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LISTS OF ABBREVIATIONS AND ACRONYMS

MACE: Major Adverse Cardiovascular Events MH: Mantel-Haenzel **OR: Odds Ratio RR: Relative Risk BMI: Body Mass Index** MD: Mean Difference (weighted) QALY: Quality Adjusted Life Years (anni di vita aggiustati per qualità) Min: Minute ICUR: Incremental Cost-Utility Ratio ICER: Incremental Cost-Effectiveness Ratio SoC: Standard of Care T2DM: Type 2 Diabetes Mellitus **RCT: Randomized controlled trials** GRADE: Grades of Recommendation, Assessment, Development, and Evaluation EtD: Evidence to Decision GLP-1 RA: Glucagon-Like Peptide-1 Receptor Agonists SGLT-2i: Sodium-Glucose coTransporter-2 inhibitors DPP-4i: DiPeptidyl Peptidase-4 inhibitors SU: Sulfonylureas CCS: Charlson Comorbidity Score WTP: willingness to pay LDL: Low-density Lipoprotein

CONTENT OF THE APPENDIX

This Appendix contains detailed information on unpublished and principal methods and results, including pharmacoeconomic evaluations, on already published systematic reviews and metaanalysis.

RECOMMENDATION # 1: THERAPEUTIC TARGETS.

1.1 HbA1c target in patients treated with drugs inducing hypoglycemia

Considered evidence: RCTs performed on patients with T2DM, up to December 1st, 2020, adopting any pharmacological regimen for intensifying glycemic control with drugs inducing hypoglycemia, fulfilling the following criteria:

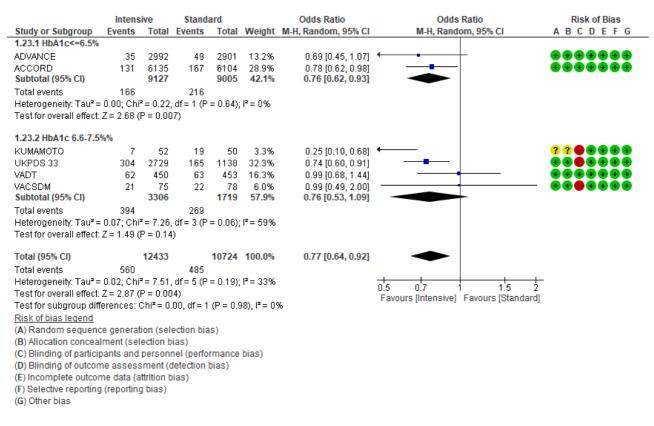
- 1) duration of treatment ≥ 2 years
- 2) between-group HbA1c difference ≥0.5% (≥ 6 mmol/mol)
- 3) primary or secondary endpoints, including at least one of the following events: MACE or microvascular complications.

The primary outcome of the present meta-analysis was to assess the effects of intensification of glycemic treatment in comparison with standard care on the risk of MACE, eye and kidney adverse events, or severe hypoglycemia. Secondary outcomes included the risk of individual components of MACE and all-cause mortality.

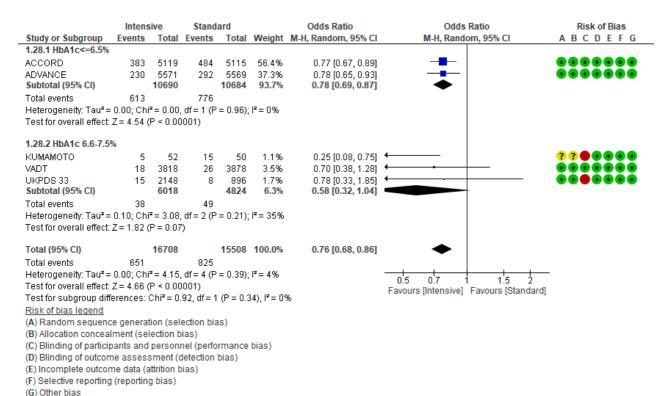
The systematic review has already been published; for complete search string, list and characteristics of included studies, and assessment of publication bias, please see the related publication¹.

1.1.1. Microvascular complications

Forest plot for trials comparing the effects of intensive glycemic control (using drugs associated with hypoglycemia) and standard care on eye adverse events.



Forest plot for trials comparing the effects of intensive glycemic control (using drugs associated with hypoglycemia) and standard care on renal adverse events.

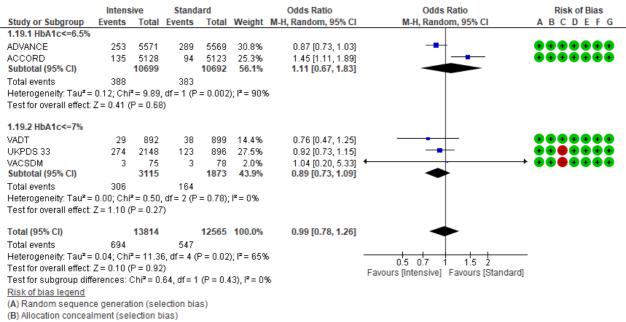


1.1.2. MACE

Forest plot for trials comparing the effects of intensive glycemic control (using drugs associated with hypoglycemia) and standard care on MACE.

	Intens	ive	Stand	ard		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
1.3.1 HbA1c<= 6.5%								
ADVANCE	557	5571	590	5569	36.5%	0.94 [0.83, 1.06]		
ACCORD	352	5128	371	5123	26.1%	0.94 [0.81, 1.10]		$\bullet \bullet \bullet \bullet \bullet \bullet \bullet \bullet \bullet$
Subtotal (95% CI)		10699		10692	62.6%	0.94 [0.85, 1.03]	-	
Total events	909		961					
Heterogeneity: Tau ² =				= 0.94);	I² = 0%			
Test for overall effect:	Z=1.27 (P = 0.20)					
1.3.2 HbA1c 6.6-7.5%	6							
UKPDS 33	559	2148	261	896	20.8%	0.86 [0.72, 1.02]		
VADT	235	892	264	899	15.3%	0.86 [0.70, 1.06]		
VACSDM	24	75	16	78	1.3%	1.82 [0.88, 3.80]		
Subtotal (95% CI)		3115		1873	37.4%	0.91 [0.73, 1.13]		
Total events	818		541					
Heterogeneity: Tau² = Test for overall effect:				= 0.14);	I ^z = 49%			
	2 - 0.01 (<i>'</i>					
Total (95% CI)		13814		12565	100.0%	0.92 [0.84, 1.00]	◆	
Total events	1727		1502					
Heterogeneity: Tau ² =				= 0.33);	I²=13%		0.7 0.85 1 1.2 1.5	
Test for overall effect:							Favours [Intensive] Favours [Standard]	
Test for subgroup dif	ferences: (Chi²=0.	08, df = 1	(P = 0.7)	78), I ² = 09	%	· · · · · · · · · · · · · · · · · · ·	
Risk of bias legend								
(A) Random sequen	-			as)				
(B) Allocation concea								
(C) Blinding of partici	•	•			bias)			
(D) Blinding of outcor				bias)				
(E) Incomplete outcom			las)					
(F) Selective reporting (G) Other bias	g (reporting	g dias)						

Forest plot for trials comparing the effects of intensive glycemic control (using drugs associated with hypoglycemia) and standard care on cardiovascular mortality.



(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

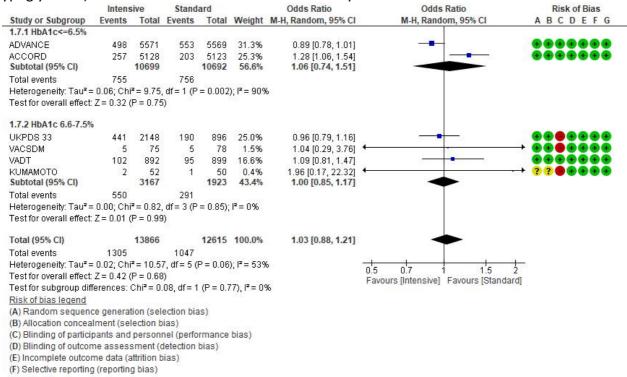
(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

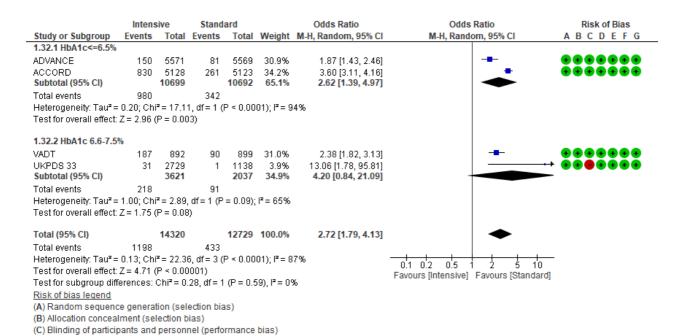
1.1.3. All-cause mortality

Forest plot for trials comparing the effects of intensive glycemic control (using drugs associated with hypoglycemia) and standard care on all-cause mortality.



1.1.4. Severe hypoglycemia

Forest plot for trials comparing the effects of intensive glycemic control (using drugs associated with hypoglycemia) and standard care on severe hypoglycaemia.



(E) Incomplete outcome data (attrition bias) (F) Selective reporting (reporting bias)

(D) Blinding of outcome assessment (detection bias)

(G) Other bias

1.1.5. GRADE evidence table

Certainty a	ssessme	ent					Summary	of findings			
							Study even	t rates (%)		Anticipa	ted absolute effects
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With Standard care	With Intensive glycemic control	Relative effect (95% Cl)	Risk in controls	Risk difference with the intervention

MACE

For HbA1c ≤48 mmol/mol (6.5%)

(2 RC13) (0.85 to 1.05) 1.000 (R0112 rewert more)	26379 (2 RCTs)	serious ^a	not serious	not serious	not serious	none	⊕⊕⊕⊖ MODERATE	961/10692 (9.0%)	909/10699 (8.5%)	OR 0.94 (0.85 to 1.03)	90 per 1.000	5 fewer per 1.000 (from 12 fewer to 2 more)
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For HbA1c 48-58 mmol/mol (6.6-7.5%)

4988 (3 RCTs)	serious ^a	serious ^b	not serious	not serious	none	⊕⊕⊖⊖ LOW	541/1873 (28.9%)	818/3115 (26.3%)	OR 0.91 (0.73 to 1.13)	289 per 1.000	<i>19 fewer per 1.000</i> (from 60 fewer to 26 more)	
------------------	----------------------	----------------------	-------------	-------------	------	-------------	---------------------	---------------------	---------------------------	------------------	--	--

All-cause mortality

For HbA1c ≤48 mmol/mol (6.5%)

21391 (2 RCTs)	serious ^a	serious ^b	not serious	not serious	none	⊕⊕⊖⊖ LOW	756/10692 (7.1%)	755/10699 (7.1%)	OR 1.06 (0.74 to 1.51)	71 per 1.000	<i>4 more per 1.000</i> (from 17 fewer to 32 more)
											52 11010)

For HbA1c 48-58 mmol/mol (6.6-7.5%)

5090 (4 RCTs)	serious ^a	not serious	not serious	not serious	none	⊕⊕⊕⊖ MODERATE	291/1923 (15.1%)	550/3167 (17.4%)	OR 1.00 (0.85 to 1.17)	151 per 1.000	<i>0 fewer per 1.000</i> (from 20 fewer to 21 more)
------------------	----------------------	-------------	-------------	-------------	------	------------------	---------------------	---------------------	----------------------------------	------------------	---

		Certa	inty assessr	nent					Summary of findi	ngs	
							Study ever	nt rates (%)		Anticipat	ted absolute effects
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectn ess	Imprecision	Publicati on bias	Overall certainty of evidence	With Standard care	With Intensive glycemic control	Relative effect (95% CI)	Risk with placebo	Risk difference with Intensive glycemic control

Cardiovascular mortality

For HbA1c ≤48 mmol/mol (6.5%)

21391 (2 RCTs)	serious ^a	serious⁵	not serious	not serious	none	⊕⊕⊖⊖ LOW	383/10692 (3.6%)	388/10699 (3.6%)	OR 1.11 (0.67 to 1.83)	36 per 1000	<i>4 more per 1000</i> (from 12 fewer to 28 more)
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For HbA1c 48-58 mmol/mol (6.6-7.5%)

4988 (3 RCTs)	seriousª	not serious	not serious	not serious	none	⊕⊕⊕⊖ MODERATE	164/1873 (8.8%)	306/3115 (9.8%)	OR 0.89 (0.73 to 1.09)	88 per 1000	<i>9 fewer per 1000</i> (from 22 fewer to 7 more)
------------------	----------	-------------	-------------	-------------	------	------------------	--------------------	--------------------	---------------------------	----------------	---

Eye adverse events

For HbA1c ≤48 mmol/mol (6.5%)

18132 (2 RCTs)	seriousª	not serious	not serious	not serious	very strong association	⊕⊕⊕○ MODERATE	216/9005 (2.4%)	166/9127 (1.8%)	OR 0.76 (0.62 to 0.93)	24 per 1000	6 fewer per 1000 (from 9 fewer to 2 f ewer)	
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For HbA1c 48-58 mmol/mol (6.6-7.5%)

ſ	5025	serious ^a	serious⁵	not serious	not serious	none	$\Theta \Theta \bigcirc \bigcirc$	269/1719	394/3306	OR 0.76	156 per	33 fewer per 1000
	(4 RCTs)						LOW	(15.6%)	(11.9%)	(0.53 to 1.09)	1000	(from 67 fewer to 1
												2 more)

Certainty as	ssessme	nt					Summary o	of findings			
							Study ever	nt rates (%)		Anticipat	ed absolute effects
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectn ess	Imprecision	Publication bias	Overall certainty of evidence	With Standard care	With Intensive glycemic control	Relative effect (95% Cl)	Risk with placebo	Risk difference with Intensive glycemic control

Kidney adverse events

For HbA1c ≤48 mmol/mol (6.5%)

21374 (2 RCTs)	serious ^a	not serious	not serious	not serious	very strong association	⊕⊕⊕⊖ MODERATE	776/10684 (7.3%)	613/10690 (5.7%)	OR 0.78 (0.69 to 0.87)	73 per 1000	15 fewer per 1000 (from 21 fewer to 9 fewer)
-------------------	----------------------	-------------	-------------	-------------	-------------------------	------------------	----------------------	----------------------	----------------------------------	----------------	---

For HbA1c 48-58 mmol/mol (6.6-7.5%)

10842 (3 RCTs)	serious ^a	serious ^b	not serious	not serious	strong association	49/4824 (1.0%)	38/6018 (0.6%)	OR 0.58 (0.32 to 1.04)	10 per 1000	<i>4 fewer per 1000</i> (from 7 fewer to 0 f
										ewer)

Severe hypoglycemia

For HbA1c ≤48 mmol/mol (6.5%)

21391 (2 RCTs)	serious ^a	serious ^b	not serious	not serious	very strong association	⊕⊕⊕⊖ MODERATE	342/10692 (3.2%)	980/10699 (9.2%)	OR 2.62 (1.39 to 4.97)	32 per 1000	48 more per 1.000 (from 12 more to 1
											09 more)

For HbA1c 48-58 mmol/mol (6.6-7.5%)

5658 (2 RCTs)	serious ^a	serious ^b	not serious	not serious	strong association	⊕⊕⊕⊖ MODERATE	91/2037 (4.5%)	218/3621 (6.0%)	OR 4.20 (0.84 to 21.1)	45 per 1000	<i>119 more per 1000</i> (from 7 fewer to 45 2 more)	
------------------	----------------------	----------------------	-------------	-------------	-----------------------	------------------	-------------------	--------------------	-------------------------------	----------------	--	--

Cl: Confidence interval; **OR:** Odds Ratio; **Explanations** a. *Open-label study; b. High/*Moderate heterogeneity.

