National Institute for Health and Care Excellence

Type 2 diabetes in adults: management

[F3] 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

February 2026

Final

This evidence review was developed by NICE

Disclaimer

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There are no forest plots reported for this comparison (all outcomes include a single study).

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There are no forest plots reported for this comparison (all outcomes include a single study).

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There are no forest plots reported for this comparison (all outcomes include a single study).

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There are no forest plots reported for this comparison (all outcomes include a single study).

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There are no forest plots reported for this comparison (all outcomes include a single study).

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There are no forest plots reported for this comparison (all outcomes include a single study).

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There are no forest plots reported for this comparison (all outcomes include a single study).

E.2.4 Adding liraglutide compared to adding placebo

There are no forest plots reported for this comparison (all outcomes include a single study).

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There are no forest plots reported for this comparison (all outcomes include a single study).

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There are no forest plots reported for this comparison (all outcomes include a single study).

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There are no forest plots reported for this comparison (all outcomes include a single study).

E.3 SGLT2 inhibitors

E.3.1 Adding canagliflozin compared to adding placebo

Figure 1: All-cause mortality at end of follow-up

Study or Subgroup	log[Hazard Ratio]	SE	Canagliflozin Total	Placebo Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Mahaffey 2018 (1)	-0.3567	0.1616	658	803	63.9%	0.70 [0.51, 0.96]
Perkovic 219	-0.0726	0.2152	329	323	36.1%	0.93 [0.61, 1.42]
Total (95% CI)			987	1126	100.0%	0.78 [0.60, 1.00]

Heterogeneity: Chi² = 1.11, df = 1 (P = 0.29); I² = 10%
Test for overall effect: Z = 1.97 (P = 0.05)

Favours canagliflozin   Favours placebo

Footnotes
(1) Data taken from subgroup analysis

Figure 2: 3-point MACE at end of follow-up

Study or Subgroup	log[Hazard Ratio]	SE	Canagliflozin Total	Placebo Total	Weight	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% CI
Mahaffey 2018 (1)	-0.2231	0.1383	658	803	66.7%	0.80 [0.61, 1.05]	
Perkovic 219	-0.0943	0.1958	329	329	33.3%	0.91 [0.62, 1.34]	
Total (95% CI)			987	1132	100.0%	0.84 [0.67, 1.04]	

Heterogeneity: Chi² = 0.29, df = 1 (P = 0.59); I² = 0%
Test for overall effect: Z = 1.60 (P = 0.11)

0.01 0.1 1 10 100
Favours canagliflozin Favours placebo

Footnotes
(1) Data taken from subgroup analysis

Figure 3: Hospitalisation for heart failure at end of follow-up

Study or Subgroup	log[Hazard Ratio]	SE	Canagliflozin Total	Placebo Total	Weight	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% CI
Mahaffey 2018 (1)	-0.6733	0.2221	658	803	52.7%	0.51 [0.33, 0.79]	
Perkovic 219	-0.2744	0.2345	329	323	47.3%	0.76 [0.48, 1.20]	
Total (95% CI)			987	1126	100.0%	0.62 [0.45, 0.84]	

Heterogeneity: Chi² = 1.53, df = 1 (P = 0.22); I² = 34%
Test for overall effect: Z = 3.01 (P = 0.003)

0.01 0.1 1 10 100
Favours canagliflozin Favours placebo
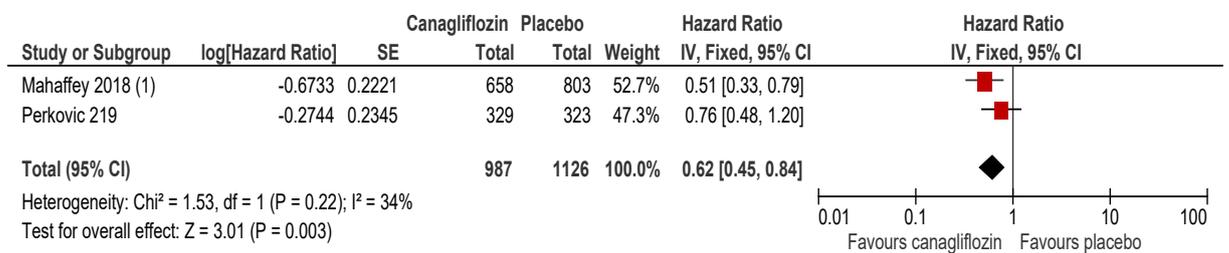
Footnotes
(1) Data taken from subgroup analysis

