# National Institute for Health and Care Excellence

Draft for consultation

# Type 2 diabetes in adults: management

## [F3] Evidence reviews for subsequent pharmacological management of type 2 diabetes

*NICE guideline GID-NG10336*

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

*August 2025*

*Draft for Consultation*

*This evidence review was developed by NICE*

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

### E.1.2 Adding linagliptin compared to adding placebo

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

### E.1.3 Adding sitagliptin compared to adding insulin

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

### E.1.4 Adding sitagliptin 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).

## E.2 GLP-1 receptor agonist

### E.2.1 Adding exenatide compared to adding insulin

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.2.3 Adding liraglutide compared to adding insulin

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.3 SGLT2 inhibitors

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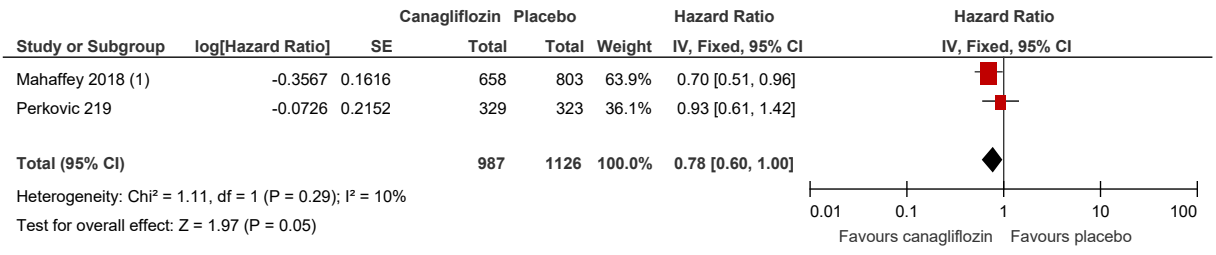
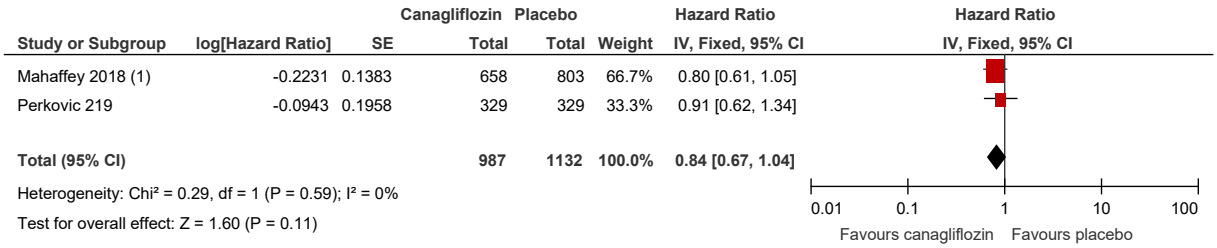
**Figure 1: All-cause mortality at end of follow-up**




Footnotes

(1) Data taken from subgroup analysis

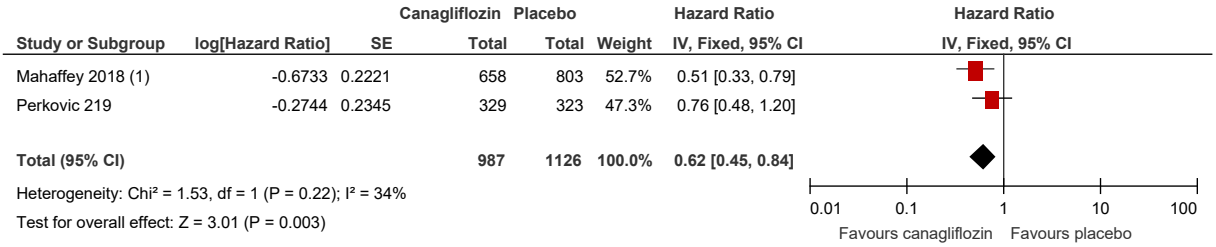
**Figure 2: 3-point MACE at end of follow-up**




Footnotes

(1) Data taken from subgroup analysis

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




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 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **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

### 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)

### 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 |
|---|---|---|---|---|---|---|---|---|---|---|---|

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **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 |
|---|---|---|---|---|---|---|---|---|---|---|---|

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **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** | | | | | | | | | | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 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 - 25.2 months** | | | | | | | | | | | |
| 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 - 25.2 months** | | | | | | | | | | | |
| 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 |

1. Only one study so no inconsistency

2. 95% confidence intervals cross both ends 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** | | | | | | | | | | | |
| 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** | | | | | | | | | | | |

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|---|---|---|---|---|---|---|---|---|---|---|---|
| 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** | | | | | | | | | | | |
| 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** | | | | | | | | | | | |
| 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 |

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)