1.2 HbA1c target in patients treated with drugs not inducing hypoglycemia

Considered evidence: RCTs performed on patients with T2DM, up to December 1st, 2020, adopting any pharmacological regimen for intensifying glycemic control with drugs not inducing hypoglycemia, fulfilling the following criteria:

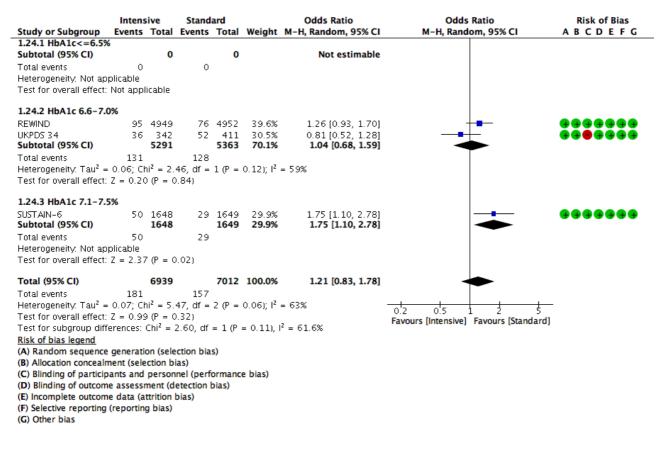
- 1) duration of treatment ≥ 2 years
- 2) between-group HbA1c difference ≥0.5% (≥ 6 mmol/mol)
- 3) primary or secondary endpoints, including at least one of the following events: MACE or microvascular complications.

The primary outcome of the present meta-analysis was to assess the effects of intensification of glycemic treatment in comparison with standard care on the risk of MACE, eye and kidney adverse events, or severe hypoglycemia. Secondary outcomes included the risk of individual components of MACE and all-cause mortality.

The systematic review has already been published; for complete search string, list and characteristics of included studies, and assessment of publication bias, please see the related publication ¹.

1.1.1. Microvascular complications

Forest plot for trials comparing the effects of intensive glycemic control (using drugs not associated with hypoglycemia) and standard care on eye adverse events.



Forest plot for trials comparing the effects of intensive glycemic control (using drugs associated with hypoglycemia) and standard care on renal adverse events.

	Inten	sive	Stand	lard		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	ABCDEFG
1.29.1 HbA1c<=6.5%	6							
Subtotal (95% CI)		0		0		Not estimable		
Total events	0		0					
Heterogeneity. Not ap	plicable							
Test for overall effect:	Not appl	icable						
1.29.2 HbA1c 6.6-7.0	0%							
UKPDS 34	2	342	2	411	1.6%	1.20 [0.17, 8.58]		
Subtotal (95% CI)		342		411	1.6%	1.20 [0.17, 8.58]		
Total events	2		2					
Heterogeneity. Not ap	plicable							
Test for overall effect:	•	B(P = 0.	85)					
1.29.3 HbA1c 7.1-7.5	5%							
Subtotal (95% CI)		0		0		Not estimable		
Total events	0		0					
Heterogeneity: Not ap	plicable							
Test for overall effect:	Not appl	icable						
1.29.4 HbA1c 7.6-8.0	0%							
CANVAS	118	5795	147	4345	49.1%	0.59 [0.46, 0.76]		6666666
VERTIS-CV	175	5499	108	2745	49.3%	0.80 [0.63, 1.02]		6666666
Subtotal (95% CI)		11294		7090	98.4%	0.69 [0.51, 0.93]	•	
Total events	293		255				-	
Heterogeneity: Tau ² =	0.03; Ch	$ni^2 = 2.9$	1, df = 1	1 (P = 0)	$(0.09); ^2 =$	66%		
Test for overall effect:	Z = 2.46	5(P = 0.	01)					
Total (95% CI)		11636		7501	100.0%	0.70 [0.54, 0.90]	•	
Total events	295		257				-	
Heterogeneity, Tau ² =	0.02: Ch	$ni^2 = 3.2$	2. df = 2	2 (P = 0	$(20)(1^2 =$	38%		.,
Test for overall effect:			· ·	, -				20
Test for subgroup diff				= 1 (P =	0.58), l ²	= 0%	Favours [Intensive] Favours [Standar	uj
Risk of bias legend				`	., .			
(A) Random sequence	generatio	on (selec	tion bias)				
(B) Allocation concealn				,				
(C) Plinding of particin					hinc)			

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

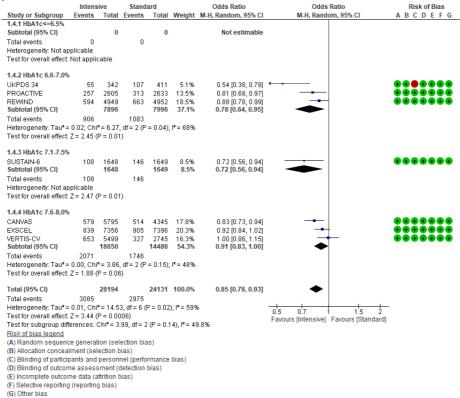
(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

1.1.2. MACE

Forest plot for trials comparing the effects of intensive glycemic control (using drugs associated with hypoglycemia) and standard care on MACE.



Forest plot for trials comparing the effects of intensive glycemic control (using drugs associated with hypoglycemia) and standard care on cardiovascular mortality.

Study or Subgroup	Intens Events		Stand Events		Weight	Odds Ratio M-H. Random, 95% Cl	Odds Ratio M-H. Random, 95% Cl	Risk of Bias ABCDEFG
1.20.1 HbA1c<=6.5%	Lventa	Total	LVCIII	Total	Weight	m-n, Kandom, 55% Cr	min, Kandoni, 55% Ci	ADCDLIG
Subtotal (95% CI)		0		0		Not estimable		
Total events	0		0					
Heterogeneity: Not app	licable							
Test for overall effect: N	lot applic	able						
1.20.2 HbA1c 6.6-7.0%								
UKPDS 34	25	342	51	411	2.6%	0.56 [0.34, 0.92]	←	
REWIND	317	4949	346	4952	26.4%	0.91 [0.78, 1.07]		
Subtotal (95% CI)		5291		5363	29.1%	0.76 [0.47, 1.21]		
Total events	342		397					
Heterogeneity: Tau ² = 0				= 0.07);	I ² = 70%			
Test for overall effect: Z	:= 1.17 (P = 0.24)					
1.20.3 HbA1c 7.1-7.5%								
SUSTAIN-6	44	1648	46	1649	3.7%	0.96 [0.63, 1.45]		•••••
Subtotal (95% CI)		1648		1649	3.7%	0.96 [0.63, 1.45]		
Total events	44		46					
Heterogeneity: Not app								
Test for overall effect: Z	.= 0.21 (P = 0.83)					
1.20.4 HbA1c 7.6-8.0%								
EXSCEL	340	7356	386	7396	29.4%	0.88 [0.76, 1.02]		
CANVAS	250	5795	209	4345	18.6%	0.89 [0.74, 1.08]		
VERTIS-CV	341	5499 18650	184	2745 14486	19.1% 67.2%	0.92 [0.76, 1.11]		
Subtotal (95% CI)	0.04	10000	779	14400	07.2%	0.89 [0.81, 0.99]	\bullet	
Total events Heterogeneity: Tau ² = 0	931 2002 ONR	- 0.14		- 0.000	12 - 00V			
Test for overall effect: Z				= 0.93),	1-= 0.%			
Total (95% CI)		25589		21400	100.0%	0.89 [0.82, 0.97]		
Total events	1317	25505	1222	21430	100.070	0.03 [0.02, 0.37]	•	
Heterogeneity: Tau ² = 0		- 2 70		- 0.60	IZ = 0.06			_
Test for overall effect: Z				- 0.58),	1 - 0 %		0.5 0.7 1 1.5 2	
Test for subgroup differ				(P = 0.7)	25) I ² = 01	*	Favours [Intensive] Favours [Standard]	
Risk of bias legend			00,01 2		•//. •	~		
(A) Random sequence	generat	ion (sel	ection bia	as)				
(B) Allocation concealn	nent (sel	ection b	ias)					
(C) Blinding of participa	ants and	personr	nel (perfo	rmance	bias)			
(D) Blinding of outcome	e assess	ment (c	letection	bias)				
(E) Incomplete outcom			ias)					
(F) Selective reporting (reporting	j bias)						
(G) Other bias								

1.1.3. All-cause mortality

Forest plot for trials comparing the effects of intensive glycemic control (using drugs associated with hypoglycemia) and standard care on all-cause mortality.

Study or Subgroup	Intens Events		Stand Events		Weight	Odds Ratio M-H, Random, 95% Cl	Odds Ratio M-H, Random, 95% Cl	Risk of Bias A B C D E F G
1.8.1 HbA1c<=6.5% Subtotal (95% CI)		0		0		Not estimable		
Total events Heterogeneity: Not ap Test for overall effect:		cable	0					
1.8.2 HbA1c 6.6-7.0%								
UKPDS 34	50	342	89	411	3.1%	0.62 [0.42, 0.91]	•	
REWIND	317	4949	346	4952	18.1%	0.91 [0.78, 1.07]		
PROACTIVE Subtotal (95% CI)	177	2605 7896	186	2633 7996	9.9% 31.1%	0.96 [0.77, 1.19] 0.87 [0.72, 1.05]	-	
Total events	544		621					
Heterogeneity: Tau ² = Test for overall effect:				= 0.13);	I² = 50%			
1.8.3 HbA1c 7.1-7.5%								
SUSTAIN-6 Subtotal (95% CI)	62	1648 1648	60	1649 1649	3.4% 3.4%	1.04 [0.72, 1.49] 1.04 [0.72, 1.49]		
Total events	62		60					
Heterogeneity: Not ap								
Test for overall effect	Z = 0.19 ((P = 0.85)					
1.8.4 HbA1c 7.6-8.0%								
EXSCEL	507	7356	584	7396	29.4%	0.86 [0.76, 0.98]		$\bullet\bullet\bullet\bullet\bullet\bullet\bullet\bullet$
CANVAS	370	5795	312	4345	18.5%	0.88 [0.75, 1.03]		
VERTIS-CV	473		254	2745	17.6%	0.92 [0.79, 1.08]		
Subtotal (95% CI)	4050	18650	4450	14486	65.5%	0.88 [0.81, 0.96]	-	
Total events Heterogeneity: Tau ² =	1350 - 0.00: Chi	8-042	1150 df = 2 /E	- 0.01\-	12 - 0.96			
Test for overall effect:				- 0.01),	1 - 0 %			
Total (95% CI)		28194		24131	100.0%	0.89 [0.83, 0.95]	•	
Total events	1956		1831					
Heterogeneity: Tau ² =				= 0.53);	I ² = 0%			-
Test for overall effect:							Favours [Intensive] Favours [Standard]	
Test for subgroup dif	ferences:	Chi ² = 0.	77, df = 3	2 (P = 0.6	58), I² = 0'	%		
Risk of bias legend		tion (a al	antina bi					
 (A) Random sequent (B) Allocation conceation 				as)				
(C) Blinding of partici				rmance	bias)			
(D) Blinding of outcor					5.00)			
(E) Incomplete outcom								
(F) Selective reporting) (reportin	g bias)						
(G) Other bias								

1.1.4. Severe hypoglycemia

Forest plot for trials comparing the effects of intensive glycemic control (using drugs associated with hypoglycemia) and standard care on severe hypoglycaemia.

