# 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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ISBN:

# **Contents**

Appendices		. 5
Appendix E	Forest plots – Model 1: People with type 2 diabetes and heart failure	. 5
Appendix F	GRADE tables – Model 1: People with type 2 diabetes and heart	^
	failure	. 8

# **Appendices**

2	Appendix E	Forest plots -	- Model 1:	<b>People</b>	with type	2
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- 3 diabetes and heart failure
- 4 E.1 DPP-4 inhibitors
- 5 E.1.1 Adding alogliptin compared to adding placebo
- 6 There are no forest plots reported for this comparison (all outcomes include a single study).
- 8 E.1.2 Adding linagliptin compared to adding placebo
- 9 There are no forest plots reported for this comparison (all outcomes include a single study).
- 11 E.1.3 Adding sitagliptin compared to adding insulin
- 12 There are no forest plots reported for this comparison (all outcomes include a single study).
- 14 E.1.4 Adding sitagliptin compared to adding placebo
- 15 There are no forest plots reported for this comparison (all outcomes include a single study).
- 17 E.1.5 Adding vildagliptin compared to adding placebo
- 18 There are no forest plots reported for this comparison (all outcomes include a single study).
- 20 E.2 GLP-1 receptor agonist
- 21 E.2.1 Adding exenatide compared to adding insulin
- There are no forest plots reported for this comparison (all outcomes include a single study).
- 24 E.2.2 Adding exenatide compared to adding placebo
- 25 There are no forest plots reported for this comparison (all outcomes include a single study).

26

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13

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19

#### 1 E.2.3 Adding liraglutide compared to adding insulin

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

3

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#### E.2.4 Adding liraglutide compared to adding placebo

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

6

#### 7 E.2.5 Adding liraglutide compared to adding sitagliptin

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

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10

#### E.2.6 Adding lixisenatide compared to adding placebo

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

12

#### 13 E.2.7 Adding semaglutide compared to adding placebo

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

15

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#### E.3 SGLT2 inhibitors

#### 17 E.3.1 Adding canagliflozin compared to adding placebo

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

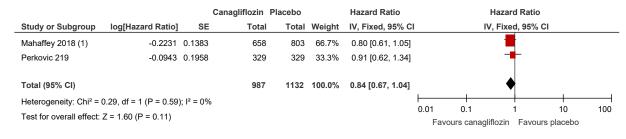
			Canagliflozin	Placebo		Hazard Ratio			Hazard Rati	0	
Study or Subgroup	log[Hazard Ratio]	SE	Total	l Total	Weight	IV, Fixed, 95% Cl	l	ľ	/, Fixed, 95%	6 CI	
Mahaffey 2018 (1)	-0.3567	0.1616	658	803	63.9%	0.70 [0.51, 0.96]			-		
Perkovic 219	-0.0726	0.2152	329	323	36.1%	0.93 [0.61, 1.42]			+		
Total (95% CI)			987	1126	100.0%	0.78 [0.60, 1.00]			•		
Heterogeneity: Chi <sup>2</sup> =	1.11, df = 1 (P = 0.29)	); I <sup>2</sup> = 10 <sup>9</sup>	%				-				
Test for overall effect:	Z = 1.97 (P = 0.05)						0.01 Fa	0.1 vours canag	1 iflozin Favo	10 ours placebo	100

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(1) Data taken from subgroup analysis

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



Footnotes

(1) Data taken from subgroup analysis

2

1

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

			Canagliflozin	Placebo		Hazard Ratio			Hazard	d Ratio		
Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	Weight	IV, Fixed, 95% Cl			IV, Fixed	d, 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: Chi <sup>2</sup> =	1.53, df = 1 (P = 0.22)	); I <sup>2</sup> = 34	%				0.01	0.1		1	10	100
Test for overall effect:	Z = 3.01 (P = 0.003)							vours cana	agliflozin	Favours p		100

