values) at end of follow up</b> <b>Mean follow-up: 24 month(s)</b>											
2	RC T	not serio us	not seriou s	very seriou s <sup>5</sup>	not seriou s	NA	560	560	MD -4.03 (-4.61, - 3.45)	MD 4.03 lower (4.61 lower to 3.45 lower)	low
<b>bmi change (kg/m2, lower values are better, change scores and final values) at end of follow up</b> <b>Mean follow-up: 24 month(s)</b>											
2	RC T	not serio us	not seriou s	not seriou s	not seriou s	NA	560	0	MD 1.79 (1.53, 2.04)	MD 1.79 higher (1.53 higher to 2.04 higher)	high

1. Only one study so no inconsistency
2. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
3. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
4. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
5. I2 > 75%

## L.1.6.10 Adding glimepiride compared to adding gliclazide

Table 68: Clinical evidence profile: Adding glimepiride compared to adding gliclazide

	De sig n	Risk of bias	Indir ectn ess	Incon sisten cy	Impr ecisi on	Other consider ations	Interv entio n N	Con trol N	Relative effect (95% CI)	Absolute effect	Cer tain ty
<b>No of studies</b>											
<b>all-cause mortality at end of follow up Mean follow-up: 5.5 month(s)</b>											
1 (xu 2017)	R C T	very serio us <sup>1</sup>	not serio us	NA <sup>2</sup>	not serio us	NA	0/549	0/5 50	RD 0.00 (- 0.00, 0.00)	0 fewer per 1000 (4 fewer to 4 more)	low
<b>cardiovascular mortality at end of follow up Mean follow-up: 5.5 month(s)</b>											
1 (xu 2017)	R C T	very serio us <sup>1</sup>	not serio us	NA <sup>2</sup>	not serio us	NA	0/549	0/5 50	RD 0.00 (- 0.00, 0.00)	0 fewer per 1000 (4 fewer to 4 more)	low
<b>non-fatal stroke at end of follow up Mean follow-up: 5.5 month(s)</b>											
1 (xu 2017)	R C T	very serio us <sup>1</sup>	not serio us	NA <sup>2</sup>	not serio us	NA	0/549	0/5 50	RD 0.00 (- 0.00, 0.00)	0 fewer per 1000 (4 fewer to 4 more)	low
<b>non-fatal myocardial infaRCTION at end of follow up Mean follow-up: 5.5 month(s)</b>											
1 (xu 2017)	R C T	very serio us <sup>1</sup>	not serio us	NA <sup>2</sup>	very serio us <sup>3</sup>	NA	0/549	2/5 50	PETO OR 0.14 (0.01, 2.17)	4 fewer per 1000 (9 fewer to 1 more)	ver y low
<b>diabetic ketoacidosis at end of follow up Mean follow-up: 5.5 month(s)</b>											
1 (xu 2017)	R C T	very serio us <sup>1</sup>	not serio us	NA <sup>2</sup>	very serio us <sup>3</sup>	NA	0/549	1/5 50	PETO OR 0.14 (0.00, 6.83)	2 fewer per 1000 (5 fewer to 2 more)	ver y low
<b>falls requiring hospitalisation at end of follow-up Mean follow-up: 5.5 month(s)</b>											

1 (xu 2017)	R C T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	0/549	0/550	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (4 fewer to 4 more)	low
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 5.5 month(s)</b>											
1 (xu 2017)	R C T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	49/549	20/550	RR 2.45 (1.48, 4.07)	53 more per 1000 (17 more to 112 more)	low
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 5.5 month(s)</b>											
1 (xu 2017)	R C T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	1/549	0/550	RR 3.01 (0.12, 73.62)	0 fewer per 1000 (0 more to 0 more)	very low
<b>hba1c change (% , lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)</b>											
1 (xu 2017)	R C T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	414	418	MD 0.05 (-0.11, 0.21)	MD 0.05 higher (0.11 lower to 0.21 higher)	low
<b>weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)</b>											
1 (xu 2017)	R C T	not serious	not serious	NA <sup>2</sup>	not serious	NA	549	550	MD 0.24 (0.05, 0.43)	MD 0.24 higher (0.05 higher to 0.43 higher)	high

1. >33.3% of the studies in the meta-analysis were at high risk of bias
2. Only one study so no inconsistency
3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

## L.1.6.11 Adding glimepiride compared to adding linagliptin

Table 69: Clinical evidence profile: Adding glimepiride compared to adding linagliptin

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>all-cause mortality at end of follow up Mean follow-up: 49.8 month(s)</b>											
2	RC T	not serio us	not seriou s	not serious	seriou s <sup>1</sup>	NA	340/37 85	312/ 3799	RR 1.09 (0.95, 1.27)	8 more per 1000 (4 fewer to 22 more)	mod erat e
<b>all-cause mortality at end of follow up Mean follow-up: 75.6 month(s)</b>											
1 (rosenstock 2019b)	RC T	not serio us	not seriou s	NA <sup>2</sup>	seriou s <sup>1</sup>	NA	3023	3010	HR 1.10 (0.94, 1.28)	Not estimable	mod erat e
<b>cardiovascular mortality at end of follow up Mean follow-up: 49.8 month(s)</b>											
2	RC T	not serio us	not seriou s	not serious	not seriou s	NA	170/37 85	171/ 3799	RR 1.00 (0.81, 1.23)	0 fewer per 1000 (8 fewer to 10 more)	high
<b>cardiovascular mortality at end of follow up Mean follow-up: 75.6 month(s)</b>											
1 (rosenstock 2019b)	RC T	not serio us	not seriou s	NA <sup>2</sup>	not seriou s	NA	3023	3010	HR 1.00 (0.81, 1.23)	Not estimable	high
<b>4-point mace at end of follow up Mean follow-up: 75.6 month(s)</b>											
1 (rosenstock 2019b)	RC T	not serio us	not seriou s	NA <sup>2</sup>	not seriou s	NA	401/30 10	398/ 3023	RR 1.01 (0.89, 1.15)	2 more per 1000	high

										(15 fewer to 20 more)	
<b>4-point mace at end of follow up</b>											
<b>Mean follow-up: 75.6 month(s)</b>											
1 (rosenstock 2019b)	RC T	not serio us	not seriou s	NA <sup>2</sup>	not seriou s	NA	3010	3023	HR 1.01 (0.88, 1.16)	Not estimable	high
<b>non-fatal stroke at end of follow up</b>											
<b>Mean follow-up: 49.8 month(s)</b>											
2	RC T	not serio us	not seriou s	serious <sup>3</sup>	very seriou s <sup>4</sup>	NA	115/37 85	94/3 799	RR 1.73 (0.58, 5.14)	18 more per 1000 (10 fewer to 103 more)	very low
<b>non-fatal stroke at end of follow up</b>											
<b>Mean follow-up: 75.6 month(s)</b>											
1 (rosenstock 2019b)	RC T	not serio us	not seriou s	NA <sup>2</sup>	seriou s <sup>1</sup>	NA	3010	3023	HR 1.15 (0.87, 1.52)	Not estimable	mod erat e
<b>non-fatal myocardial infarction at end of follow up</b>											
<b>Mean follow-up: 24 month(s)</b>											
1 (gallwitz 2012a)	RC T	not serio us	not seriou s	NA <sup>2</sup>	very seriou s <sup>4</sup>	NA	10/775	6/77 6	RR 1.67 (0.61, 4.57)	5 more per 1000 (3 fewer to 28 more)	low
<b>non-fatal myocardial infarction at end of follow-up</b>											
<b>Mean follow-up: 75.6 month(s)</b>											
1 (rosenstock 2019b)	RC T	not serio us	not seriou s	NA <sup>2</sup>	very seriou s <sup>4</sup>	NA	142	145	HR 0.99 (0.78, 1.26)	Not estimable	low
<b>unstable angina at end of follow up</b>											
<b>Mean follow-up: 49.8 month(s)</b>											
2	RC T	not serio us	not seriou s	not serious	very seriou s <sup>4</sup>	NA	59/378 5	63/3 799	RR 0.94 (0.66, 1.34)	1 fewer per 1000	low

										(6 fewer to 6 more)	
<b>unstable angina at end of follow-up</b> <b>Mean follow-up: 75.6 month(s)</b>											
1 (rosenstock 2019b)	RC T	not serious	not serious	NA <sup>2</sup>	very serious <sup>4</sup>	NA	56	60	HR 0.93 (0.65, 1.33)	Not estimable	low
<b>hospitalisation for heart failure at end of follow up</b> <b>Mean follow-up: 49.8 month(s)</b>											
2	RC T	not serious	not serious	not serious	serious <sup>1</sup>	NA	94/3785	115/3799	RR 0.82 (0.63, 1.07)	5 fewer per 1000 (11 fewer to 2 more)	moderate
<b>hospitalisation for heart failure at end of follow-up</b> <b>Mean follow-up: 75.6 month(s)</b>											
1 (rosenstock 2019b)	RC T	not serious	not serious	NA <sup>2</sup>	serious <sup>1</sup>	NA	92	112	HR 0.83 (0.63, 1.09)	Not estimable	moderate
<b>falls requiring hospitalisation at end of follow up</b> <b>Mean follow-up: 24 month(s)</b>											
1 (gallwitz 2012a)	RC T	not serious	not serious	NA <sup>2</sup>	very serious <sup>4</sup>	NA	2/775	3/776	RR 0.67 (0.11, 3.98)	1 fewer per 1000 (3 fewer to 12 more)	low
<b>hypoglycaemia episodes at end of follow up</b> <b>Mean follow-up: 49.8 month(s)</b>											
2	RC T	not serious	not serious	very serious <sup>5</sup>	not serious	NA	1412/3785	378/3799	RR 4.05 (3.00, 5.45)	303 more per 1000 (199 more to 443 more)	low
<b>hypoglycaemia episodes at end of follow up</b>											

<b>Mean follow-up: 75.6 month(s)</b>											
1 (rosenstock 2019b)	RC T	not serio us	not seriou s	NA <sup>2</sup>	not seriou s	NA	3010	3023	HR 4.35 (3.85, 4.91)	Not estimable	high
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 49.8 month(s)</b>											
2	RC T	not serio us	not seriou s	not serious	not seriou s	NA	77/378 5	11/3 799	RR 7.03 (3.74, 13.20)	17 more per 1000 (8 more to 35 more)	high
<b>severe hypoglycaemic episodes at end of follow-up Mean follow-up: 75.6 month(s)</b>											
1 (rosenstock 2019b)	RC T	not serio us	not seriou s	NA <sup>2</sup>	not seriou s	NA	3010	3023	HR 5.63 (4.76, 6.67)	Not estimable	high
<b>hba1c change (% , lower values are better, change scores) at end of follow up Mean follow-up: 49.8 month(s)</b>											
2	RC T	not serio us	not seriou s	very serious <sup>5</sup>	not seriou s	NA	3765	3787	MD -0.09 (-0.30, 0.11)	MD 0.09 lower (0.30 lower to 0.11 higher)	low
<b>weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 49.8 month(s)</b>											
2	RC T	not serio us	not seriou s	very serious <sup>5</sup>	seriou s <sup>6</sup>	NA	3786	3798	MD 2.10 (0.96, 3.24)	MD 2.10 higher (0.96 higher to 3.24 higher)	very low

1. 95% confidence intervals cross one end of the defined MID (0.80, 1.25)

2. Only one study so no inconsistency
3. I2 between 50% and 75%
4. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
5. I2 > 75%
6. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

#### L.1.6.12 Adding glimepiride compared to adding liraglutide

**Table 70: Clinical evidence profile: Adding glimepiride compared to adding liraglutide**

No of studies	De sig n	Risk of bias	Indir ectn ess	Incon sisten cy	Impr ecisi on	Other consider ations	Interv entio n N	Con trol N	Relative effect (95% CI)	Absolute effect	Cer tain ty
<b>health-related quality of life - subscale mental component (sf36, higher values are better, change scores) at end of follow up Mean follow-up: 24 month(s)</b>											
1 (group 2022)	R CT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	1222	121 8	MD 0.33 (-0.25, 0.91)	MD 0.33 higher (0.25 lower to 0.91 higher)	low
<b>health-related quality of life - subscale physical component (sf36, higher values are better, change scores) at end of follow up Mean follow-up: 12 month(s)</b>											
1 (group 2022)	R CT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	1222	121 8	MD -0.89 (-1.44, - 0.34)	MD 0.89 lower (1.44 lower to 0.34 lower)	low
<b>all-cause mortality at end of follow up Mean follow-up: 60 month(s)</b>											

1 (group 2022)	R CT	serious <sup>3</sup>	not serious	NA <sup>2</sup>	serious <sup>4</sup>	NA	43/12 54	27/ 126 2	RR 1.60 (1.00, 2.58)	13 more per 1000 (0 more to 34 more)	low
<b>all-cause mortality at end of follow up Mean follow-up: 60 month(s)</b>											
1 (group 2022)	R CT	serious <sup>3</sup>	not serious	NA <sup>2</sup>	serious <sup>4</sup>	NA	1254	126 2	HR 1.61 (1.00, 2.59)	Not estimable	low
<b>cardiovascular mortality at end of follow up Mean follow-up: 60 month(s)</b>											
1 (group 2022)	R CT	serious <sup>3</sup>	not serious	NA <sup>2</sup>	very serious <sup>5</sup>	NA	16/12 47	9/1 251	RR 1.78 (0.79, 4.02)	6 more per 1000 (2 fewer to 22 more)	very low
<b>cardiovascular mortality at end of follow up Mean follow-up: 60 month(s)</b>											
1 (group 2022)	R CT	serious <sup>3</sup>	not serious	NA <sup>2</sup>	very serious <sup>5</sup>	NA	1247	125 1	HR 1.78 (0.79, 4.01)	Not estimable	very low
<b>3-point mace at end of follow up Mean follow-up: 60 month(s)</b>											
1 (group 2022)	R CT	serious <sup>3</sup>	not serious	NA <sup>2</sup>	serious <sup>4</sup>	NA	59/12 47	48/ 125 1	RR 1.23 (0.85, 1.79)	9 more per 1000 (6 fewer to 30 more)	low
<b>3-point mace at end of follow-up Mean follow-up: 60 month(s)</b>											
1 (group 2022)	R CT	serious <sup>3</sup>	not serious	NA <sup>2</sup>	serious <sup>4</sup>	NA	1247	125 1	HR 1.24 (0.85, 1.81)	Not estimable	low
<b>4-point mace at end of follow-up Mean follow-up: 60 month(s)</b>											
1 (group 2022)	R CT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>4</sup>	NA	67/12 54	54/ 126 2	RR 1.25 (0.88, 1.77)	11 more per 1000	very low

										(5 fewer to 33 more)	
<b>hospitalisation for heart failure at end of follow up</b>											
<b>Mean follow-up: 60 month(s)</b>											
1 (group 2022)	R CT	serious <sup>3</sup>	not serious	NA <sup>2</sup>	serious <sup>4</sup>	NA	30/12 44	14/ 124 9	RR 2.15 (1.15, 4.04)	13 more per 1000 (2 more to 34 more)	low
<b>hospitalisation for heart failure at end of follow-up</b>											
<b>Mean follow-up: 60 month(s)</b>											
1 (group 2022)	R CT	serious <sup>3</sup>	not serious	NA <sup>2</sup>	serious <sup>4</sup>	NA	1254	126 2	HR 2.16 (1.14, 4.09)	Not estimable	low
<b>unstable angina at end of follow up</b>											
<b>Mean follow-up: 60 month(s)</b>											
1 (group 2022)	R CT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>5</sup>	NA	12/12 54	7/1 262	RR 1.73 (0.68, 4.37)	4 more per 1000 (2 fewer to 19 more)	very low
<b>death from renal causes at end of follow up</b>											
<b>Mean follow-up: 24 month(s)</b>											
1 (nauck 2009b)	R CT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>5</sup>	NA	0/242	1/7 24	PETO OR 0.26 (0.00, 24.26)	1 fewer per 1000 (4 fewer to 1 more)	very low
<b>hypoglycaemia episodes at end of follow up</b>											
<b>Mean follow-up: 42 month(s)</b>											
2	R CT	very serious <sup>1</sup>	not serious	very serious <sup>6</sup>	very serious <sup>5</sup>	NA	660/1 473	344 /19 57	RR 1.17 (0.32, 4.24)	29 more per 1000 (119 fewer to 569 more)	very low
<b>hypoglycaemia episodes at end of follow up</b>											
<b>Mean follow-up: 60 month(s)</b>											

1 (group 2022)	R CT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	1231	123 3	HR 2.64 (2.32, 3.00)	Not estimable	low
<b>severe hypoglycaemic episodes at end of follow up</b>											
<b>Mean follow-up: 42 month(s)</b>											
2	R CT	very serious <sup>1</sup>	not serious	not serious	serious <sup>4</sup>	NA	28/14 96	13/ 198 6	RR 2.27 (1.18, 4.37)	8 more per 1000 (1 more to 22 more)	very low
<b>hba1c change (% , lower values are better, change scores and final values) at end of follow up</b>											
<b>Mean follow-up: 42 month(s)</b>											
2	R CT	very serious <sup>1</sup>	not serious	not serious	not serious	NA	552	106 1	MD 0.00 (-0.23, 0.23)	MD 0.00 higher (0.23 lower to 0.23 higher)	low

1. >33.3% of the studies in the meta-analysis were at high risk of bias
2. Only one study so no inconsistency
3. >33.3% of the studies in the meta-analysis were at moderate risk of bias
4. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
5. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
6. I<sup>2</sup> > 75%

L.1.6.13 Adding glimepiride compared to adding saxagliptin

Table 71: Clinical evidence profile: Adding glimepiride compared to adding saxagliptin

No of studies	Des ign	Risk of bias	Indirec tness	Inconsis tency	Impreci sion	Other consideratio ns	Interven tion N	Contr ol N	Relative effect (95% CI)	Absolute effect	Certa nty
<b>all-cause mortality at end of follow up</b>											
<b>Mean follow-up: 12 month(s)</b>											
1 (scherthner 2015a)	RC T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	1/359	1/359	RR 1.00 (0.06, 15.93)	0 fewer per 1000 (3 fewer to 42 more)	very low
<b>cardiovascular mortality at end of follow up</b>											
<b>Mean follow-up: 12 month(s)</b>											
1 (scherthner 2015a)	RC T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	0/359	1/359	PETO OR 0.14 (0.00, 6.82)	3 fewer per 1000 (8 fewer to 3 more)	very low
<b>non-fatal myocardial infarction at end of follow up</b>											
<b>Mean follow-up: 11 month(s)</b>											
1 (gu 2019)	RC T	not serious	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	1/188	0/191	PETO OR 7.51 (0.15, 378.42)	5 more per 1000 (5 fewer to 16 more)	low
<b>hypoglycaemia episodes at end of follow up</b>											