	Inten		Stand			Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	ABCDEFG
1.29.1 HbA1c<=6.5%								
Subtotal (95% CI)		0		0		Not estimable		
Total events	0		0					
Heterogeneity: Not app								
Test for overall effect:	Not appli	icable						
1.29.2 HbA1c 6.6-7.0	%							
UKPDS 34	2	342	2	411	1.6%	1.20 [0.17, 8.58]		
Subtotal (95% CI)		342		411	1.6%	1.20 [0.17, 8.58]		
Total events	2		2					
Heterogeneity: Not app	olicable							
Test for overall effect:	Z = 0.18	(P = 0.3	35)					
1.29.3 HbA1c 7.1-7.5	%							
Subtotal (95% CI)		0		0		Not estimable		
Total events	0		0					
Heterogeneity: Not app	olicable							
Test for overall effect:		icable						
1.29.4 HbA1c 7.6-8.0	%							
CANVAS	118	5795	147	4345	49.1%	0.59 [0.46, 0.76]	-	
VERTIS-CV	175	5499	108	2745	49.3%	0.80 [0.63, 1.02]		
Subtotal (95% CI)		11294		7090	98.4%	0.69 [0.51, 0.93]	•	
Total events	293		255				-	
Heterogeneity: Tau ² =	0.03; Ch	$i^2 = 2.9$	1. df = 1	(P = C	$(09); ^2 = 1$	66%		
Test for overall effect:								
Total (95% CI)		11636		7501	100.0%	0.70 [0.54, 0.90]	•	
Total events	295		257					
Heterogeneity. Tau ² =				P = C	.20); 14 = 1	38%	0.05 0.2 1 5 20	<u>ਰੋ</u>
Test for overall effect:							Favours [Intensive] Favours [Standard]	i
Test for subgroup diffe	erences: ($Chi^2 = 0.$	30, df =	1 (P =	0.58), lf =	= 0%		
Risk of bias legend								
(A) Random sequence)				
(B) Allocation concealm								
(C) Blinding of particip					bias)			
(D) Blinding of outcome				as)				
(E) Incomplete outcome			as)					
(F) Selective reporting	(reporting	g bias)						
(G) Other bias								

1.1.5. GRADE evidence table

Certainty as	ssessme	ent			Summary of	findings					
Participants	Risk of		In diversion	Incomposition	Publication	Overall	Study ever	nt rates (%)	Relative effect (95% Cl)	Anticipat	ted absolute effects
(studies) Follow up	bias	Inconsistency	Indirectness	Imprecision	bias	certainty of evidence	With Standard care	With Intensive glycemic control		Risk with placebo	Risk difference with Intensive glycemic control
MACE For HbA1c ≤48	3 mmol/n	nol (6.5%)			1						

21391 (2 RCTs)	not serious	not serious	very serious ^c	not serious	none	⊕⊕⊖⊖ LOW	961/10692 (9.0%)	909/10699 (8.5%)	OR 0.94 (0.85;1.03)	90 per 1. 000	<i>5 fewer per 1000</i> (from 12 fewer to 2 more)	
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For HbA1c 49-53 mmol/mol (6.6-7.0%)

		15892 (3 RCTs)	not serious	serious ^b	not serious	not serious	very strong association	⊕⊕⊕⊕ HIGH	1083/7996 (13.5%)	906/7896 (11.5%)	OR 0.78 (0.64 to 0.95)	135 per 1000	27 fewer per 1000 (from 44 fewer to 6 fewer)
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For HbA1c 54-58 mmol/mol (7.1-7.5%)

3297 (1 RCT)	not serious	not serious	not serious	very serious ^d	very strong association	⊕⊕⊖⊖ LOW	146/1649 (8.9%)	108/1648 (6.6%)	OR 0.72 (0.56 to 0.94)	89 per 1000	23 fewer per 1000 (from 37 fewer to 5 fewer)
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For HbA1c 59-64 mmol/mol (7.6-8.0%)

33136 (3 RCTs)	not serious	serious ^b	not serious	not serious	none	⊕⊕⊕⊖ MODERATE	1746/14486 (12.1%)	2071/18650 (11.1%)	OR 0.91 (0.83 to 1.00)	121 per 1000	10 fewer per 1000 (from 18 fewer to 0 fewer)
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Certainty as	sessment						Summary of	findings			
Participants (studies) Follow up	Risk of	Inconsiste			Publication	Overall	Study ever	nt rates (%)	Relative effect (95% Cl)	Antici	oated absolute effects
	bias	ncy	Indirectness	Imprecision	bias	certainty of evidence	With Standard care	With Intensive glycemic control		Risk with placebo	Risk difference with Intensive glycemic control

All-cause mortality

For HbA1c ≤48 mmol/mol (6.5%)

21391 (2 RCTs)	not seri serious	erious ^b very serious ^c	not serious	none	⊕○○○ VERY LOW	756/10692 (7.1%)	755/10699 (7.1%)	OR 1.06 (0.74 to 1.51)	71 per 1000	4 more per 1000 (from 17 fewer to 3 2 more)
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For HbA1c 49-53 mmol/mol (6.6-7.0%)

15892 (3 RCTs)	not serious	serious ^b	not serious	not serious	strong association	⊕⊕⊕⊖ MODERATE	621/7996 (7.8%)	544/7896 (6.9%)	OR 0.87 (0.72 to 1.05)	78 per 1000	<i>9 fewer per 1000</i> (from 21 fewer to 4 more)	
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For HbA1c 54-58 mmol/mol (7.1-7.5%)

3297 (1 RCT)	not s serious	serious⁵	not serious	serious ^d	none		60/1649 (3.6%)	62/1648 (3.8%)	OR 1.04 (0.72 to 1.49)	36 per 1000	<i>1 more per 1000</i> (from 10 fewer to 1 7 more)	
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For HbA1c 59-64 mmol/mol (7.6-8.0%)

33136 (3 RCTs)	not serious	not serious	not serious	not serious	strong association	⊕⊕⊕⊕ HIGH	1150/14486 (7.9%)	1350/18650 (7.2%)	OR 0.88 (0.81 to 0.96)	79 per 1000	9 fewer per 1000 (from 14 fewer to 3
,									, , , , , , , , , , , , , , , , , , ,		fewer)

Certainty ass	essmen	t					Summary of	findings			
Participants (studies) Follow up	Risk of		1		Publication	Overall	Study ever	nt rates (%)	Relative effect (95% Cl)	Antici	pated absolute effects
	bias	Inconsistency	Indirectness	Imprecision	bias	certainty of evidence	With Standard care	With Intensive glycemic control		Risk with placebo	Risk difference with Intensive glycemic control

Cardiovascular mortality

For HbA1c ≤48 mmol/mol (6.5%)

21391 (2 RCTs)	not serious	serious ^b	not serious	very serious ^d	none	⊕○○○ VERY LOW	383/10692 (3.6%)	388/10699 (3.6%)	OR 1.11 (0.67 to 1.83)	36 per 1000	<i>4 more per 1000</i> (from 12 fewer to2 8 more)
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For HbA1c 49-53 mmol/mol (6.6-7.0%)

10654 (2 RCTs)	not serious	serious ^b	not serious	not serious	none	00000000000000000000000000000000000000	397/5363 (7.4%)	342/5291 (6.5%)	OR 0.76 (0.47 to 1.21)	74 per 1000	17 fewer per 1000 (from 38 fewer to 1 4 more)	
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For HbA1c 54-58 mmol/mol (7.1-7.5%)

3297 (1 RCT)	not not serious serious	ious not serious	serious ^d	none	⊕⊕⊕⊖ MODERATE	46/1649 (2.8%)	44/1648 (2.7%)	OR 0.96 (0.63 to 1.45)	28 per 1000	<i>1 fewer per 1000</i> (from 10 fewer to 1 2 more)	
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For HbA1c 59-64 mmol/mol (7.6-8.0%)

33136 (3 RCTs)	not not se serious	serious not serious	not serious	strong association	⊕⊕⊕⊕ HIGH	779/14486 (5.4%)	931/18650 (5.0%)	OR 0.89 (0.81 to 0.99)	54 per 1000	6 fewer per 1000 (from 10 fewer to 1 fewer)	
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Certainty as	ssessme	ent					Summary of	findings			
(studies)	Risk of				Publication	Overall	Study ever	nt rates (%)	Relative effect (95% Cl)	Antici	pated absolute effects
	bias	Inconsistency	Indirectness	Imprecision	bias	certainty of evidence	With Standard care	With Intensive glycemic control		Risk with placebo	Risk difference with Intensive glycemic control

Eye adverse events*

For HbA1c ≤48 mmol/mol (6.5%)

21391 (2 RCTs)*	not serious	serious ^b	very serious ^c	not serious	none	⊕○○○ VERY LOW	216/9005 (2.4%)	166/9127 (1.8%)	OR 0.76 (0.62;0.93)	24 per 1000	6 fewer per 1000 (from 9 fewer to 2 f ewer)
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For HbA1c 49-53 mmol/mol (6.6-7.0%)

10654 (2 RCTs)	not serious	serious ^b	not serious	not serious	none	⊕⊕⊕⊖ MODERATE	128/5363 (2.4%)	131/5291 (2.5%)	OR 1.04 (0.68 to 1.59)	24 per 1000	<i>1 more per 1000</i> (from 8 fewer to 14 more)
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For HbA1c 54-58 mmol/mol (7.1-7.5%)

3297 (1 RCT)	not serious	not serious	not serious	very serious ^c	strong association	29/1649 (1.8%)	50/1648 (3.0%)	OR 1.75 (1.10 to 2.78)	18 per 1000	13 more per 1000 (from 2 more to 30
										more)

Per HbA1c 59-64 mmol/mol (7.6-8.0%)

-	-	-	-	-	-	-	-	-	-	-	-

Certainty ass	sessme	ent					Summary of	findings			
(studies)	Risk				Publication	Overall	Study ever	nt rates (%)	Relative effect (95% Cl)	Antici	pated absolute effects
(studies) Follow up	of bias	Inconsistency	Indirectness	Imprecision	bias	certainty of evidence	With Standard care	With Intensive glycemic control		Risk with placebo	Risk difference with Intensive glycemic control

Kidney adverse events**

For HbA1c ≤48 mmol/mol (6.5%)

21374 (2 RCTs)	not serious	serious ^b	very serious ^c	not serious	strong association	⊕○○○ VERY LOW	776/10684 (7.3%)	613/10690 (5.7%)	OR 0.78 (0.69 to 0.87)	73 per 1000	15 fewer per 1000 (from 21 fewer to 9 fewer)
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For HbA1c 48-53 mmol/mol (6.6-7.0%)

753 (1 RCT)		not serious	not serious	serious ^d	none	⊕⊕⊖⊖ LOW	2/411 (0.5%)	2/342 (0.6%)	OR 1.20 (0.17 to 8.58)	5 per 1 000	1 more per 1.000 (from 4 fewer to 35 more)
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For HbA1c 59-64 mmol/mol (7.6-8.0%)

18384 (2 RCTs)	not serious s	not serious	not serious	not serious	very strong a ssociation	⊕⊕⊕⊕ HIGH	255/7090 (3.6%)	293/11294 (2.6%)	OR 0.69 (0.51 to 0.93)	36 per 1000	11 fewer per 1000 (from 17 fewer to 2 fewer)	
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Cl: Confidence interval; OR: Odds Ratio; Explanations: a. No data available; indirect results deriving from trials using drugs inducing hypoglycemia with the same HbA1c target. a. Open-label studies; b. Moderate/High heterogeneity; c. No RCT available. Data coming from trials using drugs potentially inducing hypoglycemia; d. Only one trial with relatively limited sample size or studies with relatively limited sample sixze. *No data available for HbA1c 59-64 mmo/mol (7.6-8.0%); **No data available for HbA1c 53-58 mmol/mol (7.1-7.5%)

1.1.5. Pharmacoeconomic evaluations

The search for pharmaeconomic studies has been performed including glycemic control as key-word; the study selection has been conducted considering the time horizon of the analysis, the target population, and excluding data deriving from drugs manufacturers.

Search string: Search string: (economic or cost or cost-effectiveness) and drugs and (glycemic control type 2 diabetes) Filters: in the last 10 years (up to 1st December, 2020).

Author	Country	Intervention	Type of analysis	Incremental cost	Incremental cost (QALY)	Incremental cost per QALY gained	Authors' conclusions
				Costs of hypoglycemia			
Chevalier 2016 ²	Belgium Euros	Insulin±SU Observational study	Direct costs for hospitalization for hypoglycemia. Costs consist of three components: drug costs, room/bed costs, and procedure costs.	The average cost of a hypoglycemia-related hospitalization was high (€10,258). For the purpose of comparison, the average cost of a full hospitalization for a myocardial infarction, as calculated from the same database over the same period and using the same methodology, was equal to €7,094.	-	-	Interventions that can help reduce the risk of hypoglycemia, and as a consequence decrease the patient's morbidity and its burden on hospitals and society without compromising glycemic control, will help further improve diabetes management.
Dalal 2017 ³	US US Dollars	Insulin Observational study	Direct costs for hospitalization for hypoglycemia.	Hypoglycemia was associated with significantly greater total all- cause healthcare costs (\$30,719 vs. \$19,079 per year).	-	-	This analysis shows that patients who experienced hypoglycemia shortly after basal insulin initiation were more likely to discontinue therapy and were associated with greater healthcare resource use and costs than patients with no hypoglycemia during the first 6 months following initiation.