E.3.2 Adding dapagliflozin compared to adding placebo

There are no forest plots reported for this comparison (all outcomes include a single study).

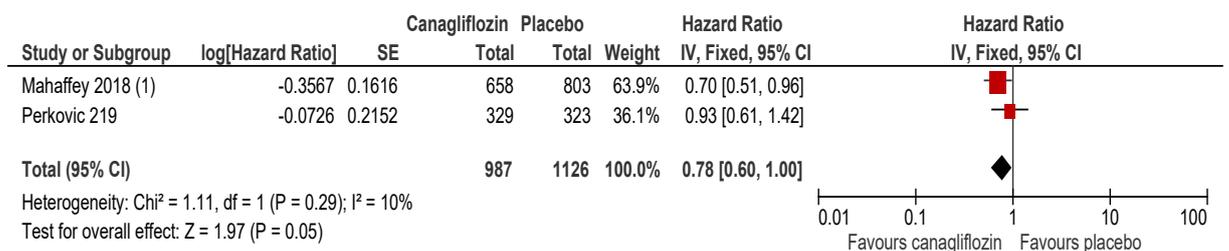### E.3.3 Adding empagliflozin compared to adding placebo

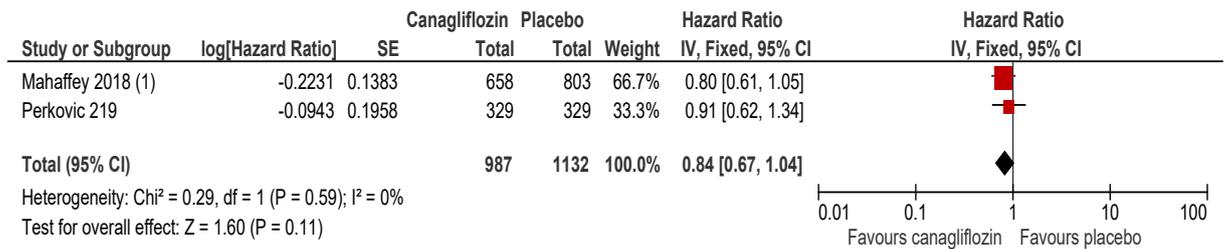There are no forest plots reported for this comparison (all outcomes include a single study).

E.3.4 Adding ertugliflozin compared to adding placebo

There are no forest plots reported for this comparison (all outcomes include a single study).

Appendix F   GRADE tables – Model 1: People with type 2 diabetes and heart failure

F.1   DPP-4 inhibitors

F.1.1   Adding alogliptin compared to adding placebo

Table 1: Clinical evidence profile : Adding alogliptin 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
cardiovascular mortality at end of follow-up - 18 months											
1 (white 2013)	RCT	very serious [1]	not serious	NA[2]	serious [3]	NA	55/771	69/762	RR 0.79 (0.56, 1.11)	19 fewer per 1000 (40 fewer to 10 more)	very low
cardiovascular mortality at end of follow-up - 18 months											
1 (white 2013)	RCT	very serious [1]	not serious	NA[2]	serious [3]	NA	771	762	HR 0.77 (0.54, 1.10)	Not estimable	very low
4-point mace at end of follow-up - 18 months											
1 (white 2013)	RCT	very serious [1]	not serious	NA[2]	serious [3]	NA	127/771	141/762	RR 0.89 (0.72, 1.11)	20 fewer per 1000 (53 fewer to 20 more)	very low
non-fatal stroke at end of follow-up - 18 months											
1 (white 2013)	RCT	very serious [1]	not serious	NA[2]	very serious [4]	NA	11/771	6/762	RR 1.81 (0.67, 4.87)	6 more per 1000 (3 fewer to 31 more)	very low