Footnotes

(1) Data taken from subgroup analysis

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#### E.3.2 Adding dapagliflozin compared to adding placebo

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

9

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

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

12

13

#### E.3.4 Adding ertugliflozin compared to adding placebo

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

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### 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

					Ŭ.	Other			Relative		
	Des	Risk of	Indirec	Inconsi	Imprec	considerati	Interve	Cont	effect (95%	Absolute	Cert
No of studies	ign	bias	tness	stency	ision	ons	ntion N	rol N	CI)	effect	ainty
cardiovascular mortality at end of follow-up - 18 months											
1 (white 2013)	RC T	very serious	not seriou s	NA <sup>2</sup>	serious	NA	55/771	69/76 2	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)	RC T	very serious	not seriou s	NA <sup>2</sup>	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)	RC T	very serious	not seriou s	NA <sup>2</sup>	serious	NA	127/771	141/7 62	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)	RC T	very serious	not seriou s	NA <sup>2</sup>	very serious	NA	11/771	6/762	RR 1.81 (0.67, 4.87)	6 more per 1000 (3 fewer to 31 more)	very low

fotal and all information of											
non-fatal myocardial infarction at end of follow-up - 18 months											
1 (white 2013) unstable angina at end of follow-up - 18 months	RC T	very serious	not seriou s	NA <sup>2</sup>	very serious 4	NA	69/771	66/76	RR 1.03 (0.75, 1.43)	3 more per 1000 (22 fewer to 37 more)	very low
1 (white 2013)	RC T	very serious	Seriou s <sup>5</sup>	NA <sup>2</sup>	very serious	NA	5/771	11/76	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)	RC T	very serious	Seriou s <sup>5</sup>	NA <sup>2</sup>	serious	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)	RC T	very serious	not seriou s	NA <sup>2</sup>	very serious	NA	63/771	65/76 2	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)	RC T	very serious	not seriou s	NA <sup>2</sup>	very serious	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

				•							
		Risk				Other			Relative		
	Des	of	Indirec	Inconsi	Imprec	considerati	Interve	Cont	effect (95%	Absolute	Cert
No of studies	ign	bias	tness	stency	ision	ons	ntion N	rol N	CI)	effect	ainty
cardiovascular mortality at end of											
follow-up - 26.4 months											
		not	not		very						
	RC	seriou	seriou		serious				HR 0.96	Not	
1 (rosenstock 2019a)	T	S	S	NA <sup>1</sup>	2	NA	952	921	(0.73, 1.26)	estimable	low
hospitalisation for heart failure at											
end of follow-up - 16.4 months											
										14 fewer	
		not	not							per 1000	
	RC	seriou	seriou		serious			122/9	RR 0.90	(39 fewer to	mod
1 (rosenstock 2019a)	Т	S	S	NA <sup>1</sup>	3	NA	113/952	21	(0.71, 1.14)	18 more)	erate
hospitalisation for heart failure at											
end of follow-up - 16.4 months											
		not	not								
	RC	seriou	seriou		serious				HR 0.88	Not	mod
1 (rosenstock 2019a)	Т	s	S	NA <sup>1</sup>	3	NA	952	921	(0.68, 1.14)	estimable	erate

- 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

	De	Risk	Indire	Incons		Other			Relative		Cert
	sig	of	ctnes	istenc	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	S	у	cision	ions	ntion N	rol N	CI)	effect	у
hospitalisation for heart failure at end of follow-up - 12 months											
1 (arturi 2017)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>3</sup>	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)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>3</sup>	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)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	Seriou s <sup>5</sup>	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