			Costs of tre	atment intensification			
Tao 2015 ⁴	UK Pounds	Intensive glycemic control vs standard care. RCT	Costing comprised the cost of delivering the intervention itself plus the routine cost to the National Health System of treating diabetes and diabetes-related events observed in the trial.	Cost per person in the intensive and standard group during the trial (5 years) was £3,773 and 2,804, respectively.	Intensive treatment was associated with positive incremental QALYs.	The unadjusted results suggest a lower point estimate QALY gain in the intensive treatment arm, which is reversed once adjustment is made for baseline differences	In conclusion, promotion of intensive multifactorial treatment compared to routine care for people with screendetected Type 2 diabetes does not appear to be cost-effective in the ADDITION-UK study. However, the intervention has the potential to be cost-effective if it can be delivered for approximately £630 per patient rather than £981. Such savings may be plausible through adaptation of pre- developed materials and economies of scale in delivery.
Diaz-Cerezo 2020 ⁵	Spain Euros	Patients with HbA1c<7% and BMI<30 Kg/m ² or >8% and BMI<30 Kg/m ² . Observational study	Direct health costs (medical visits, days of hospitalization, emergencies, diagnostic or therapeutic applications, and medicines), and indirect costs (productivity losses) related to T2DM and its complications were recorded.	The mean cost per patient was $ end{tabular} $ The mean cost per patient reference group (HbA1c>8%) and $ end{tabular} $ 1,249 for the control group (HbA1c<7%). In the reference group, 84.0% of the costs were due to healthcare costs and 16.0% to productivity losses; the percentages were similar in the control group, 83.6% ($ ell$,044) and 16.4% ($ ell$,249), respectively.	Not available Cost corrected for covariates (age, sex, time from diagnosis, BMI, HbA1c, CCS, OAD number): 1,804 and 1,309€ for reference and control group, respectively.	No data on incremental cost per QALY gained.	In conclusion, adult patients with T2DM, deficient glycaemic control and obesity require greater use of resources and involve higher costs for the national health system.

				Appenaix			
Elgart 2019 ⁶	Argentina Pesos	On target (OT; HbA1c ≤ 7%) and not on target (NOT; HbA1c > 7%). Observational study.	Monthly expenditure on drugs was estimated by micro-costing.25 For that purpose, we calculated a mean unit retail price per milligram of each drug or per insulin units in Argentina	Each month, NOT people spent AR\$19.1 and AR\$336.9 more than OT patients, respectively.	Not available Multivariable regression analysis showed that expenditure for hyperglycaemia drugs treatment was significant and independently associated with diabetes duration, LDL- c, systolic blood pressure, glycemic control and treatment of diabetes.	No data on incremental cost per QALY gained.	The association of target HbA1c levels significantly decreases costs of drugs treatment in people with T2D.
Degli Esposti 2013 ⁷	Italy Euros	Enrolled patients were subdivided into five cohorts according to HbA1c values at 7%, 7.1%–8%, 8.1%–9%, and 9%. Observational study	Costs of antidiabetic medication, hospitalizations, laboratory/instru mental tests, specialist visits.	The mean cost per patient increased progressively in patients with stable HbA1c at 7%, 7.1%–8%, 8.1%–9%, and .9%.	Analysis of the different components of health care costs showed that the progressive incremental cost was mainly because of antidiabetic drugs, hospitalizations for diabetes-related problems, and use of outpatient services.	No data on incremental cost per QALY gained.	The results indicate that glycemic control is a useful surrogate not only for diabetes-related complications but also for the associated health care costs.
Bruhn 2016 ⁸	US Healthcare payer , 2014 US dollar	Albiglutide vs insulin lispro (both combined with ins. Glargine); Albiglutide vs insulin glargine; Albiglutide vs Sitagliptin	Cost-utility (50 years)	Albiglutide increased costs as compared to insulin lispro of about \$4,332; Albiglutide increased costs as compared to insulin glargine by \$2,597; Albiglutine incresed costs compared to sitagliptin of +\$2,223	Albiglutide improved both life expectancy vs insulin lispro of +0.099 and QALYs of about +0.099; Albiglutide modestly improved life expectancy and QALY vs insulin glargine (+0.017 and +0.033 respectively) and reduced diabetes- related complications;	ICER for albiglutide vs insulin lispro was \$43,541 per QALY; ICER for albiglutide vs insulin glargine was \$79,166 per QALY; ICER vs sitagliptin aws	At a WTP of \$100,000 per QALY albiglutide was cost- effective vs all comparators; at a WTP of \$50,000 per QALY albiglutide was cost- effective vs sitagliptin and insulin ispro

Appendix

					Albiglutide increased both life expectancy of +0.11 compared to sitagliptin and QALY by +0.101 reducing diabetes-related complications	\$22,094 per QALY	
Tzanetakos 2017 ⁹	Greek thirdy payer, Euro 2016	Exenatide vs Insulin Glargine; Exanatide vs Liraglutide	Cost-utility (40 years)	Exenatide increased direct health costs vs insulin glargine of €2,061; Exenatide slightly incresed costs vs Liraglutide (+€110)	Exenatide increased both life expectancy and QALY vs Insulin glargine of +0.003 and +0.458 respectively reducing the risk of events; Compared to Liraglutide, Exenatide increased both life expectancy and QALY of +0.004 and +0.039 reducing the risk of cerebrovascular events and cardiovascular complications.	ICER for exenatide vs insulin glargine was €4,499 per QALY; ICER vs Liraglutide was €2,827 per QALY	Exenatide is a cost- effective option for T2DM poorly controlled with OAD when compared to insulin glargine at various WTP, similary when comparing exenatide to Liraglutide and considering a WTP >=€20,000 per QALY
Hunt 2017 ¹⁰	Italy NHS, Euro 2015	Liraglutide vs lixisenatide	Cost-utility (lifetime)	Liraglutide was associated with marginally higher lifetime costs (€243)	Liraglutide increased both life expectancy and QALY (+0.11 and +0.12 respectively) reducing and/or delaying diabetes- related complications	The ICER for Liraglutide vs lixisenatide was €2,001 per QALY	Liraglutide had a probability of 77.2% of beingcost-effective at the commonly quoted WTP threshold of €30,000 per QALY
Kvapil 2017 ¹¹	Czech republic public payer perspective , 2016 CZK	IdegLira vs BBT	Cost-effectiveness and cost-utility (50 years)	IDegLira also resulted in higher costs, +107,829CZK	IDegLira reduced and/or delayed onset of diabetes related complications thus increasing both life expectancy by +0.10 and QALY by +0.31	ICER was CZK 1,043,842 per LY and ICUR was CZK 345,052 per QALY	IDegLira is likely to be cost- effective versus BBI at the commonly accepted WTP threshold in the Czech Republic of CZK 1,100,000 per QALY gained.

Gu 2017 ¹²	China healthcare payer perspective, 2014 Chinese Yuan	Exenatide vs Insulin glargine	Cost-utility (40 years)	Exenatide was associated with lower costs because of lower drug costs and reduced costs of events, - 177,706 Y	Exenatide resulted in both higher QALY (+1.94) and increased LY (+0.03)	Exenatide was dominant	Exenatide was a superior therapy (with higher total QALY benefits gained but lower total costs) to insulin glargine offering an effective third-line therapy for the management of T2DM. The cost-effectiveness results
							results remained stable in the sensitivity analyses.

RECOMMENDATION # 2: NUTRIOTIONAL THERAPY.

2.1. Structured nutritional therapy

Considered evidence: RCT performed on patients with T2DM, up to December 1st, 2020, and assessing HbA1c, weight, BMI, and LDL cholesterol.

The primary outcome of the present meta-analysis was to assess the effects of the structured nutritional therapy on HbA1c, BMI, and LDL cholesterol.

The systematic review has already been published; for complete search string, list and characteristics of included studies, and assessment of publication bias, please see the related publication¹³.

2.1.1. HbA1c

Forest plot for trials comparing the effects of structured nutritional therapy and dietary advice on HbA1c (%) at endpoint.

	Inte	erventior	1		Control			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% C	I IV, Random, 95% CI	ABCDEFG
Andrews 2011	0	0.7545	246	0.26	0.7545	93	16.3%	-0.26 [-0.44, -0.08]	••••
Coppell 2010	-0.5	0.2565	45	0	0.2554	48	33.4%	-0.50 [-0.60, -0.40]] •	
Franz 1995	7.2	1.2	94	7.6	1.7	85	3.4%	-0.40 [-0.84, 0.04]	??????
Huang 2010	-0.5	1.1	75	-0.1	1.5	79	3.8%	-0.40 [-0.81, 0.01]]	
Liu 2015	-0.49	0.2014	58	-0.01	0.2321	59	43.1%	-0.48 [-0.56, -0.40]	1 •	😑 ? ? ? ? 🤁 ?
Total (95% CI)			518			364	100.0%	-0.45 [-0.53, -0.36]	1 ♦	
Heterogeneity: Tau² = Test for overall effect:					22); I² = 3	0%			-2 -1 0 1 Favors Intervention Favors Control	2

2.1.2. BMI

Forest plot for trials comparing the effects of structured nutritional therapy and dietary advice on BMI (Kg/m^2) at endpoint.

	Int	erventior	1	Control			Mean Difference		Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl	ABCDEFG
Andrews 2011	0	4.5267	246	2.41	4.5267	93	66.1%	-2.41 [-3.49, -1.33]		
Coppell 2010	-2.1	3.8692	45	-0.6	3.7868	48	31.8%	-1.50 [-3.06, 0.06]		++ ?? +++
Franz 1995	92.4	19.4	94	92	21.2	85	2.2%	0.40 [-5.57, 6.37]	1	2 ? ? ? ? 🧶 🖲
Total (95% CI)			385			226	100.0%	-2.06 [-2.94, -1.18]	. ◆	
Heterogeneity: Tau² = Test for overall effect:				(P = 0.4	46); I² = 0	%			-4 -2 0 2 4 Favors Intervention Favors Control	_

2.1.3. GRADE evidence table

Certainty a	ssessmen	t			Summary of findings					
Participants	Risk of		Indiractors		Publication	Overall certainty	Relative effect	Anticipated absolute effects		
(studies) Follow up	bias	Inconsistency	Indirectness	Imprecision	bias	of evidence	(95%, CI)	Control	Intervention	
HbA1c (%)										
912 (5 RCTs)	serious ^a	serious ^b	not serious	not serious	none	⊕⊕⊖⊖ LOW	OR 0.94 (0.85 to 1.03)	-	MD 0.45 % lower (0.53 lower to 0.36 lower)	
Body fat perc	entage at e	endpoint (%)			I		1		1	
611 (3 RCTs)	serious ^a	serious ^b	not serious	not serious	none		MD:- 2.1 [-2.9;-1.2]	-	MD 2.1 Kg lower (2.9 lower to 1.2 lower)	

CI: Confidence interval; **MD:** Mean difference; a. Randomization, allocation, and blinding procedures not adequately reported for the majority of included trials; b. Moderate heterogeneity.

2.1.4. Pharmacoeconomic evaluations

The search for pharmaeconomic studies has been performed including glycemic control as key-word; the study selection has been conducted considering the time horizon of the analysis, the target population, and excluding data deriving from drugs manufacturers.

Search string: (economic or cost or cost-effectiveness) and type 2 diabetes and "nutritional therapy" Filters: in the last 10 years. (fino al 1 Diacembre 2020).

Author	Country	Intervention	Type of analysis	Incremental cost	Incremental cost (QALY)	Incremental cost per QALY gained	Authors' conclusions
Scrafford CG, 2018 ¹⁴	2017 US dollars	Dietary pattern conformant with healthy US-Style eating pattern or with Mediterranean diet	Cost-analysis	Cost saving associated with T2DM and induced by conformance with healthy US style in the adult US population range from 6.2 billions \$ to 10.9 billions \$ per year when considering direct costs, while savings related to indirect costs varied from 2.3 billion \$ to 4 billion \$s per year. With respect to the effect of conformance with Mediterrranean diet estimetes suggest savings in direct costs from 3.4 billion \$ to 17.8 billion \$, while for indirect costs savings where in the range 1.2-6.5 billion \$.	ΝΑ	NA	The study illustrates the significant potential economic influence associatedwith greater conformance to healthy US style and Mediteranean diet included in the current 2015-2020 DGA recommendations.
Xin Y, 2019 ¹⁵	UK NHS perspective, 2017 £	Intensive weight management in routine primary care	Cost-effectiveness	Total cost per intervention participant of delivering the Direct/Counterweight-Plus programme was £1223 (95%Cl £1147-£1294) while the intervention group had significantly lower cost per participant than did controls for antidiabetes drugs (mean difference £120, 95%Cl 78-163),	Group difference in 1-year diabetes remission was 41.6%	Incremental costs per additional 1-year remission were £2564(95%CI £1867-£3453)	The offsetting cost savings seen in the intervention group in the first 12 months of the trial were modest, but reduced healthcare demand might persist into future years after the initial intervention costs are completed.

Appendix

Author	Country	Intervention	Type of analysis	Incremental cost	Incremental cost (QALY)	Incremental cost per QALY gained	Authors' conclusions
				antihypertensive drugs (£14,8- 22), diabetes-related GP visits (£17, 8-26), and diabetes- unrelated practice nurse visits (£6,1-11) with total 1-yesr costs per participant in the intervention group being £1913(sd=1161) vs £846(sd=1066) in controls.			
Lanhers C, 2017 ¹⁶	France	Lifestyle modification including high volume exercise, diet modification and education	Cost-analysis	Costs of medication in T2DM patients over 1-year were reduced as compared to baseline: €135.1±43.9 versus 212.6±35.8.	After 1-year 54% of patients stopped or decreased medication	NA	Individuals with T2DM reduced routinemedication costs following lifestyle intervention that started with a 3-week residential programme combining high exercise volume, restrictive diet and education effectively supported the health of T2DM. The main factor explaining reduced medication costs was better glycaemic control.

2.2 Different modalities of nutritional therapy

Considered evidence: RCTs performed on patients with T2DM, up to December 1st, 2020, fulfilling the following criteria:

- 1) comparison of a low-carbohydrate diet with a carbohydrate balanced diet (see below for definitions);
- 2) apart from diet composition, no difference in treatment protocol between the two arms;
- 3) duration of trial of at least 12 weeks, in order to assess difference in HbA1c;
- 4) end-of-study HbA1c reported for both treatment arm

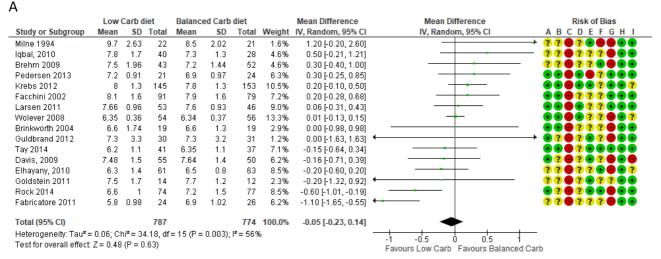
The primary outcomes of the present meta-analysis were:

- 1) Difference in mean HbA1c levels, between all LC diets and balanced carbohydrate diets after 3–4, 6–8, 12, and 24 months.
- 2) Difference in mean creatinine levels, and mean estimated glomerular filtration rate (eGFR), between all LC diets and balanced carbohydrate diets at endpoint.
- 3) Difference in mean body mass index (BMI) expressed as kg/m2 between all LC diets and balanced carbohydrate diets after 3–4, 6–8, 12, and 24 months.