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non-fatal myocardial infarction at end of follow-up - 18 months											
1 (white 2013)	RCT	very serious [1]	not serious	NA[2]	very serious [4]	NA	69/771	66/762	RR 1.03 (0.75, 1.43)	3 more per 1000 (22 fewer to 37 more)	very low
unstable angina at end of follow-up - 18 months											
1 (white 2013)	RCT	very serious [1]	Serious [5]	NA[2]	very serious [4]	NA	5/771	11/762	RR 0.45 (0.16, 1.29)	8 fewer per 1000 (12 fewer to 4 more)	very low
unstable angina at end of follow-up - 18 months											
1 (white 2013)	RCT	very serious [1]	Serious [5]	NA[2]	serious [3]	NA	771	762	HR 0.89 (0.70, 1.13)	Not estimable	very low
hospitalisation for heart failure at end of follow-up - 18 months											
1 (white 2013)	RCT	very serious [1]	not serious	NA[2]	very serious [4]	NA	63/771	65/762	RR 0.96 (0.69, 1.33)	4 fewer per 1000 (27 fewer to 29 more)	very low
hospitalisation for heart failure at end of follow-up - 18 months											
1 (white 2013)	RCT	very serious [1]	not serious	NA[2]	very serious [4]	NA	771	762	HR 1.00 (0.71, 1.41)	Not estimable	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. Largest proportion of studies in the meta-analysis came from partially direct studies

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F.1.2 Adding linagliptin compared to adding placebo

Table 2: Clinical evidence profile : Adding linagliptin 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
cardiovascular mortality at end of follow-up - 26.4 months											
1 (rosenstock 2019a)	RCT	not serious	not serious	NA[1]	very serious [2]	NA	952	921	HR 0.96 (0.73, 1.26)	Not estimable	low
hospitalisation for heart failure at end of follow-up - 16.4 months											
1 (rosenstock 2019a)	RCT	not serious	not serious	NA[1]	serious [3]	NA	113/952	122/921	RR 0.90 (0.71, 1.14)	14 fewer per 1000 (39 fewer to 18 more)	moderate
hospitalisation for heart failure at end of follow-up - 16.4 months											
1 (rosenstock 2019a)	RCT	not serious	not serious	NA[1]	serious [3]	NA	952	921	HR 0.88 (0.68, 1.14)	Not estimable	moderate

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)

F.1.3   Adding sitagliptin compared to adding insulin

Table 3: 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
hospitalisation for heart failure at end of follow-up - 12 months											
1 (arturi 2017)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/10	0/12	RD 0.00 (-0.16, 0.16)	0 fewer per 1000 (161 fewer to 161 more) [4]	very low
severe hypoglycaemic episodes at end of follow-up - 12 months											
1 (arturi 2017)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/10	0/12	RD 0.00 (-0.16, 0.16)	0 fewer per 1000 (161 fewer to 161 more) [4]	very low
hba1c change (%, lower values are better, final value) at end of follow-up - 12 months											
1 (arturi 2017)	RCT	very serious[1]	not serious	NA[2]	Serious[5]	NA	10	12	MD 1.30 (0.11, 2.49)	-	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. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.

4. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

5. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

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F.1.4 Adding sitagliptin compared to adding placebo

Table 4: Clinical evidence profile: Adding itagliptin 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
4-point mace at follow-up - 36 months											
1 (green 2015)	RCT	not serious	not serious	NA[1]	serious[2]	NA	1303	1340	HR 0.97 (0.80, 1.18)	Not estimable	moderate
hospitalisation for heart failure at follow-up - 36 months											
1 (green 2015)	RCT	not serious	not serious	NA[1]	very serious[3]	NA	1303	1340	HR 1.05 (0.79, 1.40)	Not estimable	low
hospitalisation for heart failure at follow-up - 36 months											
1 (green 2015)	RCT	not serious	not serious	NA[1]	serious[2]	NA	97/1303	94/1340	RR 1.06 (0.81, 1.39)	4 more per 1000 (14 fewer to 28 more)	moderate