	<b>Mean follow-up: 11.5 month(s)</b>											
2	RC T	serious <sup>1</sup>	not serious	not serious	not serious	NA	149/547	27/55 0	RR 5.54 (3.74, 8.18)	223 more per 1000 (135 more to 353 more)	moderate	
	<b>severe hypoglycaemic episodes at end of follow up</b>											
	<b>Mean follow-up: 11 month(s)</b>											
1 (gu 2019)	RC T	not serious	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	1/188	1/191	RR 1.02 (0.06, 16.12)	0 more per 1000 (5 fewer to 79 more)	low	
	<b>hba1c change (% , lower values are better, change scores) at end of follow up</b>											
	<b>Mean follow-up: 11 month(s)</b>											
1 (gu 2019)	RC T	not serious	not serious	NA <sup>2</sup>	not serious	NA	187	186	MD -0.06 (-0.23, 0.11)	MD 0.06 lower (0.23 lower to 0.11 higher)	high	
	<b>weight change (kg, lower values are better, change scores) at end of follow up</b>											
	<b>Mean follow-up: 11.5 month(s)</b>											
2	RC T	serious <sup>1</sup>	not serious	not serious	not serious	NA	472	475	MD 1.70 (1.32, 2.08)	MD 1.70 higher (1.32 higher to 2.08 higher)	moderate	

1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
2. Only one study so no inconsistency
3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

#### L.1.6.14 Adding glimepiride compared to adding sitagliptin

**Table 72: Clinical evidence profile: Adding glimepiride compared to adding sitagliptin**

No of studies	De sig n	Risk of bias	Indire ctnes s	Incons istenc y	Impre cision	Other considera tions	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>all-cause mortality at end of follow up Mean follow-up: 33.5 month(s)</b>											
2	RC T	serious <sup>1</sup>	not serious	serious <sup>2</sup>	very serious <sup>3</sup>	NA	44/177 0	41/1 781	RR 1.08 (0.71, 1.64)	2 more per 1000 (7 fewer to 15 more)	very low
<b>cardiovascular mortality at end of follow up Mean follow-up: 33.5 month(s)</b>											
2	RC T	serious <sup>1</sup>	not serious	serious <sup>2</sup>	very serious <sup>3</sup>	NA	17/176 3	21/1 778	RR 0.82 (0.44, 1.54)	2 fewer per 1000 (7 fewer to 6 more)	very low
<b>3-point mace at end of follow up Mean follow-up: 60 month(s)</b>											
1 (group 2022)	RC T	serious <sup>1</sup>	not serious	NA <sup>4</sup>	serious <sup>5</sup>	NA	59/124 4	69/1 262	RR 0.87 (0.62, 1.22)	7 fewer per 1000 (21 fewer to 12 more)	low
<b>non-fatal stroke at end of follow up Mean follow-up: 5.5 month(s)</b>											
1 (xiao 2016)	RC T	very serious <sup>6</sup>	not serious	NA <sup>4</sup>	very serious <sup>7</sup>	NA	0/18	0/23	RD 0.00 (-0.09, 0.09)	0 fewer per 1000	very low

										(92 fewer to 92 more)	
<b>non-fatal myocardial infarction at end of follow up</b>											
<b>Mean follow-up: 5.5 month(s)</b>											
1 (xiao 2016)	RC T	very serious <sup>6</sup>	not serious	NA <sup>4</sup>	very serious <sup>7</sup>	NA	0/18	0/23	RD 0.00 (-0.09, 0.09)	0 fewer per 1000 (92 fewer to 92 more)	very low
<b>hospitalisation for heart failure at end of follow up</b>											
<b>Mean follow-up: 32.8 month(s)</b>											
2	RC T	serious <sup>1</sup>	not serious	serious <sup>2</sup>	very serious <sup>8</sup>	NA	30/1262	30/1285	RD 0.00 (-0.01, 0.01)	0 more per 1000 (12 fewer to 12 more)	very low
<b>hypoglycaemia episodes at end of follow up</b>											
<b>Mean follow-up: 12.2 month(s)</b>											
3	RC T	not serious	not serious	serious <sup>9</sup>	not serious	NA	146/824	43/1031	RR 4.17 (1.73, 10.03)	132 more per 1000 (30 more to 377 more)	moderate
<b>severe hypoglycaemic episodes at end of follow up</b>											
<b>Mean follow-up: 24.1 month(s)</b>											
4	RC T	very serious <sup>6</sup>	not serious	serious <sup>2</sup>	not serious	NA	39/2285	11/2299	RR 3.12 (1.59, 6.11)	10 more per 1000 (3 more to 24 more)	very low
<b>hba1c change (% , lower values are better, change scores and final values) at end of follow up</b>											
<b>Mean follow-up: 6 month(s)</b>											
3	RC T	very serious <sup>6</sup>	not serious	very serious <sup>10</sup>	serious <sup>11</sup>	NA	732	745	MD 0.18 (-0.17, 0.53)	MD 0.18 higher	very low

										(0.17 lower to 0.53 higher)	
<b>weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)</b>											
3	RC T	very serious <sup>6</sup>	not serious	very serious <sup>10</sup>	serious <sup>12</sup>	NA	739	752	MD 1.52 (0.48, 2.56)	MD 1.52 higher (0.48 higher to 2.56 higher)	very low
<b>bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)</b>											
1 (kesavadev 2017)	RC T	very serious <sup>6</sup>	not serious	NA <sup>4</sup>	not serious	NA	205	213	MD 0.39 (0.15, 0.63)	MD 0.39 higher (0.15 higher to 0.63 higher)	low

1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
4. Only one study so no inconsistency
5. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
6. >33.3% of the studies in the meta-analysis were at high risk of bias
7. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
8. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.03 (0.8-0.9 = serious, <0.8 = very serious).
9. I2 between 50% and 75%

10. I2 > 75%

11. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

12. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

#### L.1.6.15 Adding glimepiride compared to adding vildagliptin

**Table 73: Clinical evidence profile: Adding glimepiride compared to adding vildagliptin**

No of studies	De sig n	Risk of bias	Indire ctnes s	Incons istenc y	Impre cision	Other considera tions	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>all-cause mortality at end of follow up Mean follow-up: 9 month(s)</b>											
2	RC T	serious <sup>1</sup>	not serious	not serious	very serious <sup>2</sup>	NA	9/2929	9/29 42	RR 1.00 (0.40, 2.53)	0 more per 1000 (2 fewer to 5 more)	very low
<b>cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)</b>											
1 (ferrannini 2009)	RC T	very serious <sup>3</sup>	not serious	NA <sup>4</sup>	very serious <sup>2</sup>	NA	1/1383	2/13 89	RR 0.50 (0.05, 5.53)	1 fewer per 1000 (1 fewer to 7 more)	very low
<b>cardiac arrhythmia at end of follow up Mean follow-up: 12 month(s)</b>											
1 (ferrannini 2009)	RC T	very serious <sup>3</sup>	not serious	NA <sup>4</sup>	very serious <sup>2</sup>	NA	5/1383	3/13 89	RR 1.67 (0.40, 6.99)	1 more per 1000 (1 fewer to 13 more)	very low
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 9 month(s)</b>											

2	RC T	serious <sup>1</sup>	not serious	not serious	not serious	NA	505/29	58/2942	RR 8.75 (6.70, 11.42)	153 more per 1000 (112 more to 205 more)	moderate
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 5.8 month(s)</b>											
2	RC T	serious <sup>1</sup>	not serious	serious <sup>5</sup>	not serious	NA	15/1568	0/1575	RD 0.01 (0.00, 0.01)	10 more per 1000 (4 more to 15 more)	low
<b>hba1c change (% , lower values are better, change values and final scores) at end of follow up Mean follow-up: 11.9 month(s)</b>											
4	RC T	very serious <sup>3</sup>	not serious	not serious	not serious	NA	2720	2785	MD -0.13 (-0.21, -0.05)	MD 0.13 lower (0.21 lower to 0.05 lower)	low
<b>weight change (kg, lower values are better, change scores and final values) at end of follow up Mean follow-up: 11.8 month(s)</b>											
3	RC T	very serious <sup>3</sup>	not serious	not serious	not serious	NA	1648	1667	MD 1.50 (1.23, 1.78)	MD 1.50 higher (1.23 higher to 1.78 higher)	low
<b>bmi change (kg/m2, lower values are better, final values) at end of follow up Mean follow-up: 6 month(s)</b>											
1 (derosa 2014a)	RC T	very serious <sup>3</sup>	not serious	NA <sup>4</sup>	serious <sup>6</sup>	NA	70	83	MD 0.60 (0.13, 1.07)	MD 0.60 higher	very low



										(22 fewer to 22 more)	
<b>hypoglycaemia episodes at end of follow up</b> <b>Mean follow-up: 6 month(s)</b>											
1 (wilding 2013b)	RC T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	6/93	0/87	PETO OR 7.32 (1.44, 37.16)	65 more per 1000 (15 more to 115 more)	moderate
<b>severe hypoglycaemic episodes at end of follow up</b> <b>Mean follow-up: 6 month(s)</b>											
1 (wilding 2013b)	RC T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>4</sup>	NA	1/93	1/87	RR 0.94 (0.06, 14.73)	1 fewer per 1000 (11 fewer to 158 more)	low
<b>hba1c change (% , lower values are better, final values) at end of follow up</b> <b>Mean follow-up: 36 month(s)</b>											
1 (camerini-davalos 1994)	RC T	very serious <sup>5</sup>	not serious	NA <sup>2</sup>	serious <sup>4</sup>	NA	34	27	MD -0.90 (-1.78, -0.02)	MD 0.90 lower (1.78 lower to 0.02 lower)	Very low

1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
2. Only one study so no inconsistency
3. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
4. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
5. >33.3% of the studies in the meta-analysis were at high risk of bias

## L.1.6.17 Adding glipizide compared to adding metformin

Table 75: Clinical evidence profile: Adding glipizide compared to adding metformin

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>hba1c change (% , lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)</b>											
1 (vähätalo 2007)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>3</sup>	NA	15	26	MD 0.50 (-0.34, 1.34)	MD 0.50 higher (0.34 lower to 1.34 higher)	very low
<b>weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)</b>											
1 (vähätalo 2007)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>4</sup>	NA	15	26	MD 1.30 (-1.35, 3.95)	MD 1.30 higher (1.35 lower to 3.95 higher)	very low

1. >33.3% of the studies in the meta-analysis were at high risk of bias
2. Only one study so no inconsistency
3. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
4. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

## L.1.6.18 Adding glipizide compared to adding alogliptin

Table 76: Clinical evidence profile: Adding glipizide compared to adding alogliptin

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>all-cause mortality at end of follow up Mean follow-up: 24 month(s)</b>											
1 (del prato 2014)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>3</sup>	NA	5/869	6/17 51	RR 1.68 (0.51, 5.49)	2 more per 1000 (2 fewer to 15 more)	very low
<b>cardiovascular mortality at end of follow up Mean follow-up: 24 month(s)</b>											
1 (del prato 2014)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>3</sup>	NA	4/869	4/17 51	RR 2.01 (0.51, 8.04)	2 more per 1000 (1 fewer to 16 more)	very low
<b>3-point mace at end of follow up Mean follow-up: 24 month(s)</b>											
1 (del prato 2014)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>3</sup>	NA	11/869	14/1 751	RR 1.58 (0.72, 3.47)	5 more per 1000 (2 fewer to 20 more)	very low
<b>non-fatal stroke at end of follow up Mean follow-up: 24 month(s)</b>											
1 (del prato 2014)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>3</sup>	NA	3/869	5/17 51	RR 1.21 (0.29, 5.05)	1 more per 1000 (2 fewer to 12 more)	very low
<b>non-fatal myocardial infarction at end of follow up Mean follow-up: 24 month(s)</b>											

1 (del prato 2014)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>3</sup>	NA	4/869	5/17 51	RR 1.61 (0.43, 5.99)	2 more per 1000 (2 fewer to 14 more)	very low
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 24 month(s)</b>											
1 (del prato 2014)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	not seriou s	NA	202/86 9	34/1 751	RR 11.97 (8.40, 17.06)	213 more per 1000 (144 more to 312 more)	low
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 24 month(s)</b>											
1 (del prato 2014)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	seriou s <sup>4</sup>	NA	5/869	1/17 51	RR 10.07 (1.18, 86.10)	5 more per 1000 (0 more to 49 more)	very low
<b>hba1c change (% , lower values are better, change scores) at end of follow up Mean follow-up: 24 month(s)</b>											
1 (del prato 2014)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	not seriou s	NA	336	753	MD 0.11 (0.02, 0.20)	MD 0.11 higher (0.02 higher to 0.20 higher)	low

1. >33.3% of the studies in the meta-analysis were at high risk of bias
2. Only one study so no inconsistency
3. 95% confidence intervals cross both ends of the defined MIDd (0.80, 1.25)
4. 95% confidence intervals cross one end of the defined MIDd (0.80, 1.25)

## L.1.6.19 Adding glipizide compared to adding dapagliflozin

Table 77: Clinical evidence profile: Adding glipizide compared to adding dapagliflozin

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerat ions	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>all-cause mortality at end of follow up</b> Mean follow-up: 48 month(s)											
1 (nauck 2011)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>3</sup>	NA	5/408	2/40 6	RR 2.49 (0.49, 12.75)	7 more per 1000 (3 fewer to 58 more)	very low
<b>hypoglycaemia episodes at end of follow up</b> Mean follow-up: 12 month(s)											
1 (nauck 2011)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	not seriou s	NA	147/40 8	7/40 6	RR 20.90 (9.91, 44.05)	343 more per 1000 (154 more to 742 more)	low
<b>severe hypoglycaemic episodes at end of follow up</b> Mean follow-up: 12 month(s)											
1 (nauck 2011)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>3</sup>	NA	3/408	0/40 6	PETO OR 7.39 (0.77, 71.24)	7 more per 1000 (1 fewer to 16 more)	very low
<b>hba1c change (% , lower values are better, change scores) at end of follow up</b> Mean follow-up: 48 month(s)											
1 (nauck 2011)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	seriou s <sup>4</sup>	NA	401	400	MD 0.30 (0.08, 0.52)	MD 0.30 higher	very low

										(0.08 higher to 0.52 higher)	
<b>weight change (kg, lower values are better, change scores) at end of follow up</b> <b>Mean follow-up: 48 month(s)</b>											
1 (nauck 2011)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	401	400	MD 4.38 (3.45, 5.31)	MD 4.38 higher (3.45 higher to 5.31 higher)	low

1. >33.3% of the studies in the meta-analysis were at high risk of bias
2. Only one study so no inconsistency
3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
4. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

#### L.1.6.20 Adding glipizide compared to adding saxagliptin

**Table 78: Clinical evidence profile: Adding glipizide compared to adding saxagliptin**

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
<b>all-cause mortality at end of follow up</b> <b>Mean follow-up: 24 month(s)</b>											
1 (göke 2010)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	2/430	4/428	RD -0.00 (-0.02, 0.01)	5 fewer per 1000 (16 fewer to 6 more)	low

<b>cardiovascular mortality at end of follow up</b> <b>Mean follow-up: 24 month(s)</b>											
1 (göke 2010)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	2/430	1/42 8	RD 0.00 (-0.01, 0.01)	2 more per 1000 (6 fewer to 10 more)	low
<b>hypoglycaemia episodes at end of follow up</b> <b>Mean follow-up: 24 month(s)</b>											
1 (göke 2010)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	39/430	0/42 8	PETO OR 8.07 (4.25, 15.33)	91 more per 1000 (64 more to 118 more)	low
<b>hba1c change (% , lower values are better, change scores) at end of follow up</b> <b>Mean follow-up: 24 month(s)</b>											
1 (göke 2010)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	423	423	MD 0.06 (-0.05, 0.17)	MD 0.06 higher (0.05 lower to 0.17 higher)	low
<b>weight change (kg, lower values are better, change scores) at end of follow up</b> <b>Mean follow-up: 24 month(s)</b>											
1 (göke 2010)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>3</sup>	NA	426	424	MD 2.80 (2.25, 3.35)	MD 2.80 higher (2.25 higher to 3.35 higher)	very low

1. >33.3% of the studies in the meta-analysis were at high risk of bias
2. Only one study so no inconsistency
3. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

## L.1.6.21 Adding glipizide compared to adding sitagliptin

Table 79: Clinical evidence profile: Adding glipizide compared to adding sitagliptin

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerat ions	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>all-cause mortality at end of follow up</b> <b>Mean follow-up: 24 month(s)</b>											
1 (nauck 2007b)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	seriou s <sup>3</sup>	NA	8/584	1/58 8	RR 8.05 (1.01, 64.20)	12 more per 1000 (0 more to 107 more)	very low
<b>cardiovascular mortality at end of follow up</b> <b>Mean follow-up: 24 month(s)</b>											
1 (nauck 2007b)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>4</sup>	NA	3/584	0/58 8	PETO OR 7.47 (0.78, 71.91)	5 more per 1000 (1 fewer to 11 more)	very low
<b>hypoglycaemia episodes at end of follow up</b> <b>Mean follow-up: 24 month(s)</b>											
1 (nauck 2007b)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	not seriou s	NA	448/58 4	31/5 88	RR 14.55 (10.30, 20.56)	714 more per 1000 (490 more to 1031 more)	low
<b>hypoglycaemia episodes at end of follow up</b> <b>Mean follow-up: 24 month(s)</b>											
1 (nauck 2007b)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	not seriou s	NA	584	588	HR 20.00 (11.11, 33.33)	Not estimable	low

<b>severe hypoglycaemic episodes at end of follow up</b> <b>Mean follow-up: 24 month(s)</b>											
1 (nauck 2007b)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	not seriou s	NA	22/584	2/58 8	RR 11.08 (2.62, 46.89)	34 more per 1000 (5 more to 156 more)	low
<b>severe hypoglycaemia episodes at end of follow-up</b> <b>Mean follow-up: 24 month(s)</b>											
1 (nauck 2007b)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	not seriou s	NA	584	588	HR 12.50 (2.13, 100)	Not estimable	low
<b>hba1c change (% , lower values are better, change scores) at end of follow up</b> <b>Mean follow-up: 24 month(s)</b>											
1 (nauck 2007b)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	not seriou s	NA	559	576	MD -0.02 (-0.14, 0.10)	MD 0.02 lower (0.14 lower to 0.10 higher)	low
<b>weight change (kg, lower values are better, change scores) at end of follow up</b> <b>Mean follow-up: 24 month(s)</b>											
1 (nauck 2007b)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	seriou s <sup>5</sup>	NA	559	576	MD 2.30 (1.38, 3.22)	MD 2.30 higher (1.38 higher to 3.22 higher)	very low

1. >33.3% of the studies in the meta-analysis were at high risk of bias

2. Only one study so no inconsistency
3. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
4. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
5. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