The systematic review has already been published; for complete search string, list and characteristics of included studies, and assessment of publication bias, please see the related publication¹⁷.

2.2.1. HbA1c

Forest plot for trials comparing the effects of low-carbohydrate diets and balanced diets on 12-month (panel A) and 24-month (Panel B) HbA1c (%).



В

	Low C	arb di	ets	Balance	d Carb d	iets		Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	ABCDEFGHI
Dyson 2007	6.7	1.3	6	6.8	1	6	2.7%	-0.10 [-1.41, 1.21]		
Guldbrand 2012	7.5	3.1	30	7.4	3.1	31	1.9%	0.10 [-1.46, 1.66]		•?•?•?••
Krebs 2012	8.2	1.5	144	8.1	1.4	150	41.8%	0.10 [-0.23, 0.43]		••••
Tay 2014	6.7	1.1	33	6.6	1.1	28	15.0%	0.10 [-0.45, 0.65]	_	
lqbal, 2010	7.8	1.7	70	7.4	1.3	74	18.7%	0.40 [-0.10, 0.90]	+	?? \varTheta ? ? ? 🕒 🖢 🕈
Facchini 2002	7.9	1.6	91	7.4	1.6	79	19.8%	0.50 [0.02, 0.98]		••••???•••
Total (95% CI)			374			368	100.0%	0.23 [0.02, 0.44]	◆	
Heterogeneity: Tau ² =	= 0.00; Ch	i ≃ = 2.1	73, df =	5 (P = 0.74	4); I ² = 09	Х6				
Test for overall effect	Z= 2.10	(P = 0)	.04)						Favours Low Carb Favours Balanced Car	b
										5
Risk of bias legend										
(A) Random sequen	ce genera	ation (s	selectio	n bias)						
(B) Allocation concea	ilment (se	election	n bias)							
(C) Blinding of partici	pants and	d pers	onnel (p	performant	ce bias)					
(D) Blinding of outcor	ne asses	smen	t (detec	tion bias)						
(E) Incomplete outco	me data (attritio	n bias)							
(F) Selective reporting	g for weig	ht (rep	orting b	oias)						
(G) Selective reportin	g for rena	l funct	ion (rep	orting bias	5)					

(H) Selective reporting (reporting bias)

(I) Other bias

2.2.2. BMI

Forest plot for trials comparing the effects of low-carbohydrate diets and balanced diets on 12month (panel A) and 24-month (Panel B) BMI (Kg/m²).

Α

	Low	Carb d	liet	Balance	ed Carb	diet		Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	ABCDEFGHI
Pedersen 2013	34	5.04	21	34	4.4	22	7.6%	0.00 [-2.83, 2.83]		
Elhayany, 2010	28.1	2.8	61	28.5	2.9	63	60.7%	-0.40 [-1.40, 0.60]		?? •?? • • •?
Rock 2014	33	5.5	77	33.5	4.7	74	23.0%	-0.50 [-2.13, 1.13]		
Guldbrand 2012	30.7	5.3	30	32.6	5.3	31	8.6%	-1.90 [-4.56, 0.76]		•••••
Total (95% CI)			189			190	100.0%	-0.52 [-1.30, 0.26]	•	
Heterogeneity: Tau ² =	: 0.00; Cl	hi ² = 1.	22, df=	3 (P = 0.3	75); I² =	0%				-
Test for overall effect:	Z=1.31	(P = 0	1.19)						Favours Low Carb Favours Balanced Ca	arb

В

	Low C	arb d	iet	Balanced Carb diet				Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	ABCDEFGHI
Tay 2014	32.1	4.4	33	32.8	4.2	28	63.3%	-0.70 [-2.86, 1.46]		
Guldbrand 2012	30.8	5.8	30	32.8	5.5	31	36.7%	-2.00 [-4.84, 0.84]		•?•?•?••
Total (95% CI)			63			59	100.0%	-1.18 [-2.90, 0.54]		
Heterogeneity: Tau ² = 0.00; Chi ² = 0.51, df = 1 (P = 0.48); $i^2 = 0\%$ Test for overall effect: Z = 1.34 (P = 0.18)									-4 -2 0 2 4 Favours Low Carb Favours Balanced C	

<u>Risk of bias legend</u> (A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting for weight (reporting bias) (G) Selective reporting for renal function (reporting bias)

(H) Selective reporting (reporting bias)

(I) Other bias

2.2.3. GRADE evidence table

Certainty as	ssessment		Summary of findings								
Participants						Overall	Deleting offers	Anticipated absolute effects			
(studies) Risk of bias Follow up		Inconsistency	Indirectness	Imprecision	Publication bias	certainty of evidence	Relative effect (95%, CI)	Balanced diet	Low-carbohydrates diet		
HbA1c a 12 mesi											
1561 (16 RCTs)	serious ^a	serious ^b	non serious	non serious	none	⊕⊕⊖⊖ LOW	- 0.05 [-0.23;0.14]	-	MD 0.05% meno (0.14 più a 0.23 meno)		
HbA1c a 24 m	esi										
742 (6 RCTs)	serious ^a	serious ^b	non serious	serious ^c	none	⊕○○○ MOLTO LOW	0.23 [0.02; 0.44]	-	MD 0.2 % più (0.02 più a 0.44 più)		
IMC a 12 mes	si				1						
379 (4 RCTs)	serious ^a	serious ^b	non serious	serious ^c	none	⊕○○○ VERY LOW	- 0.52 [-1.30; 0.26]	-	MD 0.52 Kg/m ² meno (1.30 meno a 0.26 più)		
IMC a 24 mesi	 			-		-					
122 (2 RCTs)	seriousª	serious ^b	non serious	serious ^c	none	⊕○○○ VERY LOW	- 1.18 [-2.90; 0.54]	-	MD 1.18 Kg/m² meno (2.90 meno a 0.54 più)		

CI: Confidence interval; **MD:** Mean difference; a. Randomization, allocation, and blinding procedures not adequately reported for the majority of included trials; b. Moderate heterogeneity; c. Limited sample size.

2.2.4. Pharmacoeconomic evaluations

The search for pharmaeconomic studies has been performed including glycemic control as key-word; the study selection has been conducted considering the time horizon of the analysis, the target population, and excluding data deriving from drugs manufacturers. **Search string:** : (economic or cost or cost-effectiveness) and diet and (glycemic control type 2 diabetes) Filters: in the last 10 years. (Up to January, 1st, 2021).

Author	Country	Intervention	Type of analysis	Incremental cost	Incremental cost (QALY)	Incremental cost per QALY gained	Authors' conclusions
No studies retrieved	-	-	-	-	-	-	-

RECOMMENDATION # 3: PHYSICAL EXERCISE.

3.1. Regular physical exercise

Considered evidence: RCT comparing combined regular physical exercise programs with no structured intervention in patients with type 2 diabetes, with a duration of at least 12 weeks..

The primary outcome of the present meta-analysis was to assess the effects of the intervention on HbA1c, BMI, and body fat.

The systematic review has already been published; for complete search string, list and characteristics of included studies, and assessment of publication bias, please see the related publication¹⁸.

3.1.1. HbA1c

Forest plot for trials comparing the effects of regular physical exercise and no intervention on HbA1c (%) at endpoint.

	Ae	robi	С	Co	ontro	I		Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	ABCDEFG
Gulsin 2020	7.3	1.1	22	7.2	1.1	30	2.4%	0.10 [-0.51, 0.71]		
Choi 2012	6.9	0.8	38	6.9	0.7	37	5.6%	0.00 [-0.34, 0.34]		• ? • • ? • •
Otten 2017	6.2	0.8	14	6.2	0.8	15	2.5%	0.00 [-0.58, 0.58]		
Kadoglou 2013	7.7	1.1	45	7.8	0.8	24	3.7%	-0.10 [-0.55, 0.35]		<u>???????</u> ?
Hangping 2019	6.7	0.9	165	6.8	1.2	100	7.2%	-0.10 [-0.37, 0.17]		?? 🛑 🖶 🖶 🖶
Dede 2015	6.7	1	30	6.8	1	30	3.2%	-0.10 [-0.61, 0.41]		?? 🛑 🛨 🖶 ?
Andrews 2011	6.6	0.9	246	6.7	0.9	348	11.3%	-0.10 [-0.25, 0.05]		
Stubbs 2019	7.6	1.2	33	7.7	1	12	1.8%	-0.10 [-0.80, 0.60]		
Chen 2019	7.1	0.8	36	7.2	0.8	34	4.9%	-0.10 [-0.47, 0.27]		
Tessier 2000	7.6	1.2	19	7.8	1.5	20	1.3%	-0.20 [-1.05, 0.65]		?? 🛑 🖶 🖶 🖶
Balducci 2019	7	1.6	150	7.2	1.4	150	5.6%	-0.20 [-0.54, 0.14]		
Byrkjeland 2015	7.2	0.8	52	7.4	0.8	62	6.6%	-0.20 [-0.49, 0.09]		
Magalhães 2019	7.2	1	25	7.4	1	27	2.8%	-0.20 [-0.74, 0.34]		
Balducci 2010	6.7	1.1	303	7	1.2	303	10.0%	-0.30 [-0.48, -0.12]		
Kwon 2010	7	0.9	13	7.3	0.9	15	2.0%	-0.30 [-0.97, 0.37]		?? 🛑 🛨 🖶 🛨
Church 2010	7.3	0.7	140	7.7	0.6	37	8.6%	-0.40 [-0.63, -0.17]	_ _	••?••?•
Sigal 2007	7	1.5	188	7.5	1.5	63	4.1%	-0.50 [-0.93, -0.07]		$\bullet \bullet ? \bullet \bullet \bullet \bullet$
Kadoglou 2007	7.3	1	22	7.8	0.8	24	3.0%	-0.50 [-1.03, 0.03]		<u>???????</u> ?
Rech 2019	6.7	0.5	17	7.3	1	21	3.3%	-0.60 [-1.09, -0.11]		$\bullet \bullet ? \bullet \bullet \bullet \bullet$
Cheung 2009	7.1	1.6	20	7.7	1	17	1.3%	-0.60 [-1.45, 0.25]		?? 🛑 🖶 🖶 🛨
Kadoglou 2012	7.1	1	27	7.9	1.1	27	2.7%	-0.80 [-1.36, -0.24]		<u>???????</u> ?
Kadoglou 2007	7.2	1	30	8.1	0.9	30	3.4%	-0.90 [-1.38, -0.42]		<u>???????</u> ?
Rehman_2017	7.3	1.4	51	8.2	1.4	51	2.8%	-0.90 [-1.44, -0.36]		??••••
Total (95% CI)			1686			1477	100.0%	-0.27 [-0.37, -0.17]	•	
Heterogeneity: Tau ² =	= 0.02; C	hi² =	34.00,	df = 22 ((P = 0).05); I ^z	= 35%		-1 -0.5 0 0.5 1	_
Test for overall effect:	•									
		`		·					Favours [Exercise] Favours [Control]	
Risk of bias legend										

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

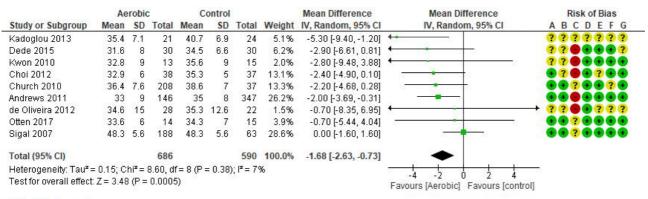
(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

3.1.2. Body fat

Forest plot for trials comparing the effects of regular physical exercise and no intervention on body fat (%) at endpoint.



Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

3.1.3. BMI

Forest plot for trials comparing the effects of regular physical exercise and no intervention on BMI (Kg/m^2) at endpoint.