				-		Other			Relative		
	Des	Risk of	Indirec	Inconsis	Impreci	consideratio	Interven	Contr	effect (95%	Absolute	Certa
No of studies	ign	bias	tness	tency	sion	ns	tion N	ol N	CI)	effect	inty
4-point mace at follow-up - 36											
months											
		not									
	RC	seriou	not		serious				HR 0.97	Not	mode
1 (green 2015)	Т	S	serious	NA <sup>1</sup>	2	NA	1303	1340	(0.80, 1.18)	estimable	rate
hospitalisation for heart failure at											
follow-up - 36 months											
		not			very						
	RC	seriou	not		serious				HR 1.05	Not	
1 (green 2015)	Т	S	serious	NA <sup>1</sup>	3	NA	1303	1340	(0.79, 1.40)	estimable	low
hospitalisation for heart failure at											
follow-up - 36 months											
			_	_				_		4 more per	
		not								1000	
	RC	seriou	not		serious			94/13	RR 1.06	(14 fewer to	mode
1 (green 2015)	Т	S	serious	$NA^1$	2	NA	97/1303	40	(0.81, 1.39)	28 more)	rate

- 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

	De	Risk	Indire	Incons		Other	Interve	Cont	Relative		Cert
	sig	of	ctnes	istenc	Impre	considerat	ntion	rol	effect (95%	Absolute	aint
No of studies	n	bias	s	у	cision	ions	N	N	CI)	effect	у
all-cause mortality at end of follow-up - 12 months				-							
1 (mcmurray 2018)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	seriou s²	NA	11/128	4/12 6	RR 2.71 (0.89, 8.28)	54 more per 1000 (4 fewer to 231 more)	mod erat e
cardiovascular mortality at end of follow-up - 12 months											
1 (mcmurray 2018) non-fatal stroke at end of follow-up - 12	RC T	not seriou s	not seriou s	NA <sup>1</sup>	very seriou s <sup>3</sup>	NA	7/128	4/12 6	RR 1.72 (0.52, 5.74)	23 more per 1000 (15 fewer to 150 more)	low
months											
1 (mcmurray 2018)	RC T	not seriou s	not seriou	NA <sup>1</sup>	very seriou s <sup>3</sup>	NA	1/128	4/12 6	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)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	not seriou s	NA	13/128	10/1 26	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)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	very seriou s <sup>3</sup>	NA	9/128	4/12 6	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)	RC	not seriou	not seriou	NA <sup>1</sup>	very seriou s <sup>3</sup>	NA	6/128	7/12 6	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	5	5	INA	5	INA	0/128	0	(0.29, 2.44)	oo more)	low
1 (mcmurray 2018)	RC T	very seriou s <sup>4</sup>	not seriou	NA <sup>1</sup>	seriou s <sup>5</sup>	NA	115	112	MD -0.36 (-0.71, -	MD 0.36 lower (0.71 lower to 0.01 lower)	very

- 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

	De	Risk	Indire	Incons		Other			Relative		Cert
	sig	of	ctnes	istenc	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	S	у	cision	ions	ntion N	rol N	CI)	effect	У

all-cause mortality at end of follow-up - 6 months											
1 (chen 2017)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>3</sup>	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)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>5</sup>	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)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	Seriou s <sup>6</sup>	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

14210 11 01111041 011401100 p1	<del>• ,</del>	10.01119	7.011.01.00	ooparo	<del>u 10 aaa.</del>	g p.a.cc.cc					
						Other					
	Des	Risk of	Indirec	Inconsis	Imprec	consideratio	Interven	Contr	Relative effect	Absolute	Certa
No of studies	ign	bias	tness	tency	ision	ns	tion N	ol N	(95% CI)	effect	inty

3-point mace at end of follow-up - 38.4 months											
1 (holman 2017)	RC T	not serious	not serious	NA <sup>1</sup>	not serious	NA	227/1161	237/1 228	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											
	RC	not	not		not				HR 0.97	Not	
1 (holman 2017)	Т	serious	serious	NA <sup>1</sup>	serious	NA	1161	1228	(0.81, 1.16)	estimable	High