## L.1.7 Thiazolidinediones

### L.1.7.1 Adding pioglitazone compared to adding placebo

**Table 80: Clinical evidence profile: Adding pioglitazone compared to adding placebo**

No of studies	De sig n	Risk of bias	Indire ctnes s	Incons istenc y	Impre cision	Other considera tions	Interv entio n N	Con trol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>all-cause mortality at end of follow up Mean follow-up: 7 month(s)</b>											
6	RC T	very seriou s <sup>1</sup>	not seriou s	seriou s <sup>2</sup>	very seriou s <sup>3</sup>	NA	5/1168	6/11 66	RD -0.00 (-0.01, 0.00)	2 fewer per 1000 (8 fewer to 5 more)	very low
<b>cardiovascular mortality at end of follow up Mean follow-up: 6 month(s)</b>											
4	RC T	very seriou s <sup>1</sup>	not seriou s	seriou s <sup>2</sup>	very seriou s <sup>4</sup>	NA	1/749	1/90 4	RD 0.00 (-0.01, 0.01)	0 more per 1000 (6 fewer to 6 more)	very low
<b>3-point mace at end of follow up Mean follow-up: 8.7 month(s)</b>											
2	RC T	very seriou s <sup>1</sup>	not seriou s	seriou s <sup>5</sup>	seriou s <sup>6</sup>	NA	45/619	15/6 56	RR 1.36 (0.38, 4.88)	8 more per 1000	very low

										(14 fewer to 89 more)	
<b>non-fatal stroke at end of follow up</b>											
<b>Mean follow-up: 5.4 month(s)</b>											
1 (punthakee 2012)	RC T	very serious <sup>1</sup>	not serious	NA <sup>7</sup>	very serious <sup>8</sup>	NA	2/392	2/54 1	PETO OR 1.39 (0.19, 10.15)	1 more per 1000 (7 fewer to 10 more)	very low
<b>non-fatal myocardial infarction at end of follow up</b>											
<b>Mean follow-up: 5.7 month(s)</b>											
2	RC T	serious <sup>9</sup>	not serious	serious <sup>2</sup>	very serious <sup>8</sup>	NA	5/494	7/64 7	RR 0.81 (0.27, 2.42)	2 fewer per 1000 (8 fewer to 15 more)	very low
<b>hospitalisation for heart failure at end of follow up</b>											
<b>Mean follow-up: 6.2 month(s)</b>											
2	RC T	very serious <sup>1</sup>	not serious	serious <sup>2</sup>	very serious <sup>10</sup>	NA	2/537	1/69 5	RD 0.00 (-0.00, 0.01)	2 more per 1000 (4 fewer to 9 more)	very low
<b>persistent signs of worsening kidney disease at end of follow up</b>											
<b>Mean follow-up: 5.4 month(s)</b>											
1 (punthakee 2012)	RC T	very serious <sup>1</sup>	not serious	NA <sup>7</sup>	serious <sup>6</sup>	NA	8/392	20/5 41	RR 0.55 (0.25, 1.24)	17 fewer per 1000 (28 fewer to 9 more)	very low
<b>hypoglycaemia episodes at end of follow up</b>											
<b>Mean follow-up: 7.3 month(s)</b>											
7	RC T	very serious <sup>1</sup>	not serious	very serious <sup>11</sup>	serious <sup>6</sup>	NA	232/74 2	107/ 598	RR 2.10 (1.12, 3.95)	198 more per 1000 (21 more to 529 more)	very low

<b>severe hypoglycaemic episodes at end of follow up</b> <b>Mean follow-up: 8.7 month(s)</b>											
2	RC T	very serious <sup>1</sup>	not serious	not serious	serious <sup>6</sup>	NA	5/669	0/656	PETO OR 6.33 (0.98, 40.83)	7 more per 1000 (1 more to 14 more)	very low
<b>hba1c change (% , lower values are better, change scores and final values) at end of follow up</b> <b>Mean follow-up: 7.2 month(s)</b>											
12	RC T	very serious <sup>1</sup>	not serious	very serious <sup>11</sup>	serious <sup>12</sup>	NA	1384	1373	MD -0.70 (-0.91, -0.48)	MD 0.70 lower (0.91 lower to 0.48 lower)	very low
<b>weight change (kg, lower values are better, change scores and final values) at end of follow up</b> <b>Mean follow-up: 7.2 month(s)</b>											
9	RC T	very serious <sup>1</sup>	not serious	serious <sup>5</sup>	not serious	NA	1149	1230	MD 3.55 (2.54, 4.55)	MD 3.55 higher (2.54 higher to 4.55 higher)	very low
<b>bmi change (kg/m2, lower values are better, final values) at end of follow up</b> <b>Mean follow-up: 5.8 month(s)</b>											
4	RC T	very serious <sup>1</sup>	not serious	not serious	serious <sup>13</sup>	NA	538	678	MD 1.03 (0.42, 1.65)	MD 1.03 higher (0.42 higher to 1.65 higher)	very low

1. >33.3% of the studies in the meta-analysis were at high risk of bias
2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

3. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.06 (0.8-0.9 = serious, <0.8 = very serious).
4. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.04 (0.8-0.9 = serious, <0.8 = very serious).
5. I<sup>2</sup> between 50% and 75%
6. 95% confidence intervals cross one end of the defined MID<sub>s</sub> (0.80, 1.25)
7. Only one study so no inconsistency
8. 95% confidence intervals cross both ends of the defined MID<sub>s</sub> (0.80, 1.25)
9. >33.3% of the studies in the meta-analysis were at moderate risk of bias
10. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.2 (0.8-0.9 = serious, <0.8 = very serious).
11. I<sup>2</sup> > 75%
12. 95% confidence intervals cross one end of the defined MID<sub>s</sub> (-0.50, 0.50)
13. 95% confidence intervals cross one end of the defined MID<sub>s</sub> (-0.80, 0.80)

#### L.1.7.2 Adding pioglitazone compared to adding metformin

**Table 81: Clinical evidence profile: Adding pioglitazone compared to adding metformin**

No of studies	De sig n	Risk of bias	Indire ctnes s	Incons istenc y	Impre cision	Other considera tions	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>all-cause mortality at end of follow up Mean follow-up: 12 month(s)</b>											
2	RC T	very serious <sup>1</sup>	not serious	serious <sup>2</sup>	very serious <sup>3</sup>	NA	1/351	3/35 1	PETO OR 0.36 (0.05, 2.60)	6 fewer per 1000	very low

										(17 fewer to 5 more)	
<b>unstable angina at end of follow up</b>											
<b>Mean follow-up: 12 month(s)</b>											
1 (morikawa 2011)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>4</sup>	very seriou s <sup>3</sup>	NA	1/32	0/31	PETO OR 7.16 (0.14, 361.11)	31 more per 1000 (29 fewer to 92 more)	very low
<b>hospitalisation for heart failure at end of follow up</b>											
<b>Mean follow-up: 5.5 month(s)</b>											
1 (van der meer 2009)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>4</sup>	seriou s <sup>5</sup>	NA	0/39	0/39	RD 0.00 (-0.05, 0.05)	0 fewer per 1000 (49 fewer to 49 more)	very low
<b>persistent signs of worsening kidney disease at end of follow up</b>											
<b>Mean follow-up: 12 month(s)</b>											
1 (morikawa 2011)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>4</sup>	very seriou s <sup>3</sup>	NA	2/32	6/31	RR 0.32 (0.07, 1.48)	131 fewer per 1000 (180 fewer to 93 more)	very low
<b>hypoglycaemia episodes at end of follow up</b>											
<b>Mean follow-up: 15 month(s)</b>											
2	RC T	very seriou s <sup>1</sup>	not seriou s	not seriou s	seriou s <sup>6</sup>	NA	44/359	59/3 62	RR 0.75 (0.53, 1.08)	40 fewer per 1000 (77 fewer to 13 more)	very low
<b>severe hypoglycaemic episodes at end of follow up</b>											
<b>Mean follow-up: 12 month(s)</b>											
1 (hanefeld 2004)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>4</sup>	not seriou s	NA	0/319	0/32 0	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	low

<b>hba1c change (% , lower values are better, change scores and final values) at end of follow up Mean follow-up: 11 month(s)</b>											
7	RC T	very serious <sup>1</sup>	not serious	not serious	not serious	NA	525	525	MD 0.10 (-0.02, 0.22)	MD 0.10 higher (0.02 lower to 0.22 higher)	low
<b>weight change (kg, lower values are better, change scores and final values) at end of follow up Mean follow-up: 9.8 month(s)</b>											
3	RC T	very serious <sup>1</sup>	not serious	not serious	serious <sup>7</sup>	NA	377	382	MD 2.47 (-0.96, 5.89)	MD 2.47 higher (0.96 lower to 5.89 higher)	very low
<b>bmi change (kg/m2, lower values are better, final values) at end of follow up Mean follow-up: 9.8 month(s)</b>											
3	RC T	very serious <sup>1</sup>	not serious	very serious <sup>8</sup>	very serious <sup>9</sup>	NA	150	103	MD 0.80 (-1.56, 3.17)	MD 0.80 higher (1.56 lower to 3.17 higher)	very low

1. >33.3% of the studies in the meta-analysis were at high risk of bias
2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
4. Only one study so no inconsistency
5. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.

6. 95% confidence intervals cross one end of the defined MID (0.80, 1.25)
7. 95% confidence intervals cross one end of the defined MID (-2.40, 2.40)
8. I<sup>2</sup> > 75%
9. 95% confidence intervals cross both ends of the defined MID (-0.80, 0.80)

### L.1.7.3 Adding pioglitazone compared to adding insulin

**Table 82: Clinical evidence profile: Adding pioglitazone compared to adding insulin**

No of studies	De sig n	Risk of bias	Indire ctnes s	Incons istenc y	Impre cision	Other considera tions	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>hypoglycaemia episodes at end of follow up</b> Mean follow-up: 8.2 month(s)											
2	RC T	very seriou s <sup>1</sup>	not seriou s	not seriou s	seriou s <sup>2</sup>	NA	7/140	14/1 34	RR 0.47 (0.24, 0.93)	56 fewer per 1000 (80 fewer to 7 fewer)	very low
<b>severe hypoglycaemic episodes at end of follow up</b> Mean follow-up: 8.2 month(s)											
2	RC T	very seriou s <sup>1</sup>	not seriou s	seriou s <sup>3</sup>	very seriou s <sup>4</sup>	NA	1/140	4/13 4	RD -0.02 (-0.06, 0.01)	23 fewer per 1000 (58 fewer to 12 more)	very low
<b>hba1c change (% , lower values are better, change scores and final values) at end of follow up</b> Mean follow-up: 7.5 month(s)											
3	RC T	very seriou s <sup>1</sup>	not seriou s	not seriou s	seriou s <sup>5</sup>	NA	155	149	MD 0.57 (0.32, 0.81)	MD 0.57 higher	very low

										(0.32 higher to 0.81 higher)	
<b>weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)</b>											
1 (hartemann-heurtier 2009)	RC T	very serious <sup>1</sup>	not serious	NA <sup>6</sup>	serious <sup>7</sup>	NA	14	13	MD 1.30 (-0.75, 3.35)	MD 1.30 higher (0.75 lower to 3.35 higher)	very low
<b>bmi change (kg/m2, lower values are better, final values) at end of follow up Mean follow-up: 6 month(s)</b>											
1 (dorkhan 2009)	RC T	very serious <sup>1</sup>	not serious	NA <sup>6</sup>	very serious <sup>8</sup>	NA	15	15	MD -0.60 (-4.93, 3.73)	MD 0.60 lower (4.93 lower to 3.73 higher)	very low

- >33.3% of the studies in the meta-analysis were at high risk of bias
- 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.51 (0.8-0.9 = serious, <0.8 = very serious).
- 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- Only one study so no inconsistency
- 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)
- 95% confidence intervals cross both ends of the defined MIDs (-0.80, 0.80)

## L.1.7.4 Adding pioglitazone compared to adding dapagliflozin

Table 83: Clinical evidence profile: Adding pioglitazone compared to adding dapagliflozin

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 6.5 month(s)</b>											
1 (kinoshita 2020)	RC T	not serio us	not seriou s	NA <sup>1</sup>	very seriou s <sup>2</sup>	NA	0/33	0/33	RD 0.00 (-0.06, 0.06)	0 fewer per 1000 (57 fewer to 57 more)	low
<b>hba1c change (% , lower values are better, change scores) at end of follow up Mean follow-up: 6.5 month(s)</b>											
1 (kinoshita 2020)	RC T	not serio us	not seriou s	NA <sup>1</sup>	not seriou s	NA	33	32	MD 0.04 (-0.38, 0.46)	MD 0.04 higher (0.38 lower to 0.46 higher)	high
<b>weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 6.5 month(s)</b>											
1 (kinoshita 2020)	RC T	not serio us	not seriou s	NA <sup>1</sup>	not seriou s	NA	33	32	MD 5.30 (4.32, 6.28)	MD 5.30 higher (4.32 higher to 6.28 higher)	high

1. Only one study so no inconsistency

2. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.

### L.1.7.5 Adding pioglitazone compared to adding empagliflozin

**Figure 84: Clinical evidence profile: Adding pioglitazone compared to adding empagliflozin**

No of studies	De sig n	Risk of bias	Indire ctnes s	Incons istenc y	Impre cision	Other considera tions	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>non-fatal stroke at end of follow up Mean follow-up: 5.5 month(s)</b>											
1 (attaran 2023)	RC T	serio us <sup>1</sup>	not seriou s	NA 2	very seriou s <sup>3</sup>	NA	0/36	1/37	PETO OR 0.14 (0.00, 7.01)	27 fewer per 1000 (79 fewer to 25 more)	very low
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 5.5 month(s)</b>											
2	RC T	serio us <sup>1</sup>	not seriou s	seriou s <sup>4</sup>	very seriou s <sup>5</sup>	NA	2/91	0/95	RD 0.02 (-0.05, 0.08)	18 more per 1000 (47 fewer to 83 more)	very low
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 5.5 month(s)</b>											
2	RC T	serio us <sup>1</sup>	not seriou s	not seriou s	seriou s <sup>6</sup>	NA	0/91	0/95	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (30 fewer to 30 more)	low
<b>hba1c change (% , lower values are better, change scores and final values) at end of follow up Mean follow-up: 5.5 month(s)</b>											

2	RC T	serious <sup>1</sup>	not serious	not serious	not serious	NA	91	95	MD 0.07 (-0.20, 0.35)	MD 0.07 higher (0.20 lower to 0.35 higher)	moderate
<p><b>bmi change (kg/m2, lower values are better, change scores and final values) at end of follow up</b>  <b>Mean follow-up: 5.5 month(s)</b></p>											
2	RC T	serious <sup>1</sup>	not serious	not serious	not serious	NA	91	95	MD 1.73 (1.32, 2.14)	MD 1.73 higher (1.32 higher to 2.14 higher)	moderate

- >33.3% of the studies in the meta-analysis were at moderate risk of bias
- Only one study so no inconsistency
- 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.53 (0.8-0.9 = serious, <0.8 = very serious).
- Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.

**L.1.7.6 Adding pioglitazone compared to adding exenatide**

**Table 85: Clinical evidence profile: Adding pioglitazone compared to adding exenatide**

No of studies	De sig n	Risk of bias	Indir ectne ss	Incons istenc y	Impre cision	Other considera tions	Interv ention N	Con trol N	Relative effect (95% CI)	Absolute effect	Cert aint y
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<b>health-related quality of life - overall (eq-5d, higher values better, change scores) at end of follow-up</b> <b>Mean follow-up: 6 month(s)</b>											
1 (bergenstal 2010)	RC T	very seriou s <sup>1</sup>	not serio us	NA <sup>2</sup>	very seriou s <sup>3</sup>	NA	130	129	MD -0.02 (-0.08, 0.04)	MD 0.02 lower (0.08 lower to 0.04 higher)	very low
<b>all-cause mortality at end of follow up</b> <b>Mean follow-up: 6 month(s)</b>											
1 (bergenstal 2010)	RC T	very seriou s <sup>1</sup>	not serio us	NA <sup>2</sup>	seriou s <sup>4</sup>	NA	0/165	0/160	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	very low
<b>cardiovascular mortality at end of follow up</b> <b>Mean follow-up: 6 month(s)</b>											
1 (bergenstal 2010)	RC T	very seriou s <sup>1</sup>	not serio us	NA <sup>2</sup>	seriou s <sup>4</sup>	NA	0/165	0/160	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	very low
<b>unstable angina at end of follow up</b> <b>Mean follow-up: 6 month(s)</b>											
1 (bergenstal 2010)	RC T	very seriou s <sup>1</sup>	not serio us	NA <sup>2</sup>	very seriou s <sup>5</sup>	NA	1/165	0/160	PETO OR 7.17 (0.14, 361.44)	6 more per 1000 (6 fewer to 18 more)	very low
<b>acute kidney injury at end of follow up</b> <b>Mean follow-up: 6 month(s)</b>											
1 (bergenstal 2010)	RC T	very seriou s <sup>1</sup>	not serio us	NA <sup>2</sup>	very seriou s <sup>5</sup>	NA	1/165	0/160	PETO OR 7.17 (0.14, 361.44)	6 more per 1000 (6 fewer to 18 more)	very low
<b>hypoglycaemia episodes at end of follow up</b> <b>Mean follow-up: 6 month(s)</b>											

1 (bergenstal 2010)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>5</sup>	NA	1/165	2/160	PETO OR 0.50 (0.05, 4.80)	6 fewer per 1000 (27 fewer to 14 more)	very low
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 6 month(s)</b>											
1 (bergenstal 2010)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>4</sup>	NA	0/165	0/160	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	very low
<b>hba1c change (% , lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)</b>											
1 (bergenstal 2010)	RC T	serious <sup>6</sup>	not serious	NA <sup>2</sup>	serious <sup>7</sup>	NA	165	160	MD 0.30 (0.05, 0.55)	MD 0.30 higher (0.05 higher to 0.55 higher)	low
<b>weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)</b>											
1 (bergenstal 2010)	RC T	serious <sup>6</sup>	not serious	NA <sup>2</sup>	not serious	NA	165	160	MD 5.10 (4.26, 5.94)	MD 5.10 higher (4.26 higher to 5.94 higher)	moderate

1. >33.3% of the studies in the meta-analysis were at high risk of bias
2. Only one study so no inconsistency
3. 95% confidence intervals cross both ends of the defined MIDs (-0.03, 0.03)
4. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
5. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

6. >33.3% of the studies in the meta-analysis were at moderate risk of bias

7. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

### L.1.7.7 Adding pioglitazone compared to adding gliclazide

**Table 86: Clinical evidence profile: Adding pioglitazone compared to adding gliclazide**

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>all-cause mortality at end of follow up Mean follow-up: 12 month(s)</b>											
1 (matthews 2005)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>3</sup>	NA	0/317	2/31 3	PETO OR 0.13 (0.01, 2.13)	6 fewer per 1000 (15 fewer to 2 more)	very low
<b>non-fatal myocardial infarction at end of follow up Mean follow-up: 12 month(s)</b>											
1 (matthews 2005)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>3</sup>	NA	1/317	0/31 3	PETO OR 7.30 (0.14, 367.74)	3 more per 1000 (3 fewer to 9 more)	very low
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 24 month(s)</b>											
1 (matthews 2005)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	not seriou s	NA	7/317	36/3 13	RR 0.19 (0.09, 0.42)	93 fewer per 1000 (105 fewer to 66 fewer)	low
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)</b>											