	Ae	robio	2	Co	ontro	I		Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	ABCDEFG
Balducci 2010	30.3	4.4	303	31.7	4.5	303	25.5%	-1.40 [-2.11, -0.69]		
Balducci 2019	28.8	4.9	150	30.1	5.3	150	13.2%	-1.30 [-2.46, -0.14]		
Cheung 2009	39.5	9	20	38.2	9.2	17	0.7%	1.30 [-4.59, 7.19]	• • • •	• ?? 🛑 🖶 🖶 🖶
Church 2010	34	5.9	208	35.2	6.2	37	4.5%	-1.20 [-3.35, 0.95]	<	••?••?•
Dede 2015	30	4.5	30	30.9	4.7	30	3.9%	-0.90 [-3.23, 1.43]	• • • •	?? 🔴 🛨 🛨 ?
Gulsin 2020	33	5.5	22	34.5	5.5	35	2.5%	-1.50 [-4.43, 1.43]	·	
Jennings 2009	31.8	5.3	50	31.5	4.8	22	3.5%	0.30 [-2.19, 2.79]		?? 🗣 ? 🗣 ? 🗣
Kadoglou 2007	32	3	30	30.7	3.6	30	7.1%	1.30 [-0.38, 2.98]		????????
Kadoglou 2012	31.3	3.1	27	32.3	2.9	27	7.7%	-1.00 [-2.60, 0.60]		????????
Kadoglou 2013	32.2	3.1	66	32.3	2.9	24	9.9%	-0.10 [-1.48, 1.28]		<u>???????</u>
Magalhães 2019	30.1	5.4	53	30.7	4.9	27	3.9%	-0.60 [-2.95, 1.75]		
Otten 2017	29.6	4.5	14	29.4	4.5	15	2.1%	0.20 [-3.08, 3.48]		• • • • • • • • •
Sigal 2007	34.2	4.8	188	34.2	4.8	63	10.1%	0.00 [-1.37, 1.37]		
Stubbs 2019	31.9	4.4	33	31.8	4.1	12	2.8%	0.10 [-2.66, 2.86]		••••
Tessier 2000	30.6	5.4	19	29.4	3.8	20	2.5%	1.20 [-1.74, 4.14]		• ?? • • • •
Total (95% CI)			1213			812	100.0%	-0.62 [-1.10, -0.14]	•	
Heterogeneity: Tau ² =	= 0.10; C	hi²=	15.90.	df = 14 (P = 0).32); I ²	= 12%			-
Test for overall effect:					. –	,,,,			-2 -1 0 1 2 Favours [Exercise] Favours [Control]	

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

3.1.3. GRADE evidence table

Certainty a	ssessmei	nt		Summary of findings					
Participants	Risk of	Inconsistence	Indianata	Incomposition	Publication	Overall	Relative effect	Anticipated	l absolute effects
(studies) Follow up	bias	Inconsistency	Indirectness	Imprecision	bias	certainty of evidence	(95%, CI)	Control	Intervention
HbA1c (%)									
3,163 (23 RCTs)	serious ^a	not serious	not serious	not serious	note	⊕⊕⊕⊖ MODERATE	-0.27 [-0.37;-0.17]	Mean HbA1c at endpoint: 7.3 %	

Body fat percentage at endpoint (%)

1,276 (9 RCTs)	serious ^a	not serious	not serious	serious ^b	possible publication bias	⊕○○○ VERY LOW	-1.68 [-2.63;-0.73]	Mean body fat at endpoint:: 35.8%	MD 1.7 % lower (2.9 lower to 0.5 lower)	
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BMI (Kg/m²)

2,025 (15 RCTs)	serious ^a	not serious	not serious	serious ^b	possible publication bias	⊕○○○ VERY LOW	-0.62 [-1.10;-0.14]	Mean BMI at endpoint: 31.2 Kg/m ²	MD 0.6 Kg/m² lower (da 0.9 a 0.2 lower)
--------------------	----------------------	-------------	----------------	----------------------	---------------------------------	------------------	------------------------	--	--

CI: Confidence interval; MD: Mean difference; a. Randomization, allocation, and blinding procedures not adequately reported for the majority of included trials; b. Limited sample size.

3.1.4. Pharmacoeconomic evaluations

The search for pharmaeconomic studies has been performed including glycemic control as key-word; the study selection has been conducted considering the time horizon of the analysis, the target population, and excluding data deriving from drugs manufacturers. **Search string:** (economic or cost or cost-effectiveness) and physical exercise and type 2 diabetes Filters: in the last 10 years. (up to December, 1st, 2020).

Author	Country	Intervention	Type of analysis	Incremental cost	Incremental cost (QALY)	Incremental cost per QALY gained	Authors' conclusions
Coyle 2012 ¹⁹	Canada	 aerobic anaerobic anaerobic combined none The patient population for the model was the same as the DARE ² clinical trial	Cost-effectiveness was assessed by incremental cost- effectiveness ratios.	In terms of total lifetime costs, the combined exercise program was the most expensive (\$40,050), followed by the aerobic program (\$39,250), the resistance program (\$38,300), and no program (\$31,075)	The incremental cost per QALY was \$206,985, \$116,793, and \$37,872 for the resistance, aerobic, and combined programs, respectively, as compared with no exercise program.	The incremental cost per QALY gained for the combined program was \$4,792 compared with the aerobic program and \$8,570 compared with the resistance program.	A combined program providing training in both resistance and aerobic exercise was the most cost- effective of the alternatives compared based on previous funding decisions. Within a public healthcare system, the funding of exercise training for individuals with type 2 diabetes can be considered an efficient use of resources.
Lanhers 2017 ¹⁶	France, Euro	Exercise 15- 20 hours/week, using endurance training (90 min daily: cycling or walking) and resistance training (90 min × 4 days a week) Single-arm trial	Cost of treatment were calculated on the basis of the cost given by the dictionary of medications (Guide thérapeutique, Elsevier-Masson, 2014) for France.	The global tendency over the whole 1-year intervention programme was a significant decrease of around $\notin 60$ in cost of medications treating for T2D (p=0.014), and a significant decrease of $\notin 50$ in cost of medications treating for high blood pressure (p=0.004).	Not evaluated.	Not evaluated.	In a small sample of type 2 diabetic patients, reducing the longterm cost of global routine medication and number of pills could be effective following a 3-week lifestyle residential combining high exercise volume, restrictive diet and education.

3.2. Duration of aerobic exercise

Considered evidence: RCT comparing combined regular aerobic physical exercise programs with no structured intervention in patients with type 2 diabetes, with a duration of at least 12 weeks..

The primary outcome of the present meta-analysis was to assess the effects of the intervention on HbA1c, BMI, and body fat.

The systematic review has already been published; for complete search string, list and characteristics of included studies, and assessment of publication bias, please see the related publication¹⁸.

3.2.1. HbA1c

Forest plot for trials comparing the effects of regular aerobic physical exercise (versus no intervention), with a duration> or \leq 150 min/week on HbA1c (%) at endpoint.

	Ae	robio		Co	ontro	1		Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl	ABCDEFG
1.1.1 <=150 min									3	
Rehman_2017	7.3	1.4	51	8.2	1.4	51	10.0%	-0.90 [-1.44, -0.36]	4	?? 🗧 🖶 🖶 🖶
Sigal 2007	7	1.5	60	7.5	1.5	63	10.4%	-0.50 [-1.03, 0.03]	< <u>→</u>	
Church 2010	7.4	0.7	69	7.7	0.6	37	24.2%	-0.30 [-0.55, -0.05]		
Magalhães 2019	7.3	1.1	28	7.4	1	27	9.7%	-0.10 [-0.66, 0.46]		
Hangping 2019	6.7	0.9	165	6.8	1.2	100	22.8%	-0.10 [-0.37, 0.17]		?? 🗧 🖶 🖶 🖶
Dede 2015	6.7	1	30	6.8	1	30	11.1%	-0.10 [-0.61, 0.41]		??
Julsin 2020	7.3	1.1	22	7.2	1.1	30	8.5%	0.10 [-0.51, 0.71]		
Stubbs 2019	8	1.5	11	7.7	1	12	3.3%	0.30 [-0.75, 1.35]		
Subtotal (95% CI)			436			350	100.0%	-0.24 [-0.44, -0.04]	•	
Heterogeneity: Tau ² =	0.03; C	hi² =	10.58,	df = 7 (F	e = 0.1	16); I ² =	34%			
Test for overall effect	1.52		and the second			6.0				
		10	162							
1.1.2 > 150 min										
Kadoglou 2007	7.2	1	30	8.1	0.9	30	14.2%	-0.90 [-1.38, -0.42]	+=	222233
Kadoglou 2012	7.1	1	27	7.9	1.1	27	12.1%	-0.80 [-1.36, -0.24]	< <u>+</u> ■	222233
Tessier 2000	7.6	1.2	19	7.8	1.5	20	7.1%	-0.20 [-1.05, 0.65]	• • • •	?? 🗧 🖶 🖶 🖶 🖷
Andrews 2011	6.6	0.9	246	6.7	0.9	348	24.5%	-0.10 [-0.25, 0.05]		
<adoglou 2013<="" td=""><td>7.7</td><td>1.1</td><td>21</td><td>7.8</td><td>0.8</td><td>24</td><td>11.9%</td><td>-0.10 [-0.67, 0.47]</td><td></td><td>222222</td></adoglou>	7.7	1.1	21	7.8	0.8	24	11.9%	-0.10 [-0.67, 0.47]		222222
Otten 2017	6.2	0.8	14	6.2	0.8	15	11.6%	0.00 [-0.58, 0.58]		
Choi 2012	6.9	0.8	38	6.9	0.7	37	18.5%	0.00 [-0.34, 0.34]		
Subtotal (95% CI)			395			501	100.0%	-0.28 [-0.54, -0.01]	-	
Heterogeneity: Tau ² =	0.07; C	hi² =	15.90.	df = 6 (F	e = 0.1	01); I ^z =	62%			
Test for overall effect:	Z = 2.03) (P =	0.04)			1.10				
		10	100							
									1. 1. 1. 1.	
									-1 -0.5 Ó 0.5	1
Test for subgroup dif	ferences	: Chi	² = 0.04	, df = 1	(P = I)	0.83), P	²= 0%		Favours [Aerobic] Favours [contr	01]
Risk of bias legend				2						

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

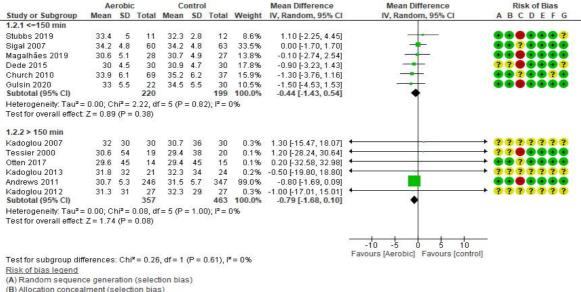
(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias) (F) Selective reporting (reporting bias)

3.2.2. Body fat

Forest plot for trials comparing the effects of regular aerobic physical exercise (versus no intervention), with a duration> or \leq 150 min/week on body fat (%) at endpoint.



(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias) (E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

3.2.3. BMI

Forest plot for trials comparing the effects of regular aerobic physical exercise (versus no intervention), with a duration> or \leq 150 min/week on BMI (Kg/m²) at endpoint.

	Ae	robio	c	Co	ontro	1		Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	ABCDEFG
2.2.1 <=150 min									3	
Dede 2015	31.6	8	30	34.5	6.6	30	16.2%	-2.90 [-6.61, 0.81]	• • · · · ·	??
Church 2010	36.5	7.6	69	38.6	7	37	26.9%	-2.10 [-4.98, 0.78]		
Sigal 2007 Subtotal (95% CI)	48	5.6	60 159	48.3	5.6	63 130	56.9% 100.0%	-0.30 [-2.28, 1.68] -1.20 [-2.70, 0.29]	-	
Heterogeneity: Tau ² =	= 0.00: C	hi² =	1.97. dt	f = 2 (P = 2)	= 0.3	7): $ ^2 = 1$	0%			
Test for overall effect	1422 0422 0228		1.							
2.2.2 > 150 min										
Kadoglou 2007	35.4	7.1	30	40.7	6.9	30	13.9%	-5.30 [-8.84, -1.76]	*=	222223
Choi 2012	32.9	6	38	35.3	5	37	26.5%	-2.40 [-4.90, 0.10]		
Andrews 2011	33	9	146	35	8	347	51.7%	-2.00 [-3.69, -0.31]		
Otten 2017 Subtotal (95% CI)	33.6	6	14 228	34.3	7	15 429	8.0% 100.0%	-0.70 [-5.44, 4.04] -2.46 [-3.82, -1.10]	•	
Heterogeneity: Tau ² =	162 Consecut			C	= 0.3	5); l² = !	3%			
Test for overall effect	: Z = 3.55	5 (P =	0.0004	4)						
										-
Test for subgroup dif	foroncoc	- Chi	Z – 1 /0) df = 1	(P -	n 77) I	- 27 7%		Favours [Aerobic] Favours [control]	
Risk of bias legend	rerences	. On	- 1.43	, ui – 1	(i –	0.22),1	- 52.7 %			
(A) Random sequen		otion	(aalaa	tion bio	~					

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

3.2.4. GRADE evidence table

Certainty a	ssessme	ent					Summary of findings						
Participants	Risk of					Overall certainty of	Relative effect	Anticipated a	bsolute effects				
(studies) Follow up	bias	Inconsistency	Indirectness	Imprecision	Publication bias	evidence	(95%, CI)	Control	Intervention				
HbA1c (%) fo	HbA1c (%) for RCT with physical exercise ≤ 150 min/week												
786 (8 RCTs)	seriousª	not serious	not serious	serious⁵	Possible publication bias ^c	⊕○○○ VERY LOW	-0.24 [-0.44;-0.04]	Mean HbA1c at the end of the study: 7.7%	MD 0.24 % lower (from 0.04 lower to 0.44 lower)				
HbA1c (Kg/m	²) for RCT	with physical e	xercise >150 m	nin/week									
896 (7 RCTs)	serious ^a	not serious	not serious	serious ^b	Possible publication bias ^c	⊕○○○ VERY LOW	-0.28 [-0.54;-0.01]	Mean HbA1c at the end of the study: 7.5%	MD 0.28 % lower (from 0.01 lower to 0.54 lower)				
Massa grassa	a (%) for R	CT with physica	l exercise ≤ 15	0 min/week									
289 (3 RCTs)	serious ^a	not serious	not serious	serious ^b	Possible publication bias ^c	⊕○○○ VERY LOW	-1.20 [-2.70;0.29]	Mean body fata at the end of the study: 40.3%	MD 1.2 % lower (from 2.7 lower to 0.3 more)				
Massa grassa	a (%) per g	gli studi dii durat	ta >150 min/ se	ettimana									

657 (4RCTs)	seriousª	not serious	not serious	serious ^b	Possible publication bias ^c	⊕○○○ VERY LOW	-2.46 [-3.82; -1.10]	Mean body fata at the end of the study: 36.5%	MD 2.5 % lower (from 3.8 to 1.1 lower)	
----------------	----------	-------------	----------------	----------------------	---	------------------	--------------------------------	---	---	--

Indice di massa corporea (Kg/m²) per gli studi dii durata ≤150 min/ settimana

820 (6 RCTs)	serious ^a	not serious	not serious	serious ^b	Possible publication bias ^c	⊕○○○ VERY LOW	-0.44 [-1.43;0.54]	Mean BMI at the end of the study: 34.0 Kg/m ²	MD 0.44 Kg/m ² lower (from 1.4 lower to 0.5 more)
Indice di ma	issa corpor	ea (Kg/m²) per	r gli studi dii dur	ata >150 min/	settimana				
657 (4RCTs)	serious ^a	not serious	not serious	serious ^b	Possible publication bias ^c	⊕○○○ VERY LOW	-0.79 [-1.68;0.10]	Mean BMlat the end of the study: 31.2 Kg/m ²	MD 0.8 Kg/m ² lower (from 1.7 lower to

CI: Confidence interval; **MD:** Mean difference; a. Randomization, allocation, and blinding procedures not adequately reported for the majority of included trials; b. Limited sample size; c. Funnel plot showing possible publication bias, confirmed by Egger's test.