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)

F.1.5 Adding vildagliptin compared to adding placebo

Table 5: 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
all-cause mortality at end of follow-up - 12 months											
1 (mcmurray 2018)	RCT	not serious	not serious	NA[1]	serious[2]	NA	11/128	4/126	RR 2.71 (0.89, 8.28)	54 more per 1000 (4 fewer to 231 more)	moderate
cardiovascular mortality at end of follow-up - 12 months											
1 (mcmurray 2018)	RCT	not serious	not serious	NA[1]	very serious[3]	NA	7/128	4/126	RR 1.72 (0.52, 5.74)	23 more per 1000 (15 fewer to 150 more)	low
non-fatal stroke at end of follow-up - 12 months											
1 (mcmurray 2018)	RCT	not serious	not serious	NA[1]	very serious[3]	NA	1/128	4/126	RR 0.25 (0.03, 2.17)	24 fewer per 1000 (31 fewer to 37 more)	low
hospitalisation for heart failure at end of follow-up - 12 months											
1 (mcmurray 2018)	RCT	not serious	not serious	NA[1]	not serious	NA	13/128	10/126	RR 1.28 (0.58, 2.81)	22 more per 1000 (33 fewer to 144 more)	high
cardiac arrhythmia at end of follow-up - 12 months											
1 (mcmurray 2018)	RCT	not serious	not serious	NA[1]	very serious[3]	NA	9/128	4/126	RR 2.21 (0.70, 7.01)	39 more per 1000 (10 fewer to 191 more)	low

hypoglycaemia episodes at end of follow-up - follow-up: 12 months											
1 (mcmurray 2018)	RCT	not serious	not serious	NA[1]	very serious[3]	NA	6/128	7/126	RR 0.84 (0.29, 2.44)	9 fewer per 1000 (39 fewer to 80 more)	low
hba1c change (%, lower values are better, change score) at end of follow-up - 12 months											
1 (mcmurray 2018)	RCT	very serious[4]	not serious	NA[1]	serious[5]	NA	115	112	MD -0.36 (-0.71, -0.01)	MD 0.36 lower (0.71 lower to 0.01 lower)	very 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 (0.80, 1.25)

4. >33.3% of the studies in the meta-analysis were at high risk of bias

5. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

F.2   GLP-1 receptor agonist

F.2.1   Adding exenatide compared to adding insulin

Table 6: Clinical evidence profile: Adding exenatide 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

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
all-cause mortality at end of follow-up - 6 months											
1 (chen 2017)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	1/14	0/12	Peto OR 6.41 (0.13, 326.59)	72 more per 1000 (63 fewer to 206 more) [4]	very low
hba1c change (%, lower values are better, final value) at end of follow-up - 6 months											
1 (chen 2017)	RCT	very serious[1]	not serious	NA[2]	very serious[5]	NA	11	12	MD 0.30 (-0.89, 1.49)	-	very low
bmi change (kg/m2, lower values are better, final value) at end of follow-up - 6 months											
1 (chen 2017)	RCT	very serious[1]	not serious	NA[2]	Serious[6]	NA	11	12	MD -2.40 (-5.14, 0.34)	-	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. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

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 (-0.80, 0.80)

F.2.2 Adding exenatide compared to adding placebo

Table 7: Clinical evidence profile; Adding exenatide 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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No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
3-point mace at end of follow-up - 38.4 months											
1 (holman 2017)	RCT	not serious	not serious	NA[1]	not serious	NA	227/1161	237/1228	RR 1.01 (0.86, 1.19)	3 more per 1000 (27 fewer to 37 more)	High
3-point mace at end of follow-up - 38.4 months											
1 (holman 2017)	RCT	not serious	not serious	NA[1]	not serious	NA	1161	1228	HR 0.97 (0.81, 1.16)	Not estimable	High