1 (matthews 2005)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	not seriou s	NA	0/317	0/31 3	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	low
<b>hba1c change (% , lower values are better, change scores) at end of follow up Mean follow-up: 24 month(s)</b>											
1 (matthews 2005)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	not seriou s	NA	317	313	MD -0.12 (-0.31, 0.07)	MD 0.12 lower (0.31 lower to 0.07 higher)	low

- >33.3% of the studies in the meta-analysis were at high risk of bias
- Only one study so no inconsistency
- 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

#### L.1.7.8 Adding pioglitazone compared to adding glimepiride

**Table 87: Clinical evidence profile: Adding pioglitazone compared to adding glimepiride**

No of studies	De sig n	Risk of bias	Indire ctnes s	Incons istenc y	Impre cision	Other considera tions	Interv ention N	Con trol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>all-cause mortality at end of follow up Mean follow-up: 18 month(s)</b>											
1 (mazzone 2006)	RC T	very seriou s <sup>1</sup>	seriou s <sup>2</sup>	NA <sup>3</sup>	very seriou s <sup>4</sup>	NA	1/230	0/22 8	PETO OR 7.33 (0.15, 369.17)	4 more per 1000 (4 fewer to 13 more)	very low
<b>cardiovascular mortality at end of follow up Mean follow-up: 18 month(s)</b>											

1 (mazzone 2006)	RC T	very seriou s <sup>1</sup>	seriou s <sup>2</sup>	NA <sup>3</sup>	not seriou s	NA	0/230	0/22 8	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	very low
<b>3-point mace at end of follow up Mean follow-up: 18 month(s)</b>											
1 (mazzone 2006)	RC T	very seriou s <sup>1</sup>	seriou s <sup>2</sup>	NA <sup>3</sup>	very seriou s <sup>4</sup>	NA	0/230	2/22 8	PETO OR 0.13 (0.01, 2.14)	9 fewer per 1000 (21 fewer to 3 more)	very low
<b>non-fatal stroke at end of follow up Mean follow-up: 11.8 month(s)</b>											
2	RC T	very seriou s <sup>1</sup>	seriou s <sup>2</sup>	seriou s <sup>5</sup>	very seriou s <sup>4</sup>	NA	1/261	1/26 0	PETO OR 1.01 (0.06, 16.18)	0 fewer per 1000 (11 fewer to 11 more)	very low
<b>non-fatal myocardial infarction at end of follow up Mean follow-up: 11.8 month(s)</b>											
2	RC T	very seriou s <sup>1</sup>	seriou s <sup>2</sup>	not seriou s	very seriou s <sup>4</sup>	NA	0/261	2/26 0	PETO OR 0.14 (0.01, 2.19)	8 fewer per 1000 (18 fewer to 3 more)	very low
<b>unstable angina at end of follow up Mean follow-up: 18 month(s)</b>											
1 (mazzone 2006)	RC T	very seriou s <sup>1</sup>	seriou s <sup>2</sup>	NA <sup>3</sup>	not seriou s	NA	0/230	0/22 8	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	very low
<b>hospitalisation for heart failure at end of follow up Mean follow-up: 8.2 month(s)</b>											
5	RC T	very seriou s <sup>1</sup>	not seriou s	seriou s <sup>5</sup>	very seriou s <sup>6</sup>	NA	5/657	2/63 8	RD 0.00 (-0.01, 0.01)	4 more per 1000 (6 fewer to 15 more)	very low

<b>acute kidney injury at end of follow up</b>											
<b>Mean follow-up: 5.5 month(s)</b>											
1 (pfützner 2011b)	RC T	serious <sup>7</sup>	not serious	NA <sup>3</sup>	very serious <sup>4</sup>	NA	0/142	1/146	PETO OR 0.14 (0.00, 7.01)	7 fewer per 1000 (20 fewer to 7 more)	very low
<b>falls requiring hospitalisation at end of follow up</b>											
<b>Mean follow-up: 6 month(s)</b>											
1 (kim 2020)	RC T	serious <sup>7</sup>	not serious	NA <sup>3</sup>	very serious <sup>4</sup>	NA	2/69	0/66	PETO OR 7.18 (0.44, 116.06)	29 more per 1000 (11 fewer to 69 more)	very low
<b>hypoglycaemia episodes at end of follow up</b>											
<b>Mean follow-up: 8.5 month(s)</b>											
7	RC T	very serious <sup>1</sup>	not serious	very serious <sup>8</sup>	serious <sup>9</sup>	NA	81/753	140/ 738	RR 0.49 (0.24, 0.99)	98 fewer per 1000 (145 fewer to 2 fewer)	very low
<b>severe hypoglycaemic episodes at end of follow up</b>											
<b>Mean follow-up: 5.8 month(s)</b>											
3	RC T	very serious <sup>1</sup>	not serious	not serious	not serious	NA	0/285	0/264	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	low
<b>hba1c change (% , lower values are better, change scores and final values) at end of follow up</b>											
<b>Mean follow-up: 6.9 month(s)</b>											
12	RC T	very serious <sup>1</sup>	not serious	serious <sup>10</sup>	not serious	NA	801	778	MD -0.07 (-0.19, 0.05)	MD 0.07 lower (0.19 lower to 0.05 higher)	very low

<b>weight change (kg, lower values are better, change scores and final values) at end of follow up</b> <b>Mean follow-up: 8.2 month(s)</b>											
8	RC T	very serious <sup>1</sup>	not serious	serious <sup>10</sup>	not serious	NA	663	656	MD 0.88 (0.02, 1.74)	MD 0.88 higher (0.02 higher to 1.74 higher)	very low
<b>bmi change (kg/m2, lower values are better, change scores and final values) at end of follow up</b> <b>Mean follow-up: 7.6 month(s)</b>											
7	RC T	very serious <sup>1</sup>	not serious	not serious	not serious	NA	441	419	MD 0.32 (-0.14, 0.79)	MD 0.32 higher (0.14 lower to 0.79 higher)	low

1. >33.3% of the studies in the meta-analysis were at high risk of bias
2. Largest proportion of studies in the meta-analysis came from partially direct studies
3. Only one study so no inconsistency
4. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
5. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
6. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.34 (0.8-0.9 = serious, <0.8 = very serious).
7. >33.3% of the studies in the meta-analysis were at moderate risk of bias
8. I2 > 75%
9. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)

10. I2 between 50% and 75%

### L.1.7.9 Adding pioglitazone compared to adding glipizide

**Table 88: Clinical evidence profile: Adding pioglitazone compared to adding glipizide**

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>hba1c change (% , lower values are better, final values) at end of follow up Mean follow-up: 5.5 month(s)</b>											
1 (xiao 2015)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	seriou s <sup>3</sup>	NA	34	36	MD 0.58 (0.34, 0.82)	MD 0.58 higher (0.34 higher to 0.82 higher)	very low

- >33.3% of the studies in the meta-analysis were at high risk of bias
- Only one study so no inconsistency
- 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

### L.1.7.10 Adding pioglitazone compared to adding sitagliptin

**Table 89: Clinical evidence profile: Adding pioglitazone compared to adding sitagliptin**

No of studies	De sig n	Risk of bias	Indir ectne ss	Incon sisten cy	Impre cision	Other considera tions	Interv ention N	Con trol N	Relative effect (95% CI)	Absolute effect	Cert aint y
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<b>health-related quality of life - overall (eq-5d, higher values are better, change scores) at end of follow-up</b> <b>Mean follow-up: 6 month(s)</b>											
1 (bergenstal 2010)	RC T	very seriou s <sup>1</sup>	not serio us	NA <sup>2</sup>	seriou s <sup>3</sup>	NA	130	139	MD -0.03 (-0.09, 0.03)	MD 0.03 lower (0.09 lower to 0.03 higher)	very low
<b>all-cause mortality at end of follow up</b> <b>Mean follow-up: 6 month(s)</b>											
1 (bergenstal 2010)	RC T	very seriou s <sup>1</sup>	not serio us	NA <sup>2</sup>	very seriou s <sup>4</sup>	NA	0/165	1/16 6	PETO OR 0.14 (0.00, 6.86)	6 fewer per 1000 (18 fewer to 6 more)	very low
<b>unstable angina at end of follow up</b> <b>Mean follow-up: 6 month(s)</b>											
1 (bergenstal 2010)	RC T	very seriou s <sup>1</sup>	not serio us	NA <sup>2</sup>	very seriou s <sup>4</sup>	NA	1/165	0/16 6	PETO OR 7.43 (0.15, 374.66)	6 more per 1000 (6 fewer to 18 more)	very low
<b>acute kidney injury at end of follow up</b> <b>Mean follow-up: 6 month(s)</b>											
1 (bergenstal 2010)	RC T	very seriou s <sup>1</sup>	not serio us	NA <sup>2</sup>	very seriou s <sup>4</sup>	NA	1/165	0/16 6	PETO OR 7.43 (0.15, 374.66)	6 more per 1000 (6 fewer to 18 more)	very low
<b>hypoglycaemia episodes at end of follow up</b> <b>Mean follow-up: 5.7 month(s)</b>											
3	RC T	seriou s <sup>5</sup>	not serio us	not seriou s	very seriou s <sup>4</sup>	NA	8/290	13/2 91	RR 0.62 (0.26, 1.45)	17 fewer per 1000 (33 fewer to 20 more)	very low
<b>severe hypoglycaemic episodes at end of follow up</b> <b>Mean follow-up: 5.7 month(s)</b>											

3	RC T	very serious <sup>1</sup>	not serious	not serious	not serious	NA	0/290	0/291	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (12 fewer to 12 more)	low
<b>hba1c change (% , lower values are better, change scores) at end of follow up Mean follow-up: 7.2 month(s)</b>											
4	RC T	serious <sup>5</sup>	not serious	very serious <sup>6</sup>	not serious	NA	391	396	MD -0.12 (-0.37, 0.14)	MD 0.12 lower (0.37 lower to 0.14 higher)	very low
<b>weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 7.2 month(s)</b>											
4	RC T	serious <sup>5</sup>	not serious	very serious <sup>6</sup>	not serious	NA	391	396	MD 1.62 (1.52, 1.73)	MD 1.62 higher (1.52 higher to 1.73 higher)	very low
<b>bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)</b>											
1 (khaloo 2019)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	110	112	MD 3.50 (2.62, 4.38)	MD 3.50 higher (2.62 higher to 4.38 higher)	low

1. >33.3% of the studies in the meta-analysis were at high risk of bias
2. Only one study so no inconsistency
3. 95% confidence intervals cross one end of the defined MIDs (-0.03, 0.03)
4. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

5. >33.3% of the studies in the meta-analysis were at moderate risk of bias

6. I<sup>2</sup> > 75%

#### L.1.7.11 Adding pioglitazone compared to adding vildagliptin

**Table 90: Clinical evidence profile: Adding pioglitazone compared to adding vildagliptin**

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert ainty
<b>non-fatal stroke at end of follow up Mean follow-up: 12 month(s)</b>											
1 (bolli 2008)	RC T	not serio us	not seriou s	NA <sup>1</sup>	very seriou s <sup>2</sup>	NA	2/280	1/29 5	RR 2.11 (0.19, 23.11)	4 more per 1000 (3 fewer to 75 more)	low
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 12 month(s)</b>											
1 (bolli 2008)	RC T	not serio us	not seriou s	NA <sup>1</sup>	very seriou s <sup>2</sup>	NA	1/280	1/29 5	RR 1.05 (0.07, 16.76)	0 more per 1000 (3 fewer to 53 more)	low
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)</b>											
1 (bolli 2008)	RC T	not serio us	not seriou s	NA <sup>1</sup>	not seriou s	NA	0/280	0/29 5	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	high
<b>hba1c change (% , lower values are better, change scores) at end of follow up</b>											

Mean follow-up: 12 month(s)											
1 (bolli 2008)	RC T	not serio us	not seriou s	NA <sup>1</sup>	not seriou s	NA	281	295	MD 0.00 (-0.18, 0.18)	MD 0.00 lower (0.18 lower to 0.18 higher)	high
<b>weight change (kg, lower values are better, change scores) at end of follow up</b> <b>Mean follow-up: 12 month(s)</b>											
1 (bolli 2008)	RC T	not serio us	not seriou s	NA <sup>1</sup>	seriou s <sup>3</sup>	NA	281	295	MD 2.40 (1.69, 3.11)	MD 2.40 higher (1.69 higher to 3.11 higher)	mod erat e

1. Only one study so no inconsistency
2. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
3. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

## L.1.8 Insulin combinations

### L.1.8.1 Adding insulin degludec/liraglutide compared to adding placebo

**Table 91: Clinical evidence profile: Adding insulin degludec/liraglutide compared to adding placebo**

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerat ions	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
all-cause mortality at end of follow up Mean follow-up: 6 month(s)											

1 (rodbard 2017)	RC T	not seriou s	not seriou s	NA <sup>2</sup>	very seriou s <sup>4</sup>	NA	1/288	0/14 6	PETO OR 4.51 (0.07, 285.77)	3 more per 1000 (3 fewer to 10 more)	low
<b>non-fatal myocardial infarction at end of follow up Mean follow-up: 6 month(s)</b>											
1 (rodbard 2017)	RC T	not seriou s	not seriou s	NA <sup>2</sup>	very seriou s <sup>4</sup>	NA	1/288	0/14 6	PETO OR 4.51 (0.07, 285.77)	3 more per 1000 (3 fewer to 10 more)	low
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 6 month(s)</b>											
1 (rodbard 2017)	RC T	not seriou s	not seriou s	NA <sup>2</sup>	not seriou s	NA	120/28 8	25/1 46	RR 2.43 (1.66, 3.57)	245 more per 1000 (113 more to 439 more)	high
<b>at night hypoglycaemic episodes at end of follow up Mean follow-up: 6 month(s)</b>											
1 (rodbard 2017)	RC T	not seriou s	not seriou s	NA <sup>2</sup>	seriou s <sup>5</sup>	NA	34/288	10/1 46	RR 1.72 (0.88, 3.39)	50 more per 1000 (8 fewer to 164 more)	mod erat e
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 6 month(s)</b>											
1 (rodbard 2017)	RC T	not seriou s	not seriou s	NA <sup>2</sup>	very seriou s <sup>4</sup>	NA	2/288	0/14 6	PETO OR 4.53 (0.24, 85.38)	7 more per 1000 (3 fewer to 17 more)	low
<b>hba1c change (% , lower values are better, mean difference) at end of follow up Mean follow-up: 6 month(s)</b>											

1 (rodbard 2017)	RC T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	289	146	MD -1.02 (-1.18, -0.86)	MD 1.02 lower (1.18 lower to 0.86 lower)	moderate
<b>weight change (kg, lower values are better, mean difference) at end of follow up Mean follow-up: 6 month(s)</b>											
1 (rodbard 2017)	RC T	very serious <sup>3</sup>	not serious	NA <sup>2</sup>	not serious	NA	289	146	MD 1.48 (0.90, 2.06)	MD 1.48 higher (0.90 higher to 2.06 higher)	low

1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
2. Only one study so no inconsistency
3. >33.3% of the studies in the meta-analysis were at high risk of bias
4. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
5. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)

**L.1.8.2 Adding insulin degludec/liraglutide compared to adding insulin**

**Table 92: Clinical evidence profile: Adding insulin degludec/liraglutide compared to adding insulin**

No of studies	D e s i g n	R i s k o f b i a s	I n d i r e c t n e s s	I n c o n s i s t e n c y	I m p r e c i s i o n	O t h e r c o n s i d e r a t i o n s	I n t e r v e n t i o n N	C o n t r o l N	R e l a t i v e e f f e c t (95% CI)	A b s o l u t e e f f e c t	C e r t a i n t y
health-related quality of life - overall eq-5d-5l index score (higher scores are better, final values) at end of follow up Mean follow-up: 6 month(s)											

1 (watada 2019)	R C T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>3</sup>	NA	105	105	MD 0.03 (-0.00, 0.06)	MD 0.03 higher (0.00 lower to 0.06 higher)	low
<b>health-related quality of life - subscale mental component (sf-36 v2, 0-100, higher scores are better, change scores and final values) at end of follow up Mean follow-up: 6 month(s)</b>											
2	R C T	very serious <sup>4</sup>	not serious	very serious <sup>5</sup>	serious <sup>6</sup>	NA	516	512	MD 0.57 (-1.91, 3.05)	MD 0.57 higher (1.91 lower to 3.05 higher)	very low
<b>health-related quality of life - subscale physical component (sf-36 v2, 0-100, higher scores are better, change scores and final values) at end of follow up Mean follow-up: 6 month(s)</b>											
2	R C T	very serious <sup>4</sup>	not serious	very serious <sup>5</sup>	serious <sup>7</sup>	NA	515	512	MD 0.55 (-1.81, 2.92)	MD 0.55 higher (1.81 lower to 2.92 higher)	very low
<b>all-cause mortality at end of follow up Mean follow-up: 8.6 month(s)</b>											
9	R C T	not serious	not serious	serious <sup>8</sup>	very serious <sup>9</sup>	NA	4/293 2	7/2 180	RD -0.00 (-0.00, 0.00)	2 fewer per 1000 (5 fewer to 2 more)	very low
<b>cardiovascular mortality at end of follow up Mean follow-up: 8.6 month(s)</b>											

9	R C T	not serio us	not serio us	serio us <sup>8</sup>	very serio us <sup>10</sup>	NA	2/293 2	5/2 180	RD -0.00 (-0.00, 0.00)	2 fewer per 1000 (5 fewer to 2 more)	ver y low
<b>3-point mace at end of follow up Mean follow-up: 8 month(s)</b>											
3	R C T	not serio us	not serio us	not serio us	very serio us <sup>11</sup>	NA	9/134 3	5/7 74	PETO OR 1.11 (0.37, 3.32)	0 more per 1000 (7 fewer to 7 more)	low
<b>non-fatal stroke at end of follow up Mean follow-up: 8.9 month(s)</b>											
6	R C T	not serio us	not serio us	serio us <sup>8</sup>	very serio us <sup>11</sup>	NA	7/173 2	4/1 398	PETO OR 1.21 (0.36, 4.11)	1 more per 1000 (3 fewer to 5 more)	ver y low
<b>non-fatal myocardial infarction at end of follow up Mean follow-up: 9.4 month(s)</b>											
7	R C T	not serio us	not serio us	serio us <sup>8</sup>	very serio us <sup>11</sup>	NA	9/240 5	5/1 835	PETO OR 1.48 (0.51, 4.30)	1 more per 1000 (2 fewer to 4 more)	ver y low
<b>unstable angina at end of follow up Mean follow-up: 12 month(s)</b>											
3	R C T	very serio us <sup>4</sup>	not serio us	serio us <sup>8</sup>	very serio us <sup>11</sup>	NA	5/111 9	1/9 36	PETO OR 3.47 (0.69, 17.50)	3 more per 1000 (1 fewer to 8 more)	ver y low
<b>hospitalisation for heart failure at end of follow up Mean follow-up: 15 month(s)</b>											
2	R C T	very serio us <sup>4</sup>	not serio us	serio us <sup>8</sup>	very serio us <sup>11</sup>	NA	1/758	2/7 57	PETO OR 0.51 (0.05, 4.93)	1 fewer per 1000 (6 fewer to 3 more)	ver y low
<b>acute kidney injury at end of follow up Mean follow-up: 6 month(s)</b>											