0.10 more)

3.2.5. Pharmacoeconomic evaluations

The search for pharmaeconomic studies has been performed including glycemic control as key-word; the study selection has been conducted considering the time horizon of the analysis, the target population, and excluding data deriving from drugs manufacturers. **Search string:** (economic or cost or cost-effectiveness) and physical exercise and type 2 diabetes Filters: in the last 10 years. (up to December, 1st, 2020).

Author	Country	Intervention	Type of analysis	Incremental cost		Incremental cost per QALY gained	Authors' conclusions
No studies retrieved	-	-	-	-	-	-	-

3.3. Different modalities of physical exercise

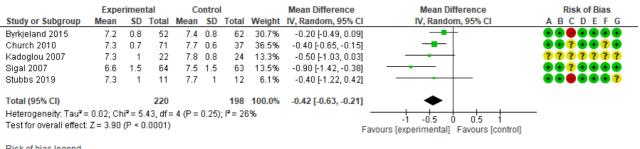
Considered evidence: RCT comparing combined regular aerobic physical exercise programs with no structured intervention in patients with type 2 diabetes, with a duration of at least 12 weeks.

The primary outcome of the present meta-analysis was to assess the effects of the intervention on HbA1c, BMI, and body fat.

The systematic review has already been published; for complete search string, list and characteristics of included studies, and assessment of publication bias, please see the related publication ¹⁸.

3.3.1. HbA1c

Forest plot for trials comparing the effects of combined exercise (aerobic and resistance) and aerobic exercise on HbA1c (%) at endpoint.



Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias) (F) Selective reporting (reporting bias)

(F) Selective rep (G) Other bias

a) other blas

3.3.2. GRADE evidence table

Certainty a	ssessme	ent			Summary of findings					
Participants	Risk of					Overall certainty of	Relative effect	Anticipated absolute effects		
(studies) Follow up	bias	Inconsistency	Indirectness	Imprecision	Publication bias	evidence	(95%, CI)	Control	Intervention	
HbA1c (%)										
418 (5 RCTs)	serious ^a	not serious	not serious	serious⁵	Possible publication bias ^c	⊕○○○ VERY LOW	-0.42 [-0.63, -0.21]	Mean HbA1c at the end of the study: 7.1%	MD 0.42 % lower (from 0.21 lower to 0.63 lower)	

Cl: Confidence interval; **MD:** Mean difference; a. Randomization, allocation, and blinding procedures not adequately reported for the majority of included trials; b. Limited sample size; c. Funnel plot showing possible publication bias, confirmed by Egger's test.

3.3.3. Pharmacoeconomic evaluations

The search for pharmaeconomic studies has been performed including glycemic control as key-word; the study selection has been conducted considering the time horizon of the analysis, the target population, and excluding data deriving from drugs manufacturers. **Search string:** (economic or cost or cost-effectiveness) and physical exercise and type 2 diabetes Filters: in the last 10 years. (up to December, 1st, 2020).

Author	Country	Intervention	Type of analysis	Incremental cost		Incremental cost per QALY gained	Authors' conclusions
No studies retrieved	-	-	-	-	-	-	-

RECOMMENDATION # 4: EDUCATIONAL THERAPY.

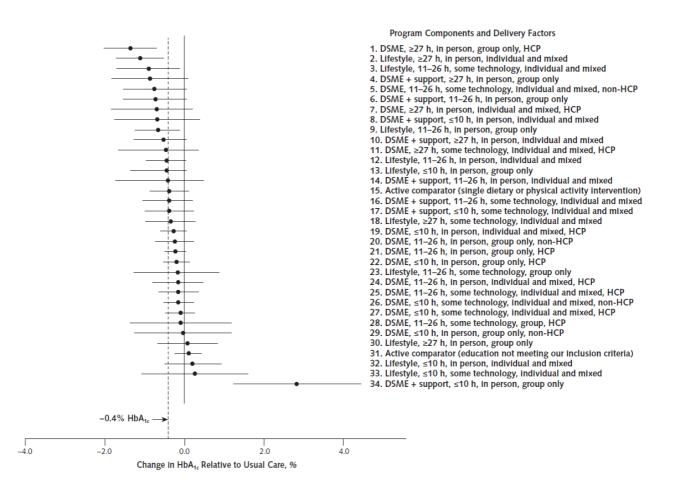
4.1. Structured educational therapy

Considered evidence: RCT comparing a behavioral program with usual care (medical management provided to all participants), an active control (intervention not meeting our definition of behavioral program), or another behavioral program (comparative effectiveness study).

The systematic review has already been published; for complete search string, list and characteristics of included studies, and assessment of publication bias, please see the related publication²¹.

4.1.1. HbA1c

Forest plot for trials comparing the effects of behavioural programs and active comparators and usual care on HbA1c (%) at endpoint.



4.1.2. GRADE evidence table

Certainty a	ssessme	ent					Summary of find	ings	
Participants	Risk of				- I.H I.I.	Overall certainty	Relative effect	Anticipa	ited absolute effects
(studies) Follow up	bias	Inconsistency	Indirectness	Imprecision	Publication bias	of evidence	(95%, CI)	Control	Intervention
HbA1c (%)									
912 (5 RCTs)	seriousª	serious ^d	not serious	not serious	none	⊕⊕⊖⊖ LOW	-0.35 [-0.56;-0.14]	-	MD 0.35% lower (from 0.53 lower to 0.14 lower)
Quality of life	e (PAID sca	ale)		1	I	I			l
753 (5 RCTs)	seriousª	serious ^d	not serious	serious ^c	none	⊕○○○ VERY LOW	- 1.82 [-3.43;-0.21]	-	MD 1.82 lower (from 3.43 lower to 0.21 lower)
Patients' adh	erence (R	R)		1	I				l
14,154 (81 RCTs)	seriousª	serious ^d	not serious	not serious	none	⊕⊕⊖⊖ LOW	1.11 [0.82;1.49]	-	RR 11 higher (from 18 lower to 49 higher)
Hypoglycemi	a (RR)	1			I	L			l
912 (5 RCTs)	serious ^a	serious ^d	not serious	not serious	none	⊕⊕⊖⊖ LOW	-	-	-

CI: Confidence interval; **MD:** Mean difference; a. Randomization, allocation, and blinding procedures not adequately reported for the majority of included trials; b. Limited sample size; c. Funnel plot showing possible publication bias, confirmed by Egger's test.

4.1.3. Pharmacoeconomic evaluations

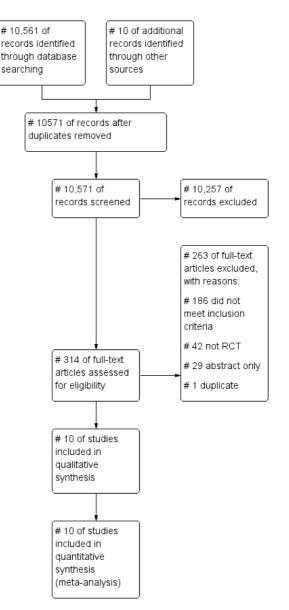
The search for pharmaeconomic studies has been performed including glycemic control as key-word; the study selection has been conducted considering the time horizon of the analysis, the target population, and excluding data deriving from drugs manufacturers. **Search string:** (economic or cost or cost-effectiveness) and physical exercise and type 2 diabetes Filters: in the last 10 years. (up to December, 1st, 2020).

Author	Country	Intervention	Type of analysis	Incremental cost		Incremental cost per QALY gained	Authors' conclusions
No studies retrieved	-	-	-	-	-	-	-

4.2. Group-based educational therapy

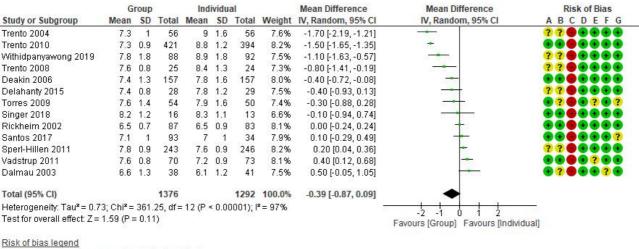
Considered evidence: A Medline and Embase search up to April 30st, 2021, was performed with the following key-words: "diabetes", "education", "group", "individual". RCT with at least a follow-up of 6 months, enrolling adult patients with type 2 diabetes and comparing individual with group settings for the administration of educational programs, in which the educational curriculum was similar across treatment groups. No language or date restriction was imposed. Trials on type 1 or other forms of diabetes were also excluded. Trials with a duration shorter than 6 months were also excluded because they could hardly provide reliable information on the effects of different treatments on one of our principal outcomes, i.e. HbA1c. The primary outcome of the present meta-analysis was to assess the effects of group-based in comparison with individual-based educational programs on HbA1c at the endpoint. Data derived from an unpublished meta-analysis, already submitted to a medical journal, and reported in this Appendix *in extenso*.

4.2.1. Trial flow summary



4.2.2. HbA1c

Forest and funnel plots for trials comparing the effects of group-based and individual-based educational therapy on HbA1c (%) at endpoint.



(A) Random sequence generation (selection bias)

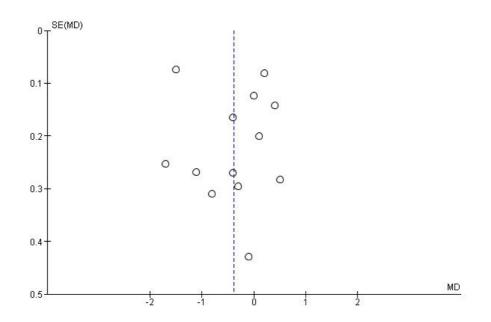
(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

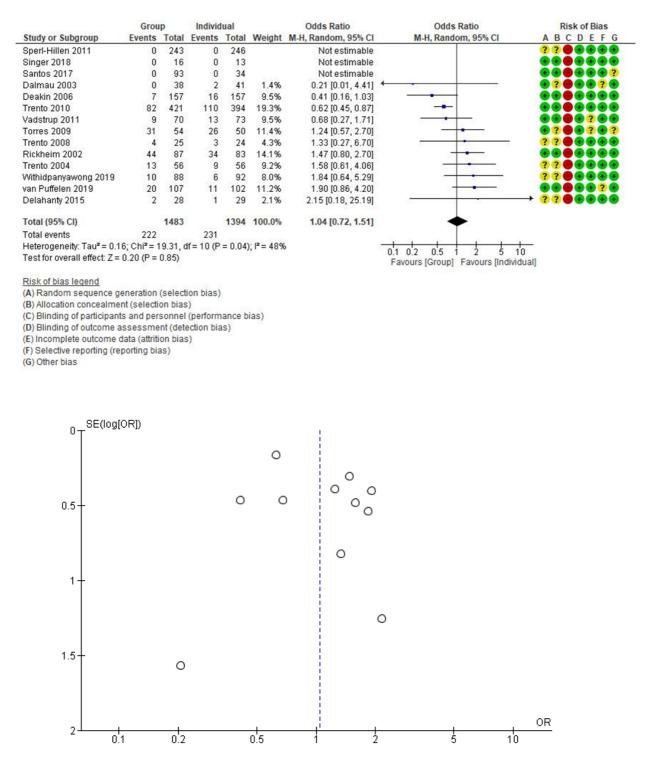
(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)



4.2.3. Patients' adherence

Forest and funnel plots for trials comparing the effects of group-based and individual-based educational therapy on patients' adherence (lost at follow-up).



4.2.4. Quality of life

Forest plot for trials comparing the effects of group-based and individual-based educational therapy on patients' quality of life (diabetes quality of life: DQOL).