<sup>1.</sup> 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

rable of emined official reading	De	Risk		Incons		Other			Relative		Cert
	sig	of	Indire	istenc	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	у	cision	ions	ntion N	rol N	CI)	effect	у
hospitalisation for heart failure at end of follow-up - 12 months											
1 (arturi 2017) severe hypoglycaemic episodes at end of	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>3</sup>	NA	0/10	0/12	rd 0.00 (-0.16, 0.16)	0 fewer per 1000 (161 fewer to 161 more) <sup>4</sup>	very low
follow-up - 12 months											
1 (arturi 2017)	RC T	very seriou s <sup>1</sup>	not seriou	NA <sup>2</sup>	very seriou s <sup>3</sup>	NA	0/10	0/12	rd 0.00 (-0.16, 0.16)	0 fewer per 1000 (161 fewer to 161 more) <sup>4</sup>	very low
hba1c change (%, lower values are better, final value) at end of follow-up - 12 months											

		very	not		very						
	RC	seriou	seriou		seriou				MD 0.20		very
1 (arturi 2017)	Т	s <sup>1</sup>	S	$NA^2$	<b>s</b> <sup>5</sup>	NA	10	12	(-0.99, 1.39)	-	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

Tubic C. Cillingal Cytachics Prome, P		Risk				Other			Relative		
	Des	of	Indirec	Inconsi	Imprec	considerati	Interve	Cont	effect (95%	Absolute	Cert
No of studies	ign	bias	tness	stency	ision	ons	ntion N	rol N	CI)	effect	ainty
all-cause mortality at end of follow- up - 45.6 months											
1 (marso 2016a)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	serious 2	NA	119/835	132/8 32	RR 0.90 (0.71, 1.13)	16 fewer per 1000 (45 fewer to 20 more)	mod erate
all-cause mortality at end of follow- up - 45.6 months											
1 (marso 2016a)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	serious 2	NA	835	832	HR 0.89 (0.70, 1.13)	Not estimable	mod erate
cardiovascular mortality at end of follow-up - 45.6 months											

1 (marso 2016a)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	serious	NA	76/835	88/83	RR 0.86 (0.64, 1.15)	15 fewer per 1000 (38 fewer to 16 more)	mod erate
cardiovascular mortality at end of follow-up - 45.6 months											
1 (marso 2016a)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	serious 2	NA	835	832	HR 0.85 (0.63, 1.15)	Not estimable	mod erate
3-point mace at end of follow-up - 45.6 months											
1 (marso 2016a)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	serious	NA	142/835	170/8 32	RR 0.83 (0.68, 1.02)	34 fewer per 1000 (65 fewer to 4 more)	mod erate
3-point mace at end of follow-up - 45.6 months											
1 (marso 2016a)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	serious 2	NA	835	832	HR 0.81 (0.65, 1.01)	Not estimable	mod erate
non-fatal stroke at end of follow-up - 45.6 months									,		
1 (marso 2016a)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	very serious	NA	27/835	30/83	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)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	very serious	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)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	serious	NA	54/835	71/83 2	RR 0.76 (0.54, 1.07)	21 fewer per 1000 (39 fewer to 6 more)	mod erate

non fatal myseculial inforation at											
non-fatal myocardial infarction at end of follow-up - 45.6 months											
1 (marso 2016a)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	serious 2	NA	835	832	HR 0.74 (0.52, 1.05)	Not estimable	mod erate
unstable angina at end of follow-up - 45.6 months									, ,		
1 (marso 2016a)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	very serious	NA	22/835	30/83	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)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	Seriou s <sup>2</sup>	NA	835	832	HR 0.72 (0.42, 1.23)	Not estimable	mod erate
hospitalisation for heart failure at end of follow-up - 45.6 months											
1 (marso 2016a)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	very serious	NA	108/835	108/8 32	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											
	RC	not seriou	not seriou		very serious		005		HR 0.98	Not	
1 (marso 2016a)	Т	S	S	NA <sup>1</sup>	3	NA	835	832	(0.75, 1.28)	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