1 (philis-tsimikas 2019)	R C T	not serio us	not serio us	NA <sup>2</sup>	very serio us <sup>11</sup>	NA	0/209	1/2 10	PETO OR 0.14 (0.00, 6.85)	5 fewer per 1000 (14 fewer to 5 more)	low
<b>persistent signs of worsening kidney disease at end of follow up</b>											
<b>Mean follow-up: 6 month(s)</b>											
1 (philis-tsimikas 2019)	R C T	not serio us	not serio us	NA <sup>2</sup>	very serio us <sup>11</sup>	NA	0/209	1/2 10	PETO OR 0.14 (0.00, 6.85)	5 fewer per 1000 (14 fewer to 5 more)	low
<b>development of end stage kidney disease at end of follow up</b>											
<b>Mean follow-up: 24 month(s)</b>											
1 (aroda 2019a)	R C T	very serio us <sup>4</sup>	not serio us	NA <sup>2</sup>	very serio us <sup>11</sup>	NA	1/506	0/5 04	PETO OR 7.36 (0.15, 370.92)	2 more per 1000 (2 fewer to 6 more)	ver y low
<b>cardiac arrhythmia at end of follow up</b>											
<b>Mean follow-up: 15 month(s)</b>											
2	R C T	very serio us <sup>4</sup>	not serio us	serio us <sup>8</sup>	very serio us <sup>11</sup>	NA	2/758	2/7 57	PETO OR 1.00 (0.14, 7.11)	0 fewer per 1000 (5 fewer to 5 more)	ver y low
<b>hypoglycaemia episodes at end of follow up</b>											
<b>Mean follow-up: 7 month(s)</b>											
6	R C T	not serio us	not serio us	not serio us	serio us <sup>12</sup>	NA	561/2 033	473 /12 85	RR 0.78 (0.70, 0.86)	82 fewer per 1000 (109 fewer to 52 fewer)	mo der ate
<b>at night hypoglycaemic episodes at end of follow up</b>											
<b>Mean follow-up: 6 month(s)</b>											
3	R C T	not serio us	serio us <sup>13</sup>	serio us <sup>14</sup>	serio us <sup>12</sup>	NA	29/81 2	69/ 631	RR 0.47 (0.20, 1.09)	58 fewer per 1000	ver y low

											(87 fewer to 10 more)	
<b>severe hypoglycaemic episodes at end of follow up</b>												
<b>Mean follow-up: 5.9 month(s)</b>												
6	R C T	not serio us	not serio us	serio us <sup>8</sup>	very serio us <sup>15</sup>	NA	16/10 62	20/ 117 6	RD -0.00 (-0.01, - 0.01)	2 fewer per 1000 (14 fewer to 9 more)	ver y low	
<b>hba1c change (% , lower values are better, change scores) at end of follow up</b>												
<b>Mean follow-up: 6.5 month(s)</b>												
11	R C T	serio us <sup>1</sup>	not serio us	very serio us <sup>5</sup>	serio us <sup>16</sup>	NA	3121	255 1	MD -0.65 (-0.82, - 0.48)	MD 0.65 lower (0.82 lower to 0.48 lower)	ver y low	
<b>hba1c change (mmol/mol, lower values are better, change scores) at end of follow up</b>												
<b>Mean follow-up: 6 month(s)</b>												
1 (wang 2022b)	R C T	not serio us	not serio us	NA <sup>2</sup>	serio us <sup>17</sup>	NA	361	179	MD -6.50 (-7.96, - 5.04)	MD 6.50 lower (7.96 lower to 5.04 lower)	mo der ate	
<b>weight change (kg, lower values are better, change scores and final values) at end of follow up</b>												
<b>Mean follow-up: 8 month(s)</b>												
12	R C T	not serio us	not serio us	very serio us <sup>5</sup>	serio us <sup>18</sup>	NA	3736	298 2	MD -2.21 (-2.79, - 1.63)	MD 2.21 lower (2.79 lower to 1.63 lower)	ver y low	

1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
2. Only one study so no inconsistency
3. 95% confidence intervals cross one end of the defined MIDs (-0.03, 0.03)
4. >33.3% of the studies in the meta-analysis were at high risk of bias
5. I<sup>2</sup> > 75%
6. 95% confidence intervals cross one end of the defined MIDs (-3.00, 3.00)
7. 95% confidence intervals cross one end of the defined MIDs (-2.00, 2.00)
8. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
9. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.5 (0.8-0.9 = serious, <0.8 = very serious).
10. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.56 (0.8-0.9 = serious, <0.8 = very serious).
11. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
12. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
13. Largest proportion of studies in the meta-analysis came from partially direct studies
14. I<sup>2</sup> between 50% and 75%
15. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.07 (0.8-0.9 = serious, <0.8 = very serious).
16. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
17. 95% confidence intervals cross one end of the defined MIDs (-5.50, 5.50)
18. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

## L.1.8.3 Adding insulin degludec/liraglutide compared to adding liraglutide

Table 93: Clinical evidence profile: Adding insulin degludec/liraglutide compared to adding liraglutide

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
<b>all-cause mortality at end of follow up Mean follow-up: 9 month(s)</b>											
2	RCT	not serious	not serious	serious <sup>1</sup>	very serious <sup>2</sup>	NA	2/1194	0/594	RD 0.00 (-0.00, 0.01)	2 more per 1000 (3 fewer to 6 more)	very low
<b>cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)</b>											
1 (gough 2014)	RCT	not serious	not serious	NA <sup>3</sup>	very serious <sup>4</sup>	NA	2/833	0/414	PETO OR 4.47 (0.24, 84.97)	2 more per 1000 (1 fewer to 6 more)	low
<b>3-point mace at end of follow up Mean follow-up: 12 month(s)</b>											
1 (gough 2014)	RCT	not serious	not serious	NA <sup>3</sup>	very serious <sup>4</sup>	NA	4/833	1/414	RR 1.99 (0.22, 17.73)	2 more per 1000 (2 fewer to 40 more)	low
<b>non-fatal stroke at end of follow up Mean follow-up: 6 month(s)</b>											
1 (wang 2022b)	RCT	not serious	not serious	NA <sup>3</sup>	very serious <sup>4</sup>	NA	2/361	4/180	RR 0.25 (0.05, 1.35)	17 fewer per 1000 (21 fewer to 8 more)	low
<b>non-fatal myocardial infarction at end of follow up Mean follow-up: 12 month(s)</b>											

1 (gough 2014)	RC T	not serio us	not seriou s	NA <sup>3</sup>	very seriou s <sup>4</sup>	NA	2/833	1/41 4	RR 0.99 (0.09, 10.93)	0 fewer per 1000 (2 fewer to 24 more)	low
<b>unstable angina at end of follow up Mean follow-up: 6 month(s)</b>											
1 (wang 2022b)	RC T	not serio us	not seriou s	NA <sup>3</sup>	not seriou s	NA	0/361	0/18 0	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	high
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 8 month(s)</b>											
3	RC T	not serio us	not seriou s	very seriou s <sup>5</sup>	not seriou s	NA	389/14 61	35/8 65	RR 8.77 (3.03, 25.43)	315 more per 1000 (82 more to 988 more)	low
<b>at night hypoglycaemic episodes at end of follow up Mean follow-up: 6 month(s)</b>											
1 (wang 2022b)	RC T	not serio us	seriou s <sup>6</sup>	NA <sup>3</sup>	very seriou s <sup>4</sup>	NA	5/361	0/18 0	PETO OR 4.53 (0.70, 29.28)	14 more per 1000 (2 more to 26 more)	very low
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 6 month(s)</b>											
1 (gough 2014)	RC T	not serio us	not seriou s	NA <sup>3</sup>	very seriou s <sup>4</sup>	NA	3/825	0/41 4	PETO OR 4.50 (0.41, 49.66)	4 more per 1000 (0 more to 8 more)	low
<b>hba1c change (% , lower values are better, mean difference) at end of follow up Mean follow-up: 9 month(s)</b>											
2	RC T	not serio us	not seriou s	not seriou s	seriou s <sup>7</sup>	NA	1195	688	MD -0.54 (-0.62, - 0.45)	MD 0.54 lower	mod erat e

										(0.62 lower to 0.45 lower)	
<b>hba1c change (mmol/mol, lower values are better, mean difference) at end of follow up Mean follow-up: 6 month(s)</b>											
1 (wang 2022b)	RC T	not serio us	not seriou s	NA <sup>3</sup>	seriou s <sup>8</sup>	NA	361	180	MD -6.87 (-8.32, - 5.42)	MD 6.87 lower (8.32 lower to 5.42 lower)	mod erat e
<b>weight change (kg, lower values are better, mean difference) at end of follow up Mean follow-up: 8 month(s)</b>											
3	RC T	not serio us	not seriou s	very seriou s <sup>5</sup>	seriou s <sup>9</sup>	NA	1470	867	MD 2.96 (2.17, 3.75)	MD 2.96 higher (2.17 higher to 3.75 higher)	very low

1. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
2. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.41 (0.8-0.9 = serious, <0.8 = very serious).
3. Only one study so no inconsistency
4. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
5. I<sup>2</sup> > 75%
6. Largest proportion of studies in the meta-analysis came from partially direct studies
7. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
8. 95% confidence intervals cross one end of the defined MIDs (-5.50, 5.50)
9. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

## L.1.8.4 Adding insulin glargine/lixisenatide compared to adding insulin

Table 94: Clinical evidence profile: Adding insulin glargine/lixisenatide compared to adding insulin

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>all-cause mortality at end of follow up Mean follow-up: 6.3 month(s)</b>											
7	RC T	serious <sup>1</sup>	not serious	serious <sup>2</sup>	very serious <sup>3</sup>	NA	4/2070	5/2073	RD -0.00 (-0.00, 0.00)	0 fewer per 1000 (4 fewer to 3 more)	very low
<b>cardiovascular mortality at end of follow up Mean follow-up: 6.3 month(s)</b>											
7	RC T	serious <sup>1</sup>	not serious	serious <sup>2</sup>	very serious <sup>4</sup>	NA	50/2070	46/2073	RD 0.00 (-0.01, 0.01)	2 more per 1000 (7 fewer to 11 more)	very low
<b>non-fatal stroke at end of follow up Mean follow-up: 7 month(s)</b>											
1 (rosenstock 2016b)	RC T	serious <sup>1</sup>	not serious	NA <sup>5</sup>	very serious <sup>6</sup>	NA	0/469	1/467	PETO OR 0.13 (0.00, 6.79)	2 fewer per 1000 (6 fewer to 2 more)	very low
<b>non-fatal myocardial infarction at end of follow up Mean follow-up: 7 month(s)</b>											
1 (rosenstock 2016b)	RC T	serious <sup>1</sup>	not serious	NA <sup>5</sup>	not serious	NA	0/469	0/467	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (4 fewer to 4 more)	mod erat e
<b>unstable angina at end of follow up Mean follow-up: 7 month(s)</b>											

1 (rosenstock 2016b)	RC T	serious <sup>1</sup>	not serious	NA <sup>5</sup>	very serious <sup>6</sup>	NA	1/469	1/467	PETO OR 1.00 (0.06, 15.94)	0 fewer per 1000 (6 fewer to 6 more)	very low
<b>hospitalisation for heart failure at end of follow up</b> <b>Mean follow-up: 7 month(s)</b>											
1 (rosenstock 2016b)	RC T	serious <sup>1</sup>	not serious	NA <sup>5</sup>	very serious <sup>6</sup>	NA	0/469	2/467	PETO OR 0.13 (0.01, 2.15)	4 fewer per 1000 (10 fewer to 2 more)	very low
<b>death from renal causes at end of follow up</b> <b>Mean follow-up: 6.9 month(s)</b>											
1 (yuan 2022)	RC T	not serious	not serious	NA <sup>5</sup>	not serious	NA	0/211	0/212	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	high
<b>hypoglycaemia episodes at end of follow up</b> <b>Mean follow-up: 6.3 month(s)</b>											
7	RC T	not serious	not serious	serious <sup>2</sup>	not serious	NA	399/2069	397/2073	RR 1.01 (0.90, 1.12)	1 more per 1000 (19 fewer to 24 more)	moderate
<b>severe hypoglycaemic episodes at end of follow up</b> <b>Mean follow-up: 6.3 month(s)</b>											
7	RC T	serious <sup>1</sup>	not serious	serious <sup>2</sup>	very serious <sup>7</sup>	NA	7/2069	6/2073	RD 0.00 (-0.00, 0.00)	0 more per 1000 (3 fewer to 4 more)	very low
<b>hba1c change (% , lower values are better, change scores) at end of follow up</b> <b>Mean follow-up: 6.3 month(s)</b>											

7	RC T	not seriou s	not seriou s	very serious <sup>8</sup>	seriou s <sup>9</sup>	NA	2068	2070	MD -0.50 (-0.64, - 0.35)	MD 0.50 lower (0.64 lower to 0.35 lower)	very low
<b>weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 6.3 month(s)</b>											
7	RC T	not seriou s	not seriou s	not serious	not seriou s	NA	2068	2070	MD -1.16 (-1.32, - 0.99)	MD 1.16 lower (1.32 lower to 0.99 lower)	high

1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
2. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
3. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.07 (0.8-0.9 = serious, <0.8 = very serious).
4. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.09 (0.8-0.9 = serious, <0.8 = very serious).
5. Only one study so no inconsistency
6. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
7. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.06 (0.8-0.9 = serious, <0.8 = very serious).
8. I<sup>2</sup> > 75%
9. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

## L.1.8.5 Adding insulin glargine/lixisenatide compared to adding lixisenatide

Table 95: Clinical evidence profile: Adding insulin glargine/lixisenatide compared to adding lixisenatide

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>all-cause mortality at end of follow up Mean follow-up: 6.2 month(s)</b>											
2	RC T	serio us <sup>1</sup>	not seriou s	serious <sup>2</sup>	very seriou s <sup>3</sup>	NA	2/817	1/40 9	RD -0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	very low
<b>cardiovascular mortality at end of follow up Mean follow-up: 6.2 month(s)</b>											
2	RC T	serio us <sup>1</sup>	not seriou s	serious <sup>2</sup>	very seriou s <sup>4</sup>	NA	1/817	1/40 9	PETO OR 0.47 (0.02, 8.90)	1 fewer per 1000 (7 fewer to 4 more)	very low
<b>non-fatal stroke at end of follow up Mean follow-up: 7 month(s)</b>											
1 (rosenstock 2016b)	RC T	serio us <sup>1</sup>	not seriou s	NA <sup>5</sup>	very seriou s <sup>6</sup>	NA	0/469	1/23 3	PETO OR 0.05 (0.00, 3.16)	4 fewer per 1000 (13 fewer to 4 more)	very low
<b>non-fatal myocardial infarction at end of follow up Mean follow-up: 7 month(s)</b>											
1 (rosenstock 2016b)	RC T	serio us <sup>1</sup>	not seriou s	NA <sup>5</sup>	not seriou s	NA	0/469	0/23 3	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	mod erat e
<b>unstable angina at end of follow up Mean follow-up: 7 month(s)</b>											

1 (rosenstock 2016b)	RC T	serious <sup>1</sup>	not serious	NA <sup>5</sup>	very serious <sup>6</sup>	NA	1/469	0/23 3	PETO OR 4.47 (0.07, 286.86)	2 more per 1000 (2 fewer to 6 more)	very low
<b>hospitalisation for heart failure at end of follow up Mean follow-up: 7 month(s)</b>											
1 (rosenstock 2016b)	RC T	serious <sup>1</sup>	not serious	NA <sup>5</sup>	not serious	NA	0/469	0/23 3	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	mod erat e
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 6.2 month(s)</b>											
2	RC T	serious <sup>1</sup>	not serious	serious <sup>7</sup>	not serious	NA	291/81 7	27/4 09	RR 5.41 (3.71, 7.87)	291 more per 1000 (179 more to 454 more)	low
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 6.2 month(s)</b>											
2	RC T	serious <sup>1</sup>	not serious	serious <sup>2</sup>	very serious <sup>4</sup>	NA	1/817	1/40 9	RD -0.00 (-0.01, 0.01)	1 fewer per 1000 (8 fewer to 5 more)	very low
<b>hba1c change (% , lower values are better, change scores) at end of follow up Mean follow-up: 6.2 month(s)</b>											
2	RC T	not serious	not serious	very serious <sup>8</sup>	not serious	NA	816	408	MD -0.85 (-1.14, - 0.55)	MD 0.85 lower (1.4 lower to 0.55 lower)	low
<b>weight change (kg, lower values are better, change scores) at end of follow up</b>											

Mean follow-up: 6.2 month(s)											
2	RC T	serious <sup>1</sup>	not serious	not serious	not serious	NA	643	581	MD 1.83 (1.40, 2.25)	MD 1.83 higher (1.40 higher to 2.25 higher)	moderate

- >33.3% of the studies in the meta-analysis were at moderate risk of bias
- Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.03 (0.8-0.9 = serious, <0.8 = very serious).
- Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.1 (0.8-0.9 = serious, <0.8 = very serious).
- Only one study so no inconsistency
- 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- I<sup>2</sup> between 50% and 75%
- I<sup>2</sup> > 75%.