1. Only one study so no inconsistency

F.2.3 Adding liraglutide compared to adding insulin

Table 8: Clinical evidence profile: Adding liraglutide 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
hospitalisation for heart failure at end of follow-up - 12 months											
1 (arturi 2017)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/10	0/12	rd 0.00 (-0.16, 0.16)	0 fewer per 1000 (161 fewer to 161 more)[4]	very low
severe hypoglycaemic episodes at end of follow-up - 12 months											
1 (arturi 2017)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/10	0/12	rd 0.00 (-0.16, 0.16)	0 fewer per 1000 (161 fewer to 161 more)[4]	very low
hba1c change (%, lower values are better, final value) at end of follow-up - 12 months											

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
1 (arturi 2017)	RCT	very serious[1]	not serious	NA[2]	very serious[5]	NA	10	12	MD 0.20 (-0.99, 1.39)	-	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. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.

4. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

5. 95% confidence intervals cross both ends of the defined MIDs (-0.50, 0.50)

F.2.4 Adding liraglutide compared to adding placebo

Table 9: Clinical evidence profile; Adding liraglutide 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
all-cause mortality at end of follow-up - 45.6 months											
1 (marso 2016a)	RCT	not serious	not serious	NA[1]	serious[2]	NA	119/835	132/832	RR 0.90 (0.71, 1.13)	16 fewer per 1000 (45 fewer to 20 more)	moderate
all-cause mortality at end of follow-up - 45.6 months											
1 (marso 2016a)	RCT	not serious	not serious	NA[1]	serious[2]	NA	835	832	HR 0.89 (0.70, 1.13)	Not estimable	moderate
cardiovascular mortality at end of follow-up - 45.6 months											

1 (marso 2016a)	RCT	not serious	not serious	NA[1]	serious [2]	NA	76/835	88/832	RR 0.86 (0.64, 1.15)	15 fewer per 1000 (38 fewer to 16 more)	moderate
cardiovascular mortality at end of follow-up - 45.6 months											
1 (marso 2016a)	RCT	not serious	not serious	NA[1]	serious [2]	NA	835	832	HR 0.85 (0.63, 1.15)	Not estimable	moderate
3-point mace at end of follow-up - 45.6 months											
1 (marso 2016a)	RCT	not serious	not serious	NA[1]	serious [2]	NA	142/835	170/832	RR 0.83 (0.68, 1.02)	34 fewer per 1000 (65 fewer to 4 more)	moderate
3-point mace at end of follow-up - 45.6 months											
1 (marso 2016a)	RCT	not serious	not serious	NA[1]	serious [2]	NA	835	832	HR 0.81 (0.65, 1.01)	Not estimable	moderate
non-fatal stroke at end of follow-up - 45.6 months											
1 (marso 2016a)	RCT	not serious	not serious	NA[1]	very serious [3]	NA	27/835	30/832	RR 0.90 (0.54, 1.49)	4 fewer per 1000 (17 fewer to 18 more)	low
non-fatal stroke at end of follow-up - 45.6 months											
1 (marso 2016a)	RCT	not serious	not serious	NA[1]	very serious [3]	NA	835	832	HR 0.89 (0.53, 1.49)	Not estimable	low
non-fatal myocardial infarction at end of follow-up - 45.6 months											
1 (marso 2016a)	RCT	not serious	not serious	NA[1]	serious [2]	NA	54/835	71/832	RR 0.76 (0.54, 1.07)	21 fewer per 1000 (39 fewer to 6 more)	moderate