	De	Risk		Incons		Other			Relative		Cert
	sig	of	Indire	istenc	Impre	considerat	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	у	cision	ions	ntion N	rol N	CI)	effect	у
hospitalisation for heart failure at end of follow-up - 12 months											
1 (arturi 2017)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>3</sup>	NA	0/10	0/10	RD 0.00 (-0.17, 0.17)	0 fewer per 1000 (174 fewer to 174 more) <sup>4</sup>	very low
severe hypoglycaemic episodes at end of follow-up - 12 months											
1 (arturi 2017)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very seriou s <sup>3</sup>	NA	0/10	0/10	RD 0.00 (-0.17, 0.17)	0 fewer per 1000 (174 fewer to 174 more) <sup>4</sup>	very low
hba1c change (%, lower values are better, final value) at end of follow-up - 12 months											
1 (arturi 2017)	RC T	very seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	seriou s <sup>5</sup>	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

		Risk		•		Other			Relative		
	Des	of	Indirec	Inconsi	Imprec	considerati	Interven	Contr	effect (95%	Absolute	Cert
No of studies	ign	bias	tness	stency	ision	ons	tion N	ol N	CI)	effect	ainty
hospitalisation for heart failure at end of follow-up - 25 months											
1 (pfeffer 2015)	RC T	not seriou s	not serious	NA <sup>1</sup>	very serious	NA	66/682	69/67 6	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)	RC T	not seriou s	not serious	NA <sup>1</sup>	very serious	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	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
3-point mace at end of follow-up - 25.2 months											
	RC	not	not	,	very			34/28	RR 1.04	5 more per 1000 (39 fewer to	
1 (marso 2016b)	T	serious	serious	NA <sup>1</sup>	serious <sup>2</sup>	NA	35/285	8	(0.67, 1.62)	73 more)	low

3-point mace at end of follow-up - 25.2 months											
1 (marso 2016b)	RC T	not serious	not serious	NA <sup>1</sup>	very serious <sup>2</sup>	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

Jane III amiliani amiliani promoti pro		Risk				Other			Relative		
	Des	of	Indirec	Inconsi	Imprec	considerati	Interve	Cont	effect (95%	Absolut	Cert
No of studies	ign	bias	tness	stency	ision	ons	ntion N	rol N	CI)	e effect	ainty
all-cause mortality at end of follow-up - mean 37.2 months											
2	RC T	not seriou s	not seriou s	not serious	serious	NA	987	1126	HR 0.78 (0.60, 1.00)	Not estimabl e	mod erate
cardiovascular mortality at end of follow-up - 43 months											
1 (mahaffey 2018)	RC T	not seriou s	not seriou s	NA <sup>2</sup>	serious	NA	658	803	HR 0.72 (0.51, 1.02)	Not estimabl e	mod erate
3-point mace at end of follow-up - mean 37.2 months									, ,		
2	RC T	not seriou s	not seriou s	not serious	serious	NA	987	1132	HR 0.84 (0.67, 1.04)	Not estimabl e	mod erate
hospitalisation for heart failure at end of follow-up - mean 37.2 months											

2	RC T	not seriou s	not seriou s	not serious	serious	NA	987	1126	HR 0.62 (0.45, 0.84)	Not estimabl e	mod erate
acute kidney injury at end of follow-up - mean 31.4 months											
1 (perkovic 2019)	RC T	not seriou s	not seriou s	NA <sup>2</sup>	very serious	NA	329	323	HR 0.75 (0.40, 1.41)	Not estimabl e	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

		Risk				Other			Relative		
	Des	of	Indirec	Inconsi	Imprec	considerati	Interve	Cont	effect (95%	Absolute	Cert
No of studies	ign	bias	tness	stency	ision	ons	ntion N	rol N	CI)	effect	ainty
all-cause mortality at end of follow-											
up - 50.4 months											
1 (wiviott 2019)	RC T	seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	serious	NA	115/852	131/8 72	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)	RC T	seriou s¹	not seriou s	NA <sup>2</sup>	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											