#### L.1.8.6 Adding dapagliflozin + exenatide compared to adding dapagliflozin

**Table 96: Clinical evidence profile: Adding dapagliflozin + exenatide compared to adding dapagliflozin**

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
<b>all-cause mortality at end of follow up Mean follow-up: 24 month(s)</b>											
1 (frias 2016)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	3/231	2/233	RR 1.51 (0.26, 8.97)	4 more per 1000	very low

										(6 fewer to 68 more)	
<b>cardiovascular mortality at end of follow up</b> <b>Mean follow-up: 24 month(s)</b>											
1 (frias 2016)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	1/231	1/233	RR 1.01 (0.06, 16.03)	0 more per 1000 (4 fewer to 65 more)	very low
<b>acute kidney injury at end of follow up</b> <b>Mean follow-up: 24 month(s)</b>											
1 (frias 2016)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	0/231	3/233	PETO OR 0.14 (0.01, 1.31)	13 fewer per 1000 (27 fewer to 2 more)	very low
<b>hypoglycaemia episodes at end of follow up</b> <b>Mean follow-up: 24 month(s)</b>											
1 (frias 2016)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	4/231	1/233	RR 4.03 (0.45, 35.83)	13 more per 1000 (2 fewer to 149 more)	very low
<b>severe hypoglycaemic episodes at end of follow up</b> <b>Mean follow-up: 24 month(s)</b>											
1 (frias 2016)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	0/231	0/233	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 8 more)	low
<b>hba1c change (% , lower values are better, change scores) at end of follow up</b> <b>Mean follow-up: 24 month(s)</b>											
1 (frias 2016)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>4</sup>	NA	228	230	MD -0.64 (-0.96, -0.32)	MD 0.64 lower	very low

										(0.96 lower to 0.32 lower)	
<b>weight change (kg, lower values are better, change scores) at end of follow up</b>											
<b>Mean follow-up: 24 month(s)</b>											
1 (frias 2016)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	228	230	MD 0.51 (-0.77, 1.79)	MD 0.51 higher (0.77 lower to 1.79 higher)	low

1. >33.3% of the studies in the meta-analysis were at high risk of bias
2. Only one study so no inconsistency
3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
4. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

#### L.1.8.7 Adding dapagliflozin + exenatide compared to adding exenatide

**Table 97: Clinical evidence profile: Adding dapagliflozin + exenatide compared to adding exenatide**

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert ainty
<b>all-cause mortality at end of follow up</b>											
<b>Mean follow-up: 24 month(s)</b>											
1 (frias 2016)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	3/231	1/230	PETO OR 2.72 (0.38, 19.46)	9 more per 1000 (8 fewer to 26 more)	very low
<b>cardiovascular mortality at end of follow up</b>											
<b>Mean follow-up: 24 month(s)</b>											

1 (frias 2016)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	1/231	1/23 0	PETO OR 1.00 (0.06, 15.97)	0 fewer per 1000 (12 fewer to 12 more)	very low
<b>acute kidney injury at end of follow up Mean follow-up: 24 month(s)</b>											
1 (frias 2016)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	0/231	2/23 0	PETO OR 0.13 (0.01, 2.15)	9 fewer per 1000 (21 fewer to 3 more)	very low
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 24 month(s)</b>											
1 (frias 2016)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>4</sup>	NA	4/231	0/23 0	PETO OR 7.45 (1.04, 53.26)	17 more per 1000 (1 more to 34 more)	very low
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 24 month(s)</b>											
1 (frias 2016)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	0/231	0/23 0	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 8 more)	low
<b>hba1c change (% , lower values are better, change scores) at end of follow up Mean follow-up: 24 month(s)</b>											
1 (frias 2016)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>5</sup>	NA	228	227	MD -0.41 (-0.73, - 0.09)	MD 0.41 lower (0.73 lower to 0.09 lower)	very low
<b>weight change (kg, lower values are better, change scores) at end of follow up</b>											

Mean follow-up: 24 month(s)											
1 (frias 2016)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>6</sup>	NA	228	227	MD -1.71 (-2.96, -0.46)	MD 1.71 lower (2.96 lower to 0.46 lower)	very low

- >33.3% of the studies in the meta-analysis were at high risk of bias
- Only one study so no inconsistency
- 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
- 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

#### L.1.8.8 Adding dapagliflozin + saxagliptin compared to adding dapagliflozin

**Table 98: Clinical evidence profile: Adding dapagliflozin + Saxagliptin compared to adding dapagliflozin**

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>all-cause mortality at end of follow up Mean follow-up: 5.5 month(s)</b>											
2	RC T	not serious	not serious	serious <sup>1</sup>	very serious <sup>2</sup>	NA	1/472	2/472	RD -0.00 (-0.01, 0.01)	2 fewer per 1000 (10 fewer to 6 more)	very low
<b>cardiovascular mortality at end of follow up Mean follow-up: 5.5 month(s)</b>											

2	RC T	not seriou s	not seriou s	serious 1	very seriou s <sup>3</sup>	NA	0/472	2/47 2	RD -0.00 (-0.01, 0.00)	4 fewer per 1000 (13 fewer to 4 more)	very low
<b>hospitalisation for heart failure at end of follow up Mean follow-up: 12 month(s)</b>											
1 (muller-wieland 2018)	RC T	not seriou s	not seriou s	NA <sup>4</sup>	not seriou s	NA	0/312	0/31 3	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	high
<b>persistent signs of worsening kidney disease at end of follow up Mean follow-up: 5.5 month(s)</b>											
1 (rosenstock 2015a)	RC T	seriou s <sup>5</sup>	not seriou s	NA <sup>4</sup>	not seriou s	NA	0/179	0/17 9	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (11 fewer to 11 more)	mod erat e
<b>diabetic ketoacidosis at end of follow up Mean follow-up: 5.5 month(s)</b>											
1 (rosenstock 2019d)	RC T	not seriou s	not seriou s	NA <sup>4</sup>	not seriou s	NA	0/293	0/29 3	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	high
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 7.7 month(s)</b>											
3	RC T	not seriou s	not seriou s	serious 1	seriou s <sup>6</sup>	NA	9/784	3/78 3	PETO OR 2.74 (0.88, 8.54)	8 more per 1000 (1 fewer to 16 more)	low
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 7.7 month(s)</b>											

3	RC T	not seriou s	not seriou s	serious <sup>1</sup>	very seriou s <sup>7</sup>	NA	1/784	1/78 3	RD 0.00 (-0.00, 0.00)	0 fewer per 1000 (5 fewer to 5 more)	very low
<b>hba1c change (% , lower values are better, change scores) at end of follow up Mean follow-up: 7.7 month(s)</b>											
3	RC T	not seriou s	not seriou s	not serious	not seriou s	NA	753	740	MD -0.37 (-0.46, - 0.27)	MD 0.37 lower (0.46 lower to 0.27 lower)	high
<b>weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 8.8 month(s)</b>											
2	RC T	not seriou s	not seriou s	not serious	not seriou s	NA	471	463	MD 0.31 (-0.12, 0.74)	MD 0.31 higher (0.12 lower to 0.74 higher)	high

1. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
2. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.13 (0.8-0.9 = serious, <0.8 = very serious).
3. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.52 (0.8-0.9 = serious, <0.8 = very serious).
4. Only one study so no inconsistency
5. >33.3% of the studies in the meta-analysis were at moderate risk of bias
6. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
7. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.03 (0.8-0.9 = serious, <0.8 = very serious)

## L.1.8.9 Adding dapagliflozin + saxagliptin compared to adding glimepiride

Table 99: Clinical evidence profile: Adding dapagliflozin + saxagliptin compared to adding glimepiride

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>all-cause mortality at end of follow up Mean follow-up: 36 month(s)</b>											
1 (frias 2020)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>3</sup>	NA	1/227	3/21 6	PETO OR 0.35 (0.05, 2.48)	9 fewer per 1000 (27 fewer to 8 more)	very low
<b>hospitalisation for heart failure at end of follow up Mean follow-up: 12 month(s)</b>											
2	RC T	not seriou s	not seriou s	serious <sup>4</sup>	very seriou s <sup>5</sup>	NA	0/539	1/52 8	RD -0.00 (-0.01, 0.00)	2 fewer per 1000 (8 fewer to 4 more)	very low
<b>diabetic ketoacidosis at end of follow up Mean follow-up: 12 month(s)</b>											
1 (frias 2020)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	not seriou s	NA	0/227	0/21 6	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (9 fewer to 9 more)	low
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 24 month(s)</b>											
2	RC T	very seriou s <sup>1</sup>	not seriou s	serious <sup>6</sup>	seriou s <sup>7</sup>	NA	20/539	66/5 25	RR 0.22 (0.06, 0.87)	98 fewer per 1000 (119 fewer to 16 fewer)	very low
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 24 month(s)</b>											

2	RC T	not serious	not serious	serious <sup>4</sup>	very serious <sup>8</sup>	NA	0/539	3/52 5	RD -0.01 (-0.02, 0.01)	6 fewer per 1000 (24 fewer to 13 more)	very low
<b>hba1c change (% , lower values are better, change scores) at end of follow up Mean follow-up: 24 month(s)</b>											
2	RC T	not serious	not serious	serious <sup>6</sup>	serious <sup>9</sup>	NA	529	517	MD -0.34 (-0.65, - 0.02)	MD 0.34 lower (0.65 lower to 0.02 lower)	low
<b>weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 24 month(s)</b>											
2	RC T	not serious	not serious	very serious <sup>10</sup>	serious <sup>11</sup>	NA	536	522	MD -4.12 (-6.12, - 2.12)	MD 4.12 lower (6.12 lower to 2.12 lower)	very low

1. >33.3% of the studies in the meta-analysis were at high risk of bias
2. Only one study so no inconsistency
3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
4. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
5. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.3 (0.8-0.9 = serious, <0.8 = very serious).
6. I2 between 50% and 75%
7. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)

8. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.69 (0.8-0.9 = serious, <0.8 = very serious).

9. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

10. I<sup>2</sup> > 75%

11. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

#### L.1.8.10 Adding dapagliflozin + saxagliptin compared to adding insulin

**Table 100: Clinical evidence profile: Adding dapagliflozin + saxagliptin compared to adding insulin**

No of studies	D e s i g n	R i s k o f b i a s	I n d i r e c t n e s s	I n c o n s i s t e n c y	I m p r e c i s i o n	O t h e r c o n s i d e r a t i o n s	I n t e r v e n t i o n N	C o n t r o l N	R e l a t i v e e f f e c t (95% CI)	A b s o l u t e e f f e c t	C e r t a i n t y
<b>health-related quality of life - subscale net benefit score (phase v health outcomes information systems diabetes module, higher scores are better, change scores) at end of follow up Mean follow-up: 12 month(s)</b>											
1 (vilsboll 2019)	R C T	not seri ous	not seri ous	NA <sup>1</sup>	not seri ous	NA	324	31 9	MD 1.10 (-0.84, 3.04)	MD 1.10 higher (0.84 lower to 3.04 higher)	high
<b>health-related quality of life - subscale regimen acceptance score (phase v health outcomes information systems diabetes module, higher scores are better, change scores) at end of follow up Mean follow-up: 12 month(s)</b>											
1 (vilsboll 2019)	R C T	not seri ous	not seri ous	NA <sup>1</sup>	not seri ous	NA	324	31 9	MD 4.20 (1.98, 6.42)	MD 4.20 higher (1.98 higher to	high

										6.42 higher)	
<b>health-related quality of life - subscale satisfaction (phase v health outcomes information systems diabetes module, higher scores are better, change scores) at end of follow up Mean follow-up: 12 month(s)</b>											
1 (vilsboll 2019)	R C T	not seri ous	not seri ous	NA <sup>1</sup>	not seri ous	NA	324	31 9	MD 3.40 (1.46, 5.34)	MD 3.40 higher (1.46 higher to 5.34 higher)	high
<b>all-cause mortality at end of follow up Mean follow-up: 12 month(s)</b>											
1 (vilsboll 2019)	R C T	not seri ous	not seri ous	NA <sup>1</sup>	very seri ous <sup>2</sup>	NA	2/32 4	0/3 19	PETO OR 7.30 (0.46, 116.95)	6 more per 1000 (2 fewer to 15 more)	low
<b>cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)</b>											
1 (vilsboll 2019)	R C T	not seri ous	not seri ous	NA <sup>1</sup>	not seri ous	NA	0/32 4	0/3 19	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	high
<b>acute kidney injury at end of follow up Mean follow-up: 12 month(s)</b>											
1 (vilsboll 2019)	R C T	not seri ous	not seri ous	NA <sup>1</sup>	not seri ous	NA	0/32 4	0/3 19	RR 0.00 (0.00, 0.00)	0 fewer per 1000 (0 more to 0 more)	high
<b>diabetic ketoacidosis at end of follow up Mean follow-up: 12 month(s)</b>											

1 (vilsboll 2019)	R C T	not seri ous	not seri ous	NA <sup>1</sup>	very seri ous <sup>2</sup>	NA	0/32 4	1/3 19	PETO OR 0.13 (0.00, 6.72)	3 fewer per 1000 (9 fewer to 3 more)	lo w
<b>hypoglycaemia episodes at end of follow up</b> <b>Mean follow-up: 12 month(s)</b>											
1 (vilsboll 2019)	R C T	not seri ous	not seri ous	NA <sup>1</sup>	not seri ous	NA	93/3 24	14 7/3 19	RR 0.62 (0.51, 0.77)	174 fewer per 1000 (228 fewer to 107 fewer)	hig h
<b>severe hypoglycaemic episodes at end of follow up</b> <b>Mean follow-up: 12 month(s)</b>											
1 (vilsboll 2019)	R C T	not seri ous	not seri ous	NA <sup>1</sup>	very seri ous <sup>2</sup>	NA	0/32 4	3/3 19	PETO OR 0.13 (0.01, 1.28)	9 fewer per 1000 (20 fewer to 1 more)	lo w
<b>hba1c change (% , lower values are better, change scores) at end of follow up</b> <b>Mean follow-up: 12 month(s)</b>											
1 (vilsboll 2019)	R C T	very seri ous <sup>3</sup>	not seri ous	NA <sup>1</sup>	not seri ous	NA	212	17 7	MD - 0.25 (-0.40, - 0.10)	MD 0.25 lower (0.40 lower to 0.10 lower)	lo w
<b>weight change (kg, lower values are better, change scores) at end of follow up</b> <b>Mean follow-up: 12 month(s)</b>											
1 (vilsboll 2019)	R C T	very seri ous <sup>3</sup>	not seri ous	NA <sup>1</sup>	not seri ous	NA	212	17 8	MD - 4.60	MD 4.60 lower	lo w



1 (rosenstock 2015a)	RC T	serious <sup>3</sup>	not serious	NA <sup>4</sup>	not serious	NA	0/179	0/176	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (11 fewer to 11 more)	moderate
<b>diabetic ketoacidosis at end of follow up</b> <b>Mean follow-up: 5.5 month(s)</b>											
1 (rosenstock 2019d)	RC T	not serious	not serious	NA <sup>4</sup>	not serious	NA	0/293	0/295	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (7 fewer to 7 more)	high
<b>hypoglycaemia episodes at end of follow up</b> <b>Mean follow-up: 5.5 month(s)</b>											
2	RC T	not serious	not serious	not serious	very serious <sup>5</sup>	NA	8/472	6/471	RR 1.33 (0.47, 3.81)	4 more per 1000 (7 fewer to 36 more)	low
<b>severe hypoglycaemic episodes at end of follow up</b> <b>Mean follow-up: 5.5 month(s)</b>											
2	RC T	not serious	not serious	serious <sup>1</sup>	very serious <sup>2</sup>	NA	1/472	0/469	RD 0.00 (-0.01, 0.01)	2 more per 1000 (5 fewer to 9 more)	very low
<b>hba1c change (% , lower values are better, change scores) at end of follow up</b> <b>Mean follow-up: 5.5 month(s)</b>											
2	RC T	not serious	not serious	very serious <sup>6</sup>	serious <sup>7</sup>	NA	443	431	MD -0.75 (-1.61, 0.12)	MD 0.75 lower (1.61 lower to 0.12 higher)	very low
<b>weight change (kg, lower values are better, change scores) at end of follow up</b> <b>Mean follow-up: 5.5 month(s)</b>											

2	RC T	not serious	not serious	not serious	not serious	NA	443	433	MD -1.79 (-2.22, - 1.36)	MD 1.79 lower (2.22 lower to 1.36 lower)	high
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1. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
2. Precision calculated through Optimal Information Size (OIS) due to zero events in some studies. OIS determined power for the sample size = 0.29 (0.8-0.9 = serious, <0.8 = very serious).
3. >33.3% of the studies in the meta-analysis were at moderate risk of bias
4. Only one study so no inconsistency
5. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
6.  $I^2 > 75\%$
7. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

#### L.1.8.12 Adding dapagliflozin + saxagliptin compared to adding sitagliptin

**Table 102: Clinical evidence profile: Adding dapagliflozin + saxagliptin compared to adding sitagliptin**

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>all-cause mortality at end of follow up Mean follow-up: 12 month(s)</b>											
1 (handelsman 2019)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	0/232	0/22 9	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 8 more)	low
<b>cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)</b>											

1 (handelsman 2019)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	0/232	0/22 9	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 8 more)	low
<b>acute kidney injury at end of follow up Mean follow-up: 12 month(s)</b>											
1 (handelsman 2019)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	1/232	0/22 9	PETO OR 7.29 (0.14, 367.63)	4 more per 1000 (4 fewer to 13 more)	very low
<b>cardiac arrhythmia at end of follow up Mean follow-up: 12 month(s)</b>											
1 (handelsman 2019)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	1/232	5/22 9	PETO OR 0.26 (0.05, 1.28)	18 fewer per 1000 (38 fewer to 3 more)	very low
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 12 month(s)</b>											
1 (handelsman 2019)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	12/232	9/22 9	RR 1.32 (0.57, 3.06)	12 more per 1000 (17 fewer to 81 more)	very low
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)</b>											
1 (handelsman 2019)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	0/232	0/22 9	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (8 fewer to 8 more)	low
<b>hba1c change (% , lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)</b>											

1 (handelsman 2019)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>4</sup>	NA	232	229	MD -0.48 (-0.72, - 0.24)	MD 0.48 lower (0.72 lower to 0.24 lower)	very low
<b>weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)</b>											
1 (handelsman 2019)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	232	229	MD -1.50 (-2.33, - 0.67)	MD 1.50 lower (2.33 lower to 0.67 lower)	low

- >33.3% of the studies in the meta-analysis were at high risk of bias
- Only one study so no inconsistency
- 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

#### L.1.8.13 Adding empagliflozin + liraglutide compared to adding empagliflozin

**Table 103: Clinical evidence profile: Adding empagliflozin + liraglutide compared to adding empagliflozin**

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert ainty
<b>hba1c change (% , lower values are better, final scores) at end of follow up Mean follow-up: 12 month(s)</b>											
1 (ikonomidis 2020)	RC T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>3</sup>	NA	40	40	MD -0.70 (-1.12, - 0.28)	MD 0.70 lower (1.12 lower to 0.28 lower)	low

<b>weight change (kg, lower values are better, final scores) at end of follow up Mean follow-up: 12 month(s)</b>											
1 (ikonomidis 2020)	RC T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>4</sup>	NA	40	40	MD 1.10 (-3.07, 5.27)	MD 1.10 higher (3.07 lower to 5.27 higher)	very low
<b>bmi change (kg/m2, lower values are better, final scores) at end of follow up Mean follow-up: 12 month(s)</b>											
1 (ikonomidis 2020)	RC T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>5</sup>	NA	40	40	MD -1.10 (-2.49, 0.29)	MD 1.10 lower (2.49 lower to 0.29 higher)	low