non-fatal myocardial infarction at end of follow-up - 45.6 months											
1 (marso 2016a)	RCT	not serious	not serious	NA[1]	serious[2]	NA	835	832	HR 0.74 (0.52, 1.05)	Not estimable	moderate
unstable angina at end of follow-up - 45.6 months											
1 (marso 2016a)	RCT	not serious	not serious	NA[1]	very serious[3]	NA	22/835	30/832	RR 0.73 (0.43, 1.26)	10 fewer per 1000 (21 fewer to 9 more)	low
unstable angina at end of follow-up - 45.6 months											
1 (marso 2016a)	RCT	not serious	not serious	NA[1]	Serious[2]	NA	835	832	HR 0.72 (0.42, 1.23)	Not estimable	moderate
hospitalisation for heart failure at end of follow-up - 45.6 months											
1 (marso 2016a)	RCT	not serious	not serious	NA[1]	very serious[3]	NA	108/835	108/832	RR 1.00 (0.78, 1.28)	0 fewer per 1000 (29 fewer to 36 more)	low
hospitalisation for heart failure at end of follow-up - 45.6 months											
1 (marso 2016a)	RCT	not serious	not serious	NA[1]	very serious[3]	NA	835	832	HR 0.98 (0.75, 1.28)	Not estimable	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 (0.80, 1.25)

F.2.5   Adding liraglutide compared to adding sitagliptin

Table 10: Clinical evidence profile: Adding liraglutide 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
hospitalisation for heart failure at end of follow-up - 12 months											
1 (arturi 2017)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/10	0/10	RD 0.00 (-0.17, 0.17)	0 fewer per 1000 (174 fewer to 174 more)[4]	very low
severe hypoglycaemic episodes at end of follow-up - 12 months											
1 (arturi 2017)	RCT	very serious[1]	not serious	NA[2]	very serious[3]	NA	0/10	0/10	RD 0.00 (-0.17, 0.17)	0 fewer per 1000 (174 fewer to 174 more)[4]	very low
hba1c change (%, lower values are better, final value) at end of follow-up - 12 months											
1 (arturi 2017)	RCT	very serious[1]	not serious	NA[2]	serious[5]	NA	10	10	MD -1.10 (-1.98, -0.22)	-	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. Sample size used to determine precision: 70-350 = serious imprecision, <70 = very serious imprecision.

4. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

5. 95% confidence intervals cross one end of the defined MIDs (-0.50, 0.50)

F.2.6 Adding lixisenatide compared to adding placebo

Table 11: Clinical evidence profile: Adding lixisenatide 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
hospitalisation for heart failure at end of follow-up - 25 months											
1 (pfeffer 2015)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	66/682	69/676	RR 0.95 (0.69, 1.31)	5 fewer per 1000 (32 fewer to 31 more)	low
hospitalisation for heart failure at end of follow-up - 25 months											
1 (pfeffer 2015)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	682	676	HR 0.93 (0.66, 1.31)	Not estimable	low

1. Only one study so no inconsistency

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

F.2.7 Adding semaglutide compared to adding placebo

Table 12 Clinical evidence profile: Adding semaglutide 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
3-point mace at end of follow-up ~ Mean follow-up: 25.2 month(s)											
1 (marso 2016b)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	35/285	34/288	RR 1.04 (0.67, 1.62)	5 more per 1000 (39 fewer to 73 more)	low

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3-point mace at end of follow-up ~ Mean follow-up: 25.2 month(s)											
1 (marso 2016b)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	285	288	HR 1.03 (0.64, 1.66)	Not estimable	low
all-cause mortality at end of follow-up ~ Mean follow-up: 12 month(s)											
1 (kosiborod 2024)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	6/310	10/306	RR 0.59 (0.22, 1.61)	13 fewer per 1000 (26 fewer to 20 more)	low
cardiovascular mortality at end of follow-up ~ Mean follow-up: 12 month(s)											
1 (kosiborod 2024)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	1/310	4/306	RR 0.25 (0.03, 2.20)	10 fewer per 1000 (13 fewer to 16 more)	low
acute kidney injury at end of follow-up ~ Mean follow-up: 12 month(s)											
1 (kosiborod 2024)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	2/310	7/306	RR 0.28 (0.06, 1.35)	16 fewer per 1000 (22 fewer to 8 more)	low
hypoglycaemia episodes at end of follow-up ~ Mean follow-up: 12 month(s)											
1 (kosiborod 2024)	RCT	not serious	not serious	NA[1]	very serious[2]	NA	13/310	13/306	RR 0.99 (0.47, 2.09)	1 fewer per 1000 (23 fewer to 47 more)	low
severe hypoglycaemic episodes at end of follow-up ~ Mean follow-up: 12 month(s)											
1 (kosiborod 2024)	RCT	not serious	not serious	NA[1]	not serious	NA	0/310	0/306	PETO OR 0.00 (0.00, 0.00)	0 fewer per 1000 (0 more to 0 more)	high
hospitalisation for heart failure at end of follow-up ~ Mean follow-up: 12 month(s)											
1 (kosiborod 2024)	RCT	not serious	not serious	NA[1]	serious[3]	NA	310	306	HR 0.40 (0.15, 1.07)	Not estimable	moderate
hospitalisation for heart failure at end of follow-up ~ Mean follow-up: 12 month(s)											