4 (	RC	seriou	not seriou	NIA 2	very serious	NA.	75/050	74/87	RR 1.04	3 more per 1000 (20 fewer to	very
1 (wiviott 2019) cardiovascular mortality at end of follow-up - 50.4 months	T	s <sup>1</sup>	S	NA <sup>2</sup>	4	NA	75/852	2	(0.76, 1.41)	35 more)	low
1 (wiviott 2019)	RC T	seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very serious	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)	RC T	seriou	not seriou s	NA <sup>2</sup>	serious	NA	153/852	151/8 72	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)	RC T	seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	serious	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)	RC T	seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	very serious	NA	40/852	34/87 2	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)	RC T	seriou s¹	not seriou s	NA <sup>2</sup>	very serious	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)	RC T	seriou	not seriou	NA <sup>2</sup>	serious	NA	66/852	76/87 2	RR 0.89	10 fewer per 1000 (31 fewer to	low
I (WIVIOU ZUIB)	ı	5	S	INA*	Ŭ	INA	00/002		(0.65, 1.22)	19 more)	low

and the first of the second se											
non-fatal myocardial infarction at end of follow-up - 50.4 months											
1 (wiviott 2019)	RC T	seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	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)	RC T	seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	serious	NA	55/852	70/87 2	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)	RC T	seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	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)	RC T	seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	serious	NA	87/852	115/8 72	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)	RC T	seriou s <sup>1</sup>	not seriou s	NA <sup>2</sup>	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

·	De	Risk				Other			Relative		Cert
	sig	of	Indire	Inconsi	Impre	considerati	Interve	Cont	effect (95%	Absolute	aint
No of studies	n	bias	ctness	stency	cision	ons	ntion N	rol N	CI)	effect	У
persistent signs of worsening kidney disease at end of follow-up - 37.2 months											
1 (zinman 2015)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	seriou s <sup>2</sup>	NA	48/394	41/2 05	RR 0.61 (0.42, 0.89)	78 fewer per 1000 (117 fewer to 22 fewer)	mod erat e
persistent signs of worsening kidney disease at end of follow-up - 37.2 months											
1 (zinman 2015)	RC T	not seriou s	not seriou s	NA <sup>1</sup>	not seriou s	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

Table 10. Chinear evidence preme.		Risk		•		Other			Relative		
	Des	of	Indirec	Inconsi	Impre	considerati	Interven	Contr	effect (95%	Absolute	Certa
No of studies	ign	bias	tness	stency	cision	ons	tion N	ol N	CI)	effect	inty
3-point mace at end of follow-up - 36 months											
		not								10 more per 1000	
	RC	seriou	not		seriou		193/128	94/67	RR 1.07	(21 fewer to	mod
1 (cannon 2020)	Τ	S	serious	NA <sup>1</sup>	s <sup>2</sup>	NA	6	1	(0.85, 1.35)	48 more)	erate

3-point mace at end of follow-up - 36 months											
1 (cannon 2020)	RC T	not seriou s	not serious	NA <sup>1</sup>	seriou s <sup>2</sup>	NA	1286	671	HR 1.05 (0.82, 1.34)	Not estimable	mod erate
hospitalisation for heart failure at end of follow-up - 36 months											
1 (cannon 2020)	RC T	not seriou s	not serious	NA <sup>1</sup>	seriou s²	NA	69/1286	55/67 2	RR 0.66 (0.47, 0.92)	28 fewer per 1000 (44 fewer to 6 fewer)	mod erate
hospitalisation for heart failure at end of follow-up - 36 months											
1 (cannon 2020)	RC T	not seriou s	not serious	NA <sup>1</sup>	seriou s <sup>2</sup>	NA	1286	672	HR 0.63 (0.44, 0.90)	Not estimable	mod erate

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