1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
2. Only one study so no inconsistency
3. 95% confidence intervals cross one end of the defined MIDd (-0.50, 0.50)
4. 95% confidence intervals cross both ends of the defined MIDd (-2.40, 2.40)
5. 95% confidence intervals cross one end of the defined MIDd (-0.80, 0.80)

**L.1.8.14 Adding empagliflozin + liraglutide compared to adding insulin**

**Table 104: Clinical evidence profile: Adding empagliflozin + liraglutide compared to adding insulin**

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>hba1c change (% , lower values are better, final scores) at end of follow up Mean follow-up: 12 month(s)</b>											

1 (ikonomidis 2020)	RC T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>3</sup>	NA	40	40	MD -0.70 (-1.15, -0.25)	MD 0.70 lower (1.15 lower to 0.25 lower)	low
<b>weight change (kg, lower values are better, final scores) at end of follow up Mean follow-up: 12 month(s)</b>											
1 (ikonomidis 2020)	RC T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>4</sup>	NA	40	40	MD -1.80 (-5.74, 2.14)	MD 1.80 lower (5.74 lower to 2.14 higher)	low
<b>bmi change (kg/m2, lower values are better, final scores) at end of follow up Mean follow-up: 12 month(s)</b>											
1 (ikonomidis 2020)	RC T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>5</sup>	NA	40	40	MD -2.30 (-3.85, -0.75)	MD 2.30 lower (3.85 lower to 0.75 lower)	low

- >33.3% of the studies in the meta-analysis were at moderate risk of bias
- Only one study so no inconsistency
- 95% confidence intervals cross one end of the defined MIDd (-0.50, 0.50)
- 95% confidence intervals cross one end of the defined MIDd (-2.40, 2.40)
- 95% confidence intervals cross one end of the defined MIDd (-0.80, 0.80)

#### L.1.8.15 Adding empagliflozin + liraglutide compared to adding liraglutide

**Table 105: Clinical evidence profile: Adding empagliflozin + liraglutide compared to adding liraglutide**

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
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<b>hba1c change (% , lower values are better, final scores) at end of follow up Mean follow-up: 12 month(s)</b>											
1 (ikonomidis 2020)	RC T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>3</sup>	NA	40	40	MD -0.30 (-0.67, 0.07)	MD 0.30 lower (0.67 lower to 0.07 higher)	low
<b>weight change (kg, lower values are better, final scores) at end of follow up Mean follow-up: 12 month(s)</b>											
1 (ikonomidis 2020)	RC T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>4</sup>	NA	40	40	MD 0.40 (-4.25, 5.05)	MD 0.40 higher (4.25 lower to 5.05 higher)	very low
<b>bmi change (kg/m2, lower values are better, final scores) at end of follow up Mean follow-up: 12 month(s)</b>											
1 (ikonomidis 2020)	RC T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>5</sup>	NA	40	40	MD -0.30 (-1.85, 1.25)	MD 0.30 lower (1.85 lower to 1.25 higher)	very low

1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
2. Only one study so no inconsistency
3. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
4. 95% confidence intervals cross both ends of the defined MIDs (-2.40, 2.40)
5. 95% confidence intervals cross both ends of the defined MIDs (-0.80, 0.80)

## L.1.8.16 Adding ertugliflozin + sitagliptin compared to adding ertugliflozin

Table 106: Clinical evidence profile: Adding ertugliflozin + sitagliptin compared to adding ertugliflozin

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerat ions	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>all-cause mortality at end of follow up Mean follow-up: 12 month(s)</b>											
1 (pratley 2018a)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	very seriou s <sup>2</sup>	NA	1/487	1/49 8	PETO OR 1.02 (0.06, 16.37)	0 more per 1000 (6 fewer to 6 more)	low
<b>cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)</b>											
1 (pratley 2018a)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	very seriou s <sup>2</sup>	NA	0/487	1/49 8	PETO OR 0.14 (0.00, 6.97)	2 fewer per 1000 (6 fewer to 2 more)	low
<b>diabetic ketoacidosis at end of follow up Mean follow-up: 12 month(s)</b>											
1 (pratley 2018a)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	very seriou s <sup>2</sup>	NA	1/487	0/49 8	PETO OR 7.56 (0.15, 380.98)	2 more per 1000 (2 fewer to 6 more)	low
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 12 month(s)</b>											
1 (pratley 2018a)	RC T	very seriou s <sup>3</sup>	not seriou s	NA <sup>1</sup>	very seriou s <sup>2</sup>	NA	22/487	15/4 98	RR 1.50 (0.79, 2.86)	15 more per 1000 (6 fewer to 56 more)	very low
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)</b>											

1 (pratley 2018a)	RC T	very serious <sup>3</sup>	not serious	NA <sup>1</sup>	very serious <sup>2</sup>	NA	0/487	2/49 8	PETO OR 0.14 (0.01, 2.21)	4 fewer per 1000 (10 fewer to 2 more)	very low
<b>hba1c change (% , lower values are better, change scores) at end of follow up</b>											
<b>Mean follow-up: 12 month(s)</b>											
1 (pratley 2018a)	RC T	very serious <sup>3</sup>	not serious	NA <sup>1</sup>	serious <sup>4</sup>	NA	487	498	MD -0.50 (-0.64, - 0.36)	MD 0.50 lower (0.64 lower to 0.36 lower)	very low
<b>weight change (kg, lower values are better, change scores) at end of follow up</b>											
<b>Mean follow-up: 12 month(s)</b>											
1 (pratley 2018a)	RC T	very serious <sup>3</sup>	not serious	NA <sup>1</sup>	not serious	NA	487	498	MD 0.20 (-0.37, 0.77)	MD 0.20 higher (0.37 lower to 0.77 higher)	low

1. Only one study so no inconsistency
2. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
3. >33.3% of the studies in the meta-analysis were at high risk of bias
4. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

#### L.1.8.17 Adding ertugliflozin + sitagliptin compared to adding sitagliptin

**Table 107: Clinical evidence profile: Adding ertugliflozin + sitagliptin compared to adding sitagliptin**

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y

<b>all-cause mortality at end of follow up</b> <b>Mean follow-up: 12 month(s)</b>											
1 (pratley 2018a)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	very seriou s <sup>2</sup>	NA	1/487	0/24 7	PETO OR 4.51 (0.07, 285.75)	2 more per 1000 (2 fewer to 6 more)	low
<b>cardiovascular mortality at end of follow up</b> <b>Mean follow-up: 12 month(s)</b>											
1 (pratley 2018a)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	not seriou s	NA	0/487	0/24 7	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	high
<b>diabetic ketoacidosis at end of follow up</b> <b>Mean follow-up: 12 month(s)</b>											
1 (pratley 2018a)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	very seriou s <sup>2</sup>	NA	1/487	0/24 7	PETO OR 4.51 (0.07, 285.75)	2 more per 1000 (2 fewer to 6 more)	low
<b>hypoglycaemia episodes at end of follow up</b> <b>Mean follow-up: 12 month(s)</b>											
1 (pratley 2018a)	RC T	very seriou s <sup>3</sup>	not seriou s	NA <sup>1</sup>	very seriou s <sup>2</sup>	NA	22/487	7/24 7	RR 1.59 (0.69, 3.68)	17 more per 1000 (9 fewer to 76 more)	very low
<b>severe hypoglycaemic episodes at end of follow up</b> <b>Mean follow-up: 12 month(s)</b>											
1 (pratley 2018a)	RC T	very seriou s <sup>3</sup>	not seriou s	NA <sup>1</sup>	not seriou s	NA	0/487	0/24 7	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (6 fewer to 6 more)	low
<b>hba1c change (% , lower values are better, change scores) at end of follow up</b>											

Mean follow-up: 12 month(s)											
1 (pratley 2018a)	RC T	very serious <sup>3</sup>	not serious	NA <sup>1</sup>	serious <sup>4</sup>	NA	487	247	MD -0.60 (-0.77, - 0.43)	MD 0.60 lower (0.77 lower to 0.43 lower)	very low
<b>weight change (kg, lower values are better, change scores) at end of follow up</b> <b>Mean follow-up: 12 month(s)</b>											
1 (pratley 2018a)	RC T	very serious <sup>3</sup>	not serious	NA <sup>1</sup>	serious <sup>5</sup>	NA	487	247	MD -2.50 (-3.23, - 1.77)	MD 2.50 lower (3.23 lower to 1.77 lower)	very low

1. Only one study so no inconsistency
2. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
3. >33.3% of the studies in the meta-analysis were at high risk of bias
4. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
5. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)

#### L.1.8.18 Adding glimepiride + metformin compared to adding glimepiride

**Table 108: Clinical evidence profile: Adding glimepiride + metformin compared to adding glimepiride**

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerat ions	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
hypoglycaemia episodes at end of follow up Mean follow-up: 5.5 month(s)											

1 (park 2014)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	17/32	20/3 4	RR 0.90 (0.59, 1.39)	57 fewer per 1000 (243 fewer to 229 more)	very low
<b>at night hypoglycaemic episodes at end of follow up</b>											
<b>Mean follow-up: 5.5 month(s)</b>											
1 (park 2014)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	3/32	6/34	RR 0.53 (0.14, 1.95)	83 fewer per 1000 (151 fewer to 167 more)	very low
<b>severe hypoglycaemic episodes at end of follow up</b>											
<b>Mean follow-up: 5.5 month(s)</b>											
1 (park 2014)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>4</sup>	NA	0/32	0/34	RD 0.00 (-0.06, 0.06)	0 fewer per 1000 (57 fewer to 57 more)	very low
<b>hba1c change (% , lower values are better, change scores) at end of follow up</b>											
<b>Mean follow-up: 5.5 month(s)</b>											
1 (park 2014)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>5</sup>	NA	32	32	MD -0.71 (-1.20, - 0.22)	MD 0.71 lower (1.20 lower to 0.22 lower)	very low
<b>weight change (kg, lower values are better, change scores) at end of follow up</b>											
<b>Mean follow-up: 5.5 month(s)</b>											
1 (park 2014)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	32	32	MD 0.12 (-1.25, 1.49)	MD 0.12 higher (1.25 lower to 1.49 higher)	low

1. >33.3% of the studies in the meta-analysis were at high risk of bias

2. Only one study so no inconsistency
3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
4. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
5. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

#### L.1.8.19 Adding glimepiride + metformin compared to adding metformin

**Table 109: Clinical evidence profile: Adding glimepiride + metformin compared to adding metformin**

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerat ions	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>hypoglycaemia episodes at end of follow up</b> <b>Mean follow-up: 5.5 month(s)</b>											
1 (park 2014)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>3</sup>	NA	17/32	20/3 4	RR 0.90 (0.59, 1.39)	57 fewer per 1000 (243 fewer to 229 more)	very low
<b>at night hypoglycaemic episodes at end of follow up</b> <b>Mean follow-up: 5.5 month(s)</b>											
1 (park 2014)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>3</sup>	NA	3/32	6/34	RR 0.53 (0.14, 1.95)	83 fewer per 1000 (151 fewer to 167 more)	very low
<b>severe hypoglycaemic episodes at end of follow up</b> <b>Mean follow-up: 5.5 month(s)</b>											
1 (park 2014)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>4</sup>	NA	0/32	0/34	RD 0.00 (-0.06, 0.06)	0 fewer per 1000	very low

											(57 fewer to 57 more)	
<b>hba1c change (% lower values are better, change scores) at end of follow up</b>												
<b>Mean follow-up: 5.5 month(s)</b>												
1 (park 2014)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>5</sup>	NA	32	32	MD -0.71 (-1.20, -0.22)	MD 0.71 lower (1.20 lower to 0.22 lower)	very low	
<b>weight change (kg, lower values are better, change scores) at end of follow up</b>												
<b>Mean follow-up: 5.5 month(s)</b>												
1 (park 2014)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	32	32	MD 0.12 (-1.25, 1.49)	MD 0.12 higher (1.25 lower to 1.49 higher)	low	

- >33.3% of the studies in the meta-analysis were at moderate risk of bias
- Only one study so no inconsistency
- 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
- 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

**L.1.8.20 Adding glimepiride + metformin slow release compared to adding glimepiride + metformin standard release**

**Table 110: Clinical evidence profile: Adding glimepiride + metformin slow release compared to adding glimepiride + metformin standard release**

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
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hypoglycaemia episodes at end of follow up Mean follow-up: 5.8 month(s)											
1 (kim 2018)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>3</sup>	NA	19/86	10/86	RR 1.90 (0.94, 3.85)	105 more per 1000 (7 fewer to 331 more)	very low
at night hypoglycaemic episodes at end of follow up Mean follow-up: 5.8 month(s)											
1 (kim 2018)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>4</sup>	NA	3/86	5/86	RR 0.60 (0.15, 2.43)	23 fewer per 1000 (50 fewer to 83 more)	very low

1. >33.3% of the studies in the meta-analysis were at high risk of bias
2. Only one study so no inconsistency
3. 95% confidence intervals cross one end of the defined MID (0.80, 1.25)
4. 95% confidence intervals cross both ends of the defined MID (0.80, 1.25)

#### L.1.8.21 Adding liraglutide + metformin compared to adding metformin

**Table 111: Clinical evidence profile: Adding liraglutide + metformin compared to adding metformin**

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
hba1c change (% lower values are better, final values) at end of follow up Mean follow-up: 6 month(s)											

1 (iacobellis 2017)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>3</sup>	NA	49	36	MD -0.80 (-1.13, - 0.47)	MD 0.80 lower (1.13 lower to 0.47 lower)	very low
<b>bmi change (kg/m2, lower values are better, final values) at end of follow up Mean follow-up: 6 month(s)</b>											
1 (iacobellis 2017)	RC T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	49	36	MD 4.00 (1.92, 6.08)	MD 4.00 higher (1.92 higher to 6.08 higher)	low

- >33.3% of the studies in the meta-analysis were at high risk of bias
- Only one study so no inconsistency
- 95% confidence intervals cross one end of the defined MID (s) (-0.50, 0.50)

**L.1.8.22 Adding pioglitazone + alogliptin compared to adding pioglitazone**

**Table 112: Clinical evidence profile: Adding pioglitazone + alogliptin compared to adding pioglitazone**

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>all-cause mortality at end of follow up</b>											

<b>Mean follow-up: 6 month(s)</b>												
1 (defronzo 2012)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>3</sup>	NA	0/780	1/38 7	PETO OR 0.05 (0.00, 3.15)	3 fewer per 1000 (8 fewer to 2 more)	very low	
<b>cardiovascular mortality at end of follow up Mean follow-up: 6 month(s)</b>												
1 (defronzo 2012)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>3</sup>	NA	0/780	1/38 7	PETO OR 0.05 (0.00, 3.15)	3 fewer per 1000 (8 fewer to 2 more)	very low	
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 6 month(s)</b>												
1 (defronzo 2012)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>3</sup>	NA	10/780	8/38 7	RR 0.62 (0.25, 1.56)	8 fewer per 1000 (16 fewer to 12 more)	very low	
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 6 month(s)</b>												
1 (defronzo 2012)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>3</sup>	NA	1/780	2/38 7	PETO OR 0.22 (0.02, 2.44)	4 fewer per 1000 (11 fewer to 4 more)	very low	
<b>hba1c change (% , lower values are better, change scores) at end of follow up Mean follow-up: 6 month(s)</b>												
1 (defronzo 2012)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	seriou s <sup>4</sup>	NA	659	274	MD -0.50 (-0.62, - 0.38)	MD 0.50 lower (0.62 lower to 0.38 lower)	very low	

1. >33.3% of the studies in the meta-analysis were at high risk of bias
2. Only one study so no inconsistency
3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
4. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

### L.1.8.23 Adding pioglitazone + exenatide compared to adding insulin

**Table 113: Clinical evidence profile: Adding pioglitazone + exenatide compared to adding insulin**

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert ainty
<b>all-cause mortality at end of follow up Mean follow-up: 36 month(s)</b>											
1 (abdul-ghani 2017)	RC T	seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>3</sup>	NA	1/146	2/14 0	PETO OR 0.49 (0.05, 4.75)	7 fewer per 1000 (31 fewer to 16 more)	very low
<b>non-fatal stroke at end of follow up Mean follow-up: 36 month(s)</b>											
1 (abdul-ghani 2017)	RC T	seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>3</sup>	NA	0/146	2/14 0	PETO OR 0.13 (0.01, 2.07)	14 fewer per 1000 (34 fewer to 5 more)	very low
<b>hospitalisation for heart failure at end of follow up Mean follow-up: 36 month(s)</b>											
1 (abdul-ghani 2017)	RC T	seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	seriou s <sup>4</sup>	NA	0/146	0/14 0	RD 0.00 (-0.01, 0.01)	0 fewer per 1000 (14 fewer to 14 more)	low

<b>hypoglycaemia episodes at end of follow up</b> <b>Mean follow-up: 36 month(s)</b>											
1 (abdul-ghani 2017)	RC T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>4</sup>	NA	99/146	125/140	RR 0.76 (0.67, 0.86)	215 fewer per 1000 (295 fewer to 124 fewer)	low
<b>severe hypoglycaemic episodes at end of follow up</b> <b>Mean follow-up: 36 month(s)</b>											
1 (abdul-ghani 2017)	RC T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	0/146	1/140	PETO OR 0.13 (0.00, 6.54)	7 fewer per 1000 (21 fewer to 7 more)	very low
<b>weight change (kg, lower values are better, change scores) at end of follow up</b> <b>Mean follow-up: 36 month(s)</b>											
1 (abdul-ghani 2017)	RC T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	146	140	MD -4.40 (-4.73, -4.07)	MD 4.40 lower (4.73 lower to 4.07 lower)	moderate

1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
2. Only one study so no inconsistency
3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
4. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
5. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)

## L.1.8.24 Adding pioglitazone + exenatide compared to adding pioglitazone

Table 114: Clinical evidence profile: Adding pioglitazone + exenatide compared to adding pioglitazone

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
<b>hba1c change (% , lower values are better, final values) at end of follow up Mean follow-up: 12 month(s)</b>											
1 (sathyanarayana 2011)	RCT	very serious <sup>1</sup>	serious <sup>2</sup>	NA <sup>3</sup>	serious <sup>4</sup>	NA	11	10	MD -0.50 (-0.80, -0.20)	MD 0.50 lower (0.80 lower to 0.20 lower)	very low
<b>weight change (kg, lower values are better, final values) at end of follow up Mean follow-up: 12 month(s)</b>											
1 (sathyanarayana 2011)	RCT	very serious <sup>1</sup>	serious <sup>2</sup>	NA <sup>3</sup>	very serious <sup>5</sup>	NA	11	10	MD -1.10 (-6.54, 4.34)	MD 1.10 lower (6.54 lower to 4.34 higher)	very low
<b>bmi change (kg/m2, lower values are better, final values) at end of follow up Mean follow-up: 12 month(s)</b>											
1 (sathyanarayana 2011)	RCT	very serious <sup>1</sup>	serious <sup>2</sup>	NA <sup>3</sup>	not serious	NA	11	10	MD 3.40 (1.83, 4.97)	MD 3.40 higher (1.83 higher to 4.97 higher)	very low