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1 (kosiborod 2024)	RCT	not serious	not serious	NA[1]	serious[3]	NA	7/310	18/306	RR 0.38 (0.16, 0.91)	36 fewer per 1000 (49 fewer to 6 fewer)	moderate
hba1c change at the end of follow-up ~ Mean follow-up: 12 month(s)											
1 (kosiborod 2024)	RCT	not serious	not serious	NA[1]	not serious	NA	310	306	MD -0.80 (-1.00, -0.60)	MD 0.80 lower (1.00 lower to 0.60 lower)	high
weight change at the end of follow-up ~ Mean follow-up: 12 month(s)											
1 (kosiborod 2024)	RCT	not serious	not serious	NA[1]	not serious	NA	310	306	MD -6.40 (-7.60, -5.20)	MD 6.40 lower (7.60 lower to 5.20 lower)	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)

F.3 SGLT2 inhibitors

F.3.1 Adding canagliflozin compared to adding placebo

Figure 4: Clinical evidence profile: Adding canagliflozin 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
all-cause mortality at end of follow-up - mean 37.2 months											

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2	RCT	not serious	not serious	not serious	serious [1]	NA	987	1126	HR 0.78 (0.60, 1.00)	Not estimable	moderate
cardiovascular mortality at end of follow-up - 43 months											
1 (mahaffey 2018)	RCT	not serious	not serious	NA[2]	serious [1]	NA	658	803	HR 0.72 (0.51, 1.02)	Not estimable	moderate
3-point mace at end of follow-up - mean 37.2 months											
2	RCT	not serious	not serious	not serious	serious [1]	NA	987	1132	HR 0.84 (0.67, 1.04)	Not estimable	moderate
hospitalisation for heart failure at end of follow-up - mean 37.2 months											
2	RCT	not serious	not serious	not serious	serious [1]	NA	987	1126	HR 0.62 (0.45, 0.84)	Not estimable	moderate
acute kidney injury at end of follow-up - mean 31.4 months											
1 (perkovic 2019)	RCT	not serious	not serious	NA[2]	very serious [3]	NA	329	323	HR 0.75 (0.40, 1.41)	Not estimable	low

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

2. Only one study so no inconsistency

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

F.3.2   Adding dapagliflozin compared to adding placebo

Table 13: 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
all-cause mortality at end of follow-up - 50.4 months											
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[2]	serious[3]	NA	115/852	131/872	RR 0.90 (0.71, 1.13)	15 fewer per 1000 (43 fewer to 20 more)	low
all-cause mortality at end of follow-up - 50.4 months											
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[2]	serious[3]	NA	852	872	HR 0.87 (0.68, 1.12)	Not estimable	low
cardiovascular mortality at end of follow-up - 50.4 months											
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[2]	very serious[4]	NA	75/852	74/872	RR 1.04 (0.76, 1.41)	3 more per 1000 (20 fewer to 35 more)	very low
cardiovascular mortality at end of follow-up - 50.4 months											
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[2]	very serious[4]	NA	852	872	HR 1.01 (0.73, 1.40)	Not estimable	very low
3-point mace at end of follow-up - 50.4 months											
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[2]	serious[3]	NA	153/852	151/872	RR 1.04 (0.85, 1.27)	6 more per 1000 (27 fewer to 47 more)	low
3-point mace at end of follow-up - 50.4 months											

Studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Intervention	Control	Relative effect	Absolute effect	Certainty
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[2]	serious[3]	NA	852	872	HR 1.01 (0.81, 1.26)	Not estimable	low
non-fatal stroke at end of follow-up - 50.4 months											
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[2]	very serious[4]	NA	40/852	34/872	RR 1.20 (0.77, 1.88)	8 more per 1000 (9 fewer to 34 more)	very low
non-fatal stroke at end of follow-up - 50.4 months											
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[2]	very serious[4]	NA	852	872	HR 1.21 (0.77, 1.90)	Not estimable	very low
non-fatal myocardial infarction at end of follow-up - 50.4 months											
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[2]	serious[3]	NA	66/852	76/872	RR 0.89 (0.65, 1.22)	10 fewer per 1000 (31 fewer to 19 more)	low
non-fatal myocardial infarction at end of follow-up - 50.4 months											
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[2]	serious[3]	NA	852	872	HR 0.85 (0.61, 1.18)	Not estimable	low
cardiac arrhythmia at end of follow-up - 50.4 months											
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[2]	serious[3]	NA	55/852	70/872	RR 0.80 (0.57, 1.13)	16 fewer per 1000 (34 fewer to 10 more)	low
cardiac arrhythmia at end of follow-up - 50.4 months											
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[2]	serious[3]	NA	852	872	HR 0.78 (0.55, 1.11)	Not estimable	low
hospitalisation for heart failure at end of follow-up - 50.4 months											

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Intervention N	Control N	Relative effect (95% CI)	Absolute effect	Certainty
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[2]	serious[3]	NA	87/852	115/872	RR 0.77 (0.60, 1.01)	30 fewer per 1000 (53 fewer to 1 more)	low
hospitalisation for heart failure at end of follow-up - 50.4 months											
1 (wiviott 2019)	RCT	serious[1]	not serious	NA[2]	serious[3]	NA	852	872	HR 0.73 (0.55, 0.97)	Not estimable	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 (0.80, 1.25)

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

F.3.3   Adding empagliflozin compared to adding placebo

Table 14: Clinical evidence profile: Adding empagliflozin 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
persistent signs of worsening kidney disease at end of follow-up - 37.2 months											
1 (zinman 2015)	RCT	not serious	not serious	NA[1]	serious[2]	NA	48/394	41/205	RR 0.61 (0.42, 0.89)	78 fewer per 1000 (117 fewer to 22 fewer)	moderate
persistent signs of worsening kidney disease at end of follow-up - 37.2 months											
1 (zinman 2015)	RCT	not serious	not serious	NA[1]	not serious	NA	394	205	HR 0.50 (0.33, 0.76)	Not estimable	high

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1. Only one study so no inconsistency

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

F.3.4   Adding ertugliflozin compared to adding placebo

Table 15: Clinical evidence profile: Adding ertugliflozin 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
3-point mace at end of follow-up - 36 months											
1 (cannon 2020)	RCT	not serious	not serious	NA[1]	serious[2]	NA	193/1286	94/671	RR 1.07 (0.85, 1.35)	10 more per 1000 (21 fewer to 48 more)	moderate
3-point mace at end of follow-up - 36 months											
1 (cannon 2020)	RCT	not serious	not serious	NA[1]	serious[2]	NA	1286	671	HR 1.05 (0.82, 1.34)	Not estimable	moderate
hospitalisation for heart failure at end of follow-up - 36 months											
1 (cannon 2020)	RCT	not serious	not serious	NA[1]	serious[2]	NA	69/1286	55/672	RR 0.66 (0.47, 0.92)	28 fewer per 1000 (44 fewer to 6 fewer)	moderate
hospitalisation for heart failure at end of follow-up - 36 months											
1 (cannon 2020)	RCT	not serious	not serious	NA[1]	serious[2]	NA	1286	672	HR 0.63 (0.44, 0.90)	Not estimable	moderate

1. Only one study so no inconsistency

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