- >33.3% of the studies in the meta-analysis were at high risk of bias
- Largest proportion of studies in the meta-analysis came from partially direct studies
- Only one study so no inconsistency
- 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

5. 95% confidence intervals cross both ends of the defined MIDs (-2.40, 2.40)

#### L.1.8.25 Adding pioglitazone + metformin compared to adding metformin

**Table 115: Clinical evidence profile: Adding pioglitazone + metformin compared to adding metformin**

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 6 month(s)</b>											
1 (hanefeld 2011)	RC T	seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>3</sup>	NA	11/39	9/42	RR 1.32 (0.61, 2.83)	68 more per 1000 (83 fewer to 392 more)	very low
<b>hba1c change (% , lower values are better, final values) at end of follow up Mean follow-up: 6 month(s)</b>											
1 (hanefeld 2011)	RC T	seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	seriou s <sup>4</sup>	NA	37	39	MD -0.38 (-0.70, - 0.06)	MD 0.38 lower (0.70 lower to 0.06 lower)	low

- >33.3% of the studies in the meta-analysis were at moderate risk of bias
- Only one study so no inconsistency
- 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

## L.1.8.26 Adding pioglitazone + metformin compared to adding pioglitazone

Table 116: Clinical evidence profile: Adding pioglitazone + metformin compared to adding pioglitazone

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>hypoglycaemia episodes at end of follow up Mean follow-up: 6 month(s)</b>											
1 (hanefeld 2011)	RC T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	11/39	8/40	RR 1.41 (0.64, 3.13)	82 more per 1000 (73 fewer to 426 more)	very low
<b>hba1c change (% , lower values are better, final values) at end of follow up Mean follow-up: 6 month(s)</b>											
1 (hanefeld 2011)	RC T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>4</sup>	NA	37	37	MD -0.34 (-0.68, - 0.00)	MD 0.34 lower (0.68 lower to 0.00 lower)	low

- >33.3% of the studies in the meta-analysis were at moderate risk of bias
- Only one study so no inconsistency
- 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

## L.2 Switching

### L.2.1 Metformin

#### L.2.1.1 Switching to metformin slow release compared to staying on metformin standard release

Table 117: Clinical evidence profile: Switching to metformin slow release compared to staying on metformin standard release

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
<b>all-cause mortality at end of follow up</b> Mean follow-up: 6 month(s)											
1 (fujioka 2003)	RCT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	1/146	0/75	PETO OR 4.54 (0.07, 285.16)	7 more per 1000 (7 fewer to 20 more)	very low
<b>hypoglycaemia episodes at end of follow up</b> Mean follow-up: 6 month(s)											
1 (fujioka 2003)	RCT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	1/146	1/75	RR 0.51 (0.03, 8.10)	6 fewer per 1000 (13 fewer to 95 more)	very low
<b>severe hypoglycaemic episodes at end of follow up</b> Mean follow-up: 6 month(s)											
1 (fujioka 2003)	RCT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>4</sup>	NA	0/146	0/75	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	very low

1. >33.3% of the studies in the meta-analysis were at high risk of bias

2. Only one study so no inconsistency
3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
4. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.

## L.2.2 DPP-4 inhibitors

### L.2.2.1 Switching to sitagliptin compared to switching to placebo

**Table 118: Clinical evidence profile: Switching to sitagliptin compared to switching to placebo**

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
hypoglycaemia episodes at end of follow up											
1 (retnakaran 2010)	RCT	very serious <sup>1</sup>	serious <sup>2</sup>	NA <sup>3</sup>	very serious <sup>4</sup>	NA	1/10	1/11	RR 1.10 (0.08, 15.36)	9 more per 1000 (84 fewer to 1305 more)	very low

1. >33.3% of the studies in the meta-analysis were at high risk of bias
2. Largest proportion of studies in the meta-analysis came from partially direct studies
3. Only one study so no inconsistency
4. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)

## L.2.2.2 Switching to vildagliptin compared to switching to alogliptin

Table 119: Clinical evidence profile: Switching to vildagliptin compared to Switching to alogliptin

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>hypoglycaemia episodes at end of follow-up Mean follow-up: 5.5 month(s)</b>											
1 (tanaka 2017)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	not seriou s	NA	68/68	62/62	RR 1.00 (0.97, 1.03)	0 fewer per 1000 (29 fewer to 30 more)	low
<b>severe hypoglycaemic episodes at end of follow-up Mean follow-up: 5.5 month(s)</b>											
1 (tanaka 2017)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	seriou s <sup>3</sup>	NA	0/68	0/62	RD 0.00 (-0.03, 0.03)	0 fewer per 1000 (30 fewer to 30 more)	very low
<b>hba1c change (% , lower values are better, change score) at end of follow-up Mean follow-up: 5.5 month(s)</b>											
1 (tanaka 2017)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	not seriou s	NA	63	62	MD -0.20 (-0.43, 0.03)	MD 0.20 lower (0.43 lower to 0.03 higher)	low
<b>weight change (kg, lower values are better, change scores) at end of follow- up Mean follow-up: 5.5 month(s)</b>											
1 (tanaka 2017)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	not seriou s	NA	63	62	MD -0.10 (-0.74, 0.54)	MD 0.10 lower (0.74 lower to 0.54 higher)	low

1. >33.3% of the studies in the meta-analysis were at high risk of bias
2. Only one study so no inconsistency
3. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.

### L.2.3 GLP-1 receptor agonist

#### L.2.3.1 Switching to liraglutide compared to staying on sitagliptin

**Table 120: Clinical evidence profile: Switching to liraglutide compared to staying on sitagliptin**

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>all-cause mortality at the end of follow-up Mean follow-up: 5.5 month(s)</b>											
1 (bailey 2016)	RC T	seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>3</sup>	NA	1/204	0/20 2	PETO OR 7.32 (0.15, 368.77)	5 more per 1000 (5 fewer to 14 more)	very low
<b>hypoglycaemia episodes at the end of follow-up Mean follow-up: 5.5 month(s)</b>											
1 (bailey 2016)	RC T	seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>3</sup>	NA	0/204	3/20 2	PETO OR 0.13 (0.01, 1.28)	15 fewer per 1000 (32 fewer to 2 more)	very low
<b>severe hypoglycaemic episodes at the end of follow-up Mean follow-up: 5.5 month(s)</b>											
1 (bailey 2016)	RC T	seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	not seriou s	NA	0/204	0/20 2	RD 0.00 (-0.01, 0.01)	0 fewer per 1000	mod erate

										(10 fewer to 10 more)	
<b>hba1c change (% , lower values are better, final values) at the end of follow-up</b>											
<b>Mean follow-up: 5.5 month(s)</b>											
1 (bailey 2016)	RC T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>4</sup>	NA	204	202	MD -0.61 (-0.82, -0.40)	MD 0.61 lower (0.82 lower to 0.40 lower)	low
<b>weight change (kg, lower values are better, change scores) at end of follow-up</b>											
<b>Mean follow-up: 5.5 month(s)</b>											
1 (bailey 2016)	RC T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	204	202	MD -1.67 (-2.34, -1.00)	MD 1.67 lower (2.34 lower to 1.00 lower)	moderate

1. >33.3% of the studies in the meta-analysis were at moderate risk of bias
2. Only one study so no inconsistency
3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
4. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

## L.2.3.2 Switching to semaglutide compared to switching to dulaglutide

Table 121: Clinical evidence profile: Switching to semaglutide compared to switching to dulaglutide

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>hypoglycaemia episodes at end of follow up</b> Mean follow-up: 6 month(s)											
1 (Iijima 2023)	RC T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	0/16	0/16	RD 0.00 (-0.11, 0.11)	0 fewer per 1000 (114 fewer to 114 more)	very low
<b>hba1c change (% , lower values are better, change scores) at end of follow up</b> Mean follow-up: 6 month(s)											
1 (Iijima 2023)	RC T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>4</sup>	NA	16	16	MD -0.42 (-0.71, - 0.13)	MD 0.42 lower (0.71 lower to 0.13 lower)	low
<b>weight change (kg, lower values are better, change scores) at end of follow up</b> Mean follow-up: 6 month(s)											
1 (Iijima 2023)	RC T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>5</sup>	NA	16	16	MD -2.50 (-4.70, - 0.30)	MD 2.50 lower (4.70 lower to 0.30 lower)	low

- >33.3% of the studies in the meta-analysis were at moderate risk of bias
- Only one study so no inconsistency
- Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.

4. 95% confidence intervals cross one end of the defined MID (-0.50, 0.50)

5. 95% confidence intervals cross one end of the defined MID (-2.40, 2.40)

### L.2.3.3 Switching to semaglutide compared to staying on sitagliptin

**Table 122: Clinical evidence profile - Switching to semaglutide compared to staying on sitagliptin**

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>all-cause mortality at end of follow up Mean follow-up: 12 month(s)</b>											
1 (buse 2020)	RC T	not serio us	not seriou s	NA <sup>1</sup>	seriou s <sup>2</sup>	NA	0/100	0/97	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	mod erat e
<b>cardiovascular mortality at end of follow up Mean follow-up: 12 month(s)</b>											
1 (buse 2020)	RC T	not serio us	not seriou s	NA <sup>1</sup>	seriou s <sup>2</sup>	NA	0/100	0/97	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	mod erat e
<b>non-fatal myocardial infarction at end of follow up Mean follow-up: 12 month(s)</b>											
1 (buse 2020)	RC T	not serio us	not seriou s	NA <sup>1</sup>	seriou s <sup>2</sup>	NA	0/100	0/97	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	mod erat e
<b>hospitalisation for heart failure at end of follow up Mean follow-up: 12 month(s)</b>											

1 (buse 2020)	RC T	not serio us	not seriou s	NA <sup>1</sup>	very seriou s <sup>3</sup>	NA	0/100	1/97	PETO OR 0.13 (0.00, 6.62)	10 fewer per 1000 (30 fewer to 10 more)	low
<b>acute kidney injury at end of follow up Mean follow-up: 12 month(s)</b>											
1 (buse 2020)	RC T	not serio us	not seriou s	NA <sup>1</sup>	seriou s <sup>2</sup>	NA	0/100	0/97	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	mod erat e
<b>at night hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)</b>											
1 (buse 2020)	RC T	not serio us	not seriou s	NA <sup>1</sup>	seriou s <sup>2</sup>	NA	0/100	0/97	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	mod erat e
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 12 month(s)</b>											
1 (buse 2020)	RC T	not serio us	not seriou s	NA <sup>1</sup>	seriou s <sup>2</sup>	NA	0/100	0/97	RD 0.00 (-0.02, 0.02)	0 fewer per 1000 (20 fewer to 20 more)	mod erat e
<b>hba1c change (% , lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)</b>											
1 (buse 2020)	RC T	serio us <sup>4</sup>	not seriou s	NA <sup>1</sup>	seriou s <sup>5</sup>	NA	100	98	MD -0.30 (-0.60, 0.00)	MD 0.30 lower (0.60 lower to 0.00 higher)	low
<b>weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)</b>											

1 (buse 2020)	RC T	serious <sup>4</sup>	not serious	NA <sup>1</sup>	serious <sup>6</sup>	NA	100	98	MD -1.50 (-2.85, -0.15)	MD 1.50 lower (2.85 lower to 0.15 lower)	low
<b>bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 12 month(s)</b>											
1 (buse 2020)	RC T	serious <sup>4</sup>	not serious	NA <sup>1</sup>	serious <sup>7</sup>	NA	100	98	MD -0.40 (-0.90, 0.10)	MD 0.40 lower (0.90 lower to 0.10 higher)	low

1. Only one study so no inconsistency
2. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
3. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
4. >33.3% of the studies in the meta-analysis were at moderate risk of bias
5. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
6. 95% confidence intervals cross one end of the defined MIDs (-2.40, 2.40)
7. 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

## L.2.4 SGLT2 inhibitors

### L.2.4.1 Switching to canagliflozin compared to switching to liraglutide

**Table 123: Clinical evidence profile: Switching to canagliflozin compared to switching to liraglutide**

No of studies	De sig n	Risk of bias	Indir ectn ess	Incon siste ncy	Impr ecisi on	Other consider ations	Interv entio n N	Con trol N	Relative effect (95% CI)	Absolute effect	Cer tain ty
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<b>health-related quality of life - overall (diabetes therapy-related qol, 0-100, higher values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)</b>											
1 (ando 2021)	R C T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>3</sup>	NA	17	17	MD 6.50 (0.14, 12.86)	MD 6.50 higher (0.14 higher to 12.86 higher)	very low
<b>severe hypoglycaemic episodes at end of follow up Mean follow-up: 5.5 month(s)</b>											
1 (ando 2021)	R C T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>4</sup>	NA	0/20	0/19	RD 0.00 (-0.09, 0.09)	0 fewer per 1000 (95 fewer to 95 more)	very low
<b>hba1c change (% , lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)</b>											
1 (ando 2021)	R C T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>5</sup>	NA	17	17	MD 0.10 (-0.30, 0.50)	MD 0.10 higher (0.30 lower to 0.50 higher)	very low
<b>weight change (kg, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)</b>											
1 (ando 2021)	R C T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	17	17	MD 0.20 (-1.89, 2.29)	MD 0.20 higher (1.89 lower to 2.29 higher)	low
<b>bmi change (kg/m2, lower values are better, change scores) at end of follow up Mean follow-up: 5.5 month(s)</b>											

1 (ando 2021)	R C T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>6</sup>	NA	17	17	MD 0.10 (-0.61, 0.81)	MD 0.10 higher (0.61 lower to 0.81 higher)	very low
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- >33.3% of the studies in the meta-analysis were at high risk of bias
- Only one study so no inconsistency
- 95% confidence intervals cross one end of the defined MIDs (-4.95, 4.95)
- Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
- 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)
- 95% confidence intervals cross one end of the defined MIDs (-0.80, 0.80)

## L.2.1 Sulfonylureas

### L.2.1.1 Switching to glimepiride compared to switching to liraglutide

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
hba1c change (% lower values are better) at end of follow-up Mean follow-up: 12 month(s)											
1 (garber 2009)	R C T	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>3</sup>	NA	154	320	MD 0.42 (0.21, 0.63)	MD 0.42 higher (0.21 higher to 0.63 higher)	very low

- >33.3% of the studies in the meta-analysis were at high risk of bias
- Only one study so no inconsistency
- 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

## L.2.2 Thiazolidinediones

### L.2.2.1 Staying on pioglitazone compared to switching to dapagliflozin

Table 124: Clinical evidence profile: Staying on pioglitazone compared to switching to dapagliflozin

No of studies	De sig n	Risk of bias	Indire ctness	Inconsi stency	Impre cision	Other considerati ons	Interve ntion N	Cont rol N	Relative effect (95% CI)	Absolute effect	Cert aint y
<b>hypoglycaemia episodes at end of follow up</b> Mean follow-up: 5.5 month(s)											
1 (cho 2019)	RC T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>3</sup>	NA	9/35	7/36	RR 1.32 (0.55, 3.16)	63 more per 1000 (87 fewer to 420 more)	very low
<b>severe hypoglycaemic episodes at end of follow up</b> Mean follow-up: 5.5 month(s)											
1 (cho 2019)	RC T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>4</sup>	NA	0/35	0/36	RD 0.00 (-0.05, 0.05)	0 fewer per 1000 (53 fewer to 53 more)	low
<b>hba1c change (% , lower values are better, final values) at end of follow up</b> Mean follow-up: 5.5 month(s)											
1 (cho 2019)	RC T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	not serious	NA	35	36	MD 0.10 (-0.25, 0.45)	MD 0.10 higher (0.25 lower to 0.45 higher)	mod erate
<b>weight change (kg, lower values are better, final values) at end of follow up</b> Mean follow-up: 5.5 month(s)											

1 (cho 2019)	RC T	serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>5</sup>	NA	35	36	MD 3.90 (-2.85, 10.65)	MD 3.90 higher (2.85 lower to 10.65 higher)	very low
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- >33.3% of the studies in the meta-analysis were at moderate risk of bias
- Only one study so no inconsistency
- 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)
- Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.
- 95% confidence intervals cross both ends of the defined MIDs (-2.40, 2.40)

#### L.2.2.2 Switching to pioglitazone compared to switching to glimepiride

**Table 125: Clinical evidence profile: Switching to pioglitazone compared with switching to glimepiride**

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
<b>hypoglycaemia episodes at end of follow up</b>											
<b>Mean follow-up: 12 month(s)</b>											
1 (tan 2004)	RC T	not serious	not serious	NA <sup>1</sup>	serious <sup>2</sup>	NA	19/121	38/123	RR 0.51 (0.31, 0.83)	152 fewer per 1000 (213 fewer to 53 fewer)	moderate
<b>hba1c change (% , lower values are better, change scores) at end of follow up</b>											
<b>Mean follow-up: 12 month(s)</b>											
1 (tan 2004)	RC T	not serious	not serious	NA <sup>1</sup>	very serious <sup>3</sup>	NA	109	109	MD -0.10 (-1.49, 1.29)	MD 0.10 lower (1.49 lower to 1.29 higher)	low

1. Only one study so no inconsistency
2. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
3. 95% confidence intervals cross both ends of the defined MIDs (-0.50, 0.50)

## L.2.3 Combinations

### L.2.3.1 Switching to fixed-dose combination glimepiride/metformin slow release compared to staying on fixed-dose combination glimepiride/metformin standard release

**Table 126: Clinical evidence profile: Fixed-dose combination glimepiride/metformin slow release compared to staying on fixed-dose combination glimepiride/metformin standard release**

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
<b>hypoglycaemia episodes at end of follow up</b>											
<b>Mean follow-up: 5.8 month(s)</b>											
1 (kim 2018)	RCT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	serious <sup>3</sup>	NA	19/86	10/86	RR 1.90 (0.94, 3.85)	105 more per 1000 (7 fewer to 331 more)	very low
<b>at night hypoglycaemic episodes at end of follow up</b>											
<b>Mean follow-up: 5.8 month(s)</b>											
1 (kim 2018)	RCT	very serious <sup>1</sup>	not serious	NA <sup>2</sup>	very serious <sup>4</sup>	NA	3/86	5/86	RR 0.60 (0.15, 2.43)	23 fewer per 1000 (50 fewer to 83 more)	very low

1. >33.3% of the studies in the meta-analysis were at high risk of bias
2. Only one study so no inconsistency

3. 95% confidence intervals cross one end of the defined MIDs (0.80, 1.25)
4. 95% confidence intervals cross both ends of the defined MIDs (0.80, 1.25)