	G	roup		Ind	lividua	1		Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	ABCDEFG
Trento 2008	65	11	25	78.4	19.6	24	32.3%	-13.40 [-22.35, -4.45]	-	?? 🕈 🗣 🗣 🗣
Trento 2010	63.2	10.7	421	77.9	13.1	394	34.9%	-14.70 [-16.35, -13.05]		
Trento 2004	43.7	7.2	56	89.2	30.1	56	32.8%	-45.50 [-53.61, -37.39]		?? 🗧 🖶 🖶 🖶 🖷
Total (95% CI)			502			474	100.0%	-24.38 [-42.91, -5.84]	•	
Heterogeneity: Tau ² =	255.66;	Chi ² =	53.55	df = 2 (P < 0.	00001)	I [≠] = 96%			
Test for overall effect:							2		-50 -25 0 25 5 Favours [Group] Favours [Indi	50 vidual]

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

4.2.5. Trials' characteristics

Baseline characteristics of the trials included in the meta-analysis

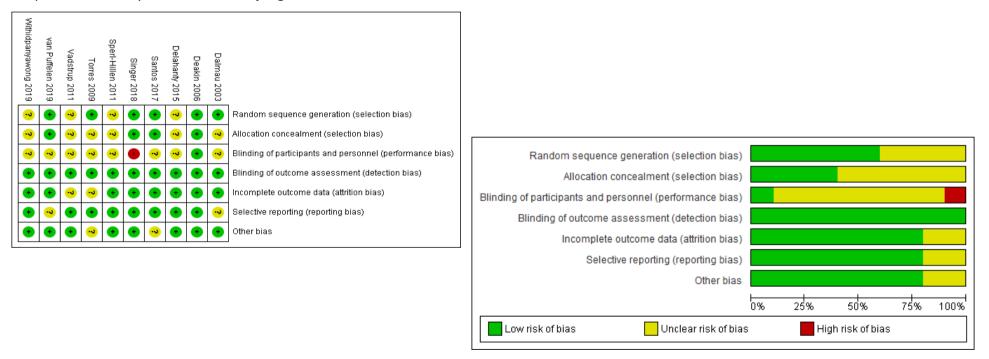
First author (ref)	Group education (#patients)	Indivdual education (#patients)	Trial duration(months)	# sessions	Session lenght (min.)	Profess.	HbA1 _c (%)	BMI (Kg/m ²)	Duration of diabetes (years)	Pts on insulin (%)	Lost at follow-up (GE/IE)
Dalmau Llorca ²²	38	41	12	3	40	N <i>,</i> P	6.9	29.6	8.5	8	0/2
Deakin ²³	157	157	14	6	120	NR	7.7	30.7	6.7	17	11/21
Delahanty ²⁴	28	29	12	19	90	D	8.2	35.5	11	61	2/1
Santos ²⁵	93	34	12	10	120	P,D,N	7.6	NR	NR	0	0/0
Singer ²⁶	16	13	12	4	120	N,P	8.2	29.3	22.5	66	0/0
Sperl-Hillen ²⁷	243	246	6.8	4	120	N,P	NR	34.5	8.2	NR	0/0
Torres Hde ²⁸	54	50	6	NR	NR	NR	9.3	NR	NR	NR	31/26
Trento ²⁹	56	56	24	4	NR	P, Psyc.	7.4	29.5	9.6	0	13/9
Trento ³⁰	25	24	24	8	NR	N, D; Ped.	8.0	27.0	12.5	0	4/3
Trento ³¹	421	394	48	16	NR	P, Psyc.	7.8	29.6	16.2	0	82/110
Rickheim ³²	87	83	6	4	360	N, D	8.5	34.4	1.0	0	44/34
Vadstrup ³³	70	73	6	6	90	N,P,D,P	7.8	NR	6.5	17	9/13

Van Puffelen ³⁴	107	102	6	4	120	N,P,PH	NR	NR	2	2.5	10/6
Withdpanywong ³⁵	98	98	9	4	45	Ν	9.1	27.6	6	0	10/6

N: Nurse; P: Physicians; PH: Pharmacist; D: Dietitian; P: Podiatrist; PH: Physical therapist; Psyc.: Psycologist; Ped.: Pedagogist; Profess.: Professionists.

4.2.6. Risk of bias

Graph and summary: review authors' judgements about each risk of bias item.



4.2.7. GRADE evidence table

Certainty a	ssessme	ent					Summary of findings			
Participants	Risk of					Overall certainty of	Relative effect	Anticipa	ted absolute effects	
(studies) Follow up	bias	Inconsistency	Indirectness	Imprecision	Publication bias	evidence	(95%, CI)	Control	Intervention	
HbA1c (%)										
1,522 (9 RCTs)	serious ^a	serious ^d	not serious	not serious	none		-0.10 [-0.39;0.20]	-	DM 0.10% lower (from 0.20 higher to 0.39 lower)	
Aderenza al tr	attament	o (persi al follov	w-up)				1			
742 (6 RCTs)	seriousa	serious ^d	not serious	serious ^c	none	⊕○○○ VERY LOW	1.25 [0.72; 2.19]	107 per 1.000	RR 23 higher per 1000 (from 28 lower a 101 higher)	
Qualità della	vita									
1,041 (6 RCTs)	seriousª	serious ^d	not serious	serious ^c	none	⊕○○○ VERY LOW	-	-	-	

CI: Confidence interval; **MD:** Mean difference; a. Randomization, allocation, and blinding procedures not adequately reported for the majority of included trials; b. Limited sample size; c. Funnel plot showing possible publication bias, confirmed by Egger's test.

4.2.8. Pharmacoeconomic evaluations

The search for pharmaeconomic studies has been performed including glycemic control as key-word; the study selection has been conducted considering the time horizon of the analysis, the target population, and excluding data deriving from drugs manufacturers. **Search string:** (economic or cost or cost-effectiveness) and physical exercise and type 2 diabetes Filters: in the last 10 years. (up to December, 1st, 2020).

Author	Country	Intervention	Type of analysis	Incremental cost	Incremental cost (QALY)	Incremental cost per QALY gained	Authors' conclusions
Gillet 2010 ³⁶	UK NHS and personal social services perspective, £ 2008	Structured educational intervention vs SoC	Cost- utility analysis, over a lifetime perspective	Cost of the program £203 based on trial data; £76 based on real world. Moreover costs were almost identical at £15836 in the control arm and £15826 in the intervention arm, a difference of just £10	QALY gain with the intervention was 0.0392	Diabetes education and self management program vs usual care: £5,387 per QALY gained based on trial data, £2,092 per QALY gained based on the "real world" intervention cost.	Results suggested that the structured educational intervention is likely to be cost effective compared with usual care
Prezio 2014 ³⁷	Mexico Healthcare payer	Education management intervention vs SoC	20 years	Cost of the program USD 0.68 per day per subject	The intervention led to significant decrease in HA1c levels, incidence of foot ulcera and reduced number of food amputation	The Community Diabetes Education program vs usual care: USD 355 per QALY gained over 20 years	Community health worker-led diabetes intervention is a cost- effective way to reduce diabetes-related complications for uninsured Mexican Americans during a 20-year horizon in comparison to usual medical care
Mash 2015 ³⁸	South Africa	Group educational program vs SoC	Cost-utility analysis, over a lifetime horizon	Incremental savings/costs ranged from -398USD to 125USD	Incremental QALY ranged from 0.0044 to 0.0673	Group diabetes education program vs usual care: US\$1,862 per QALY gained, based on the assumption of annual intervention cost and persistent effect	This intervention, despite its effectiveness being limited to a reduction in blood pressure, would be cost-effective if implemented in South Africa

Author	Country	Intervention	Type of analysis	Incremental cost	Incremental cost (QALY)	Incremental cost per QALY gained	Authors' conclusions
Molsted 2012 ³⁹	Denmark, payer perspective	Self management programme for chronic disease vs SoC	Cost-consequence analysis over 12 months	Cost of the programme was DKK3,640 (\$540) per patient, over 1 year the programme induce savings of about DKK423 (\$63) per patients	HbA1c HbA1c improved from 7.3% to 6.9% and body weight decreased from 90.9kg to 87.1kg following the education programme	-	The intervention can be implemented in a primary care setting and can improve glycaemic control and other metabolic parameters as well as change lifestyle in patients with Type 2 DM

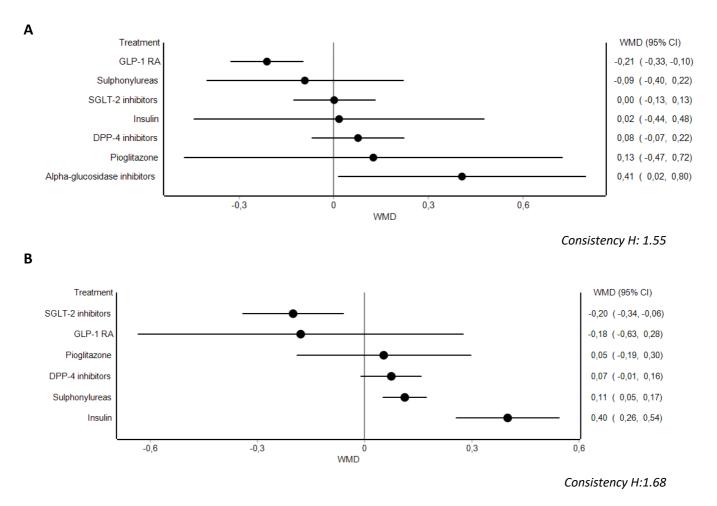
RECOMMENDATION # 5: PHARMACOLOGICAL THERAPY.

Considered evidence: Data on the effects of glucose-lowering agents on the medium- and long-term HbA1c and body weight are reported in an already published network metanalysis⁹. Data on the cardiovascular safety (MACE and hospitalization for heart failure) and mortality for each classes of drugs are reported in already published meta-analysis (i.e.: GLP-1⁸, SGLT-2i¹⁵, metformina⁷, and insulin secretagogues⁹). All these systematic review and meta-analyses, with the exception for α -glucosidase inhibitors and pioglitazone (submitted to a medical journal), have already been published; for complete search string, list and characteristics of included studies, and assessment of publication bias, please see the related publication.

5.1. HbA1c

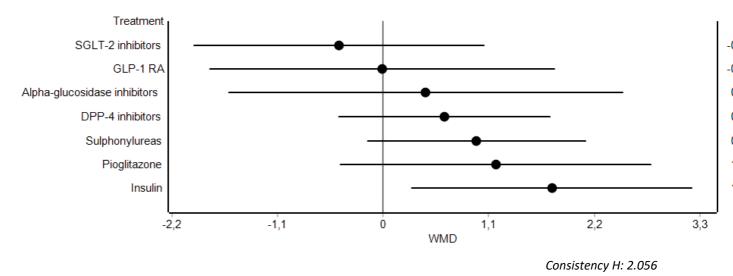
RCTs comparing different glucose-lowering agents versus other active drugs, with a duration \geq of 52 weeks⁴⁰.

Network metanalysis of different glucose-lowering agents: forest plots of comparisons versus metformin. Panel A: 52 weeks; Panel B: ≥104 weeks. GLP-1 RA: Glucagon-Like Peptide-1 Receptor Agonists; SGLT-2: Sodium-Glucose Transporter-2; Sulfonylureas include also glinides.



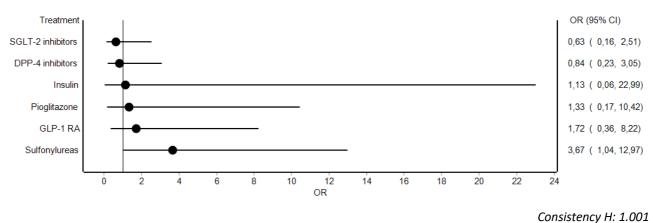
5.2. BMI

Network metanalysis of different glucose-lowering agents: forest plots of comparisons versus metformin for BMI at endpoint ⁴⁰.



5.3. Severe hypoglycemia

Network metanalysis of different glucose-lowering agents: forest plots of comparisons versus metformin for severe hypoglycemia⁴⁰.



consistency II. 1.

5.4. MACE, mortality, and heart failure hospitalization.

RCT with duration \geq 52 weeks (published up to August 2020), in which metformin was compared with either placebo/no therapy or active comparators. MACEs (restricted for RCT reporting MACEs within their study endpoints) and all-cause mortality (irrespective of the inclusion of MACEs among the pre-specified endpoints) were considered as the primary endpoints.

The two principal outcomes of the meta-analysis were as follows: 1) 3-point MACEs was defined as non-fatal myocardial infarction, non-fatal ischemic stroke, or cardiovascular mortality; 2) hospitalization for heart failure; 3) all-cause mortality (including also RCTs not reporting MACEs within the primary study endpoint, or as predefined secondary endpoints).

5.4.1. Metformin

The systematic review has already been published; for complete search string, list and characteristics of included studies, and assessment of publication bias, please see the related publication ⁴¹.

Forest plot for trials comparing the effects of metformin and other glucose-lowering agents/placebo on MACE (Panel A), all-cause mortality (Panel B), and heart failure (Panel C).

Α								
	Metfor	min	Cont	rol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	ABCDEFG
Hong 2013	7	156	14	148	13.0%	0.45 [0.18, 1.15]		
UKPDS 34	55	342	109	411	87.0%	0.53 [0.37, 0.76]		
Total (95% CI)		498		559	100.0%	0.52 [0.37, 0.73]	•	
Total events	62		123					
Heterogeneity: Tau ² =	0.00; Cl	$ni^2 = 0.$	11, df =	1 (P =	0.75); l ²	= 0%		10
Test for overall effect:	Z = 3.80) (P = 0	0.0001)				Favours [metformin] Favours [control	

В

	Metfor	min	Conti	rol		Odds Ratio	Odds Ra	tio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random	n, 95% CI	ABCDEFG
Pfützner 2011	5	328	2	335	3.1%	2.58 [0.50, 13.38]			9999999
Schweizer 2007	2	254	2	526	2.2%	2.08 [0.29, 14.85]			???
Kooy 2009	9	196	6	194	7.4%	1.51 [0.53, 4.32]			6666666
Williams-Herman 2010	1	364	0	179	0.8%	1.48 [0.06, 36.55]			
Araki 2015	0	63	1	273	0.8%	1.43 [0.06, 35.52]			
Kahn 2006	31	1454	31	1441	28.7%	0.99 [0.60, 1.64]	-+-	-	
Schernthaner 2004	2	597	3	597	2.6%	0.67 [0.11, 4.00]			???
JKPDS 34	50	342	89	411	45.2%	0.62 [0.42, 0.91]			0070000
Hong 2013	7	156	14	148	9.2%	0.45 [0.18, 1.15]			
Gregorio 1999	0	89	0	85		Not estimable			0000000
Ferrannini 2013	0	56	0	215		Not estimable			
Umpierrez 2014	0	268	0	539		Not estimable			
Teupe 1991	0	50	0	50		Not estimable			????999
Total (95% CI)		4217		4993	100.0%	0.80 [0.60, 1.07]	•		
Total events	107		148				-		
Heterogeneity: Tau ² = 0.	01; Chi ² :	= 8.41.	df = 8 (P = 0.3	9); $ ^2 = 5$	%		1 1	-
Test for overall effect: Z =					., -		0.1 0.2 0.5 1 Favours [metformin] Fa	2 5 10	

С

	Metfor	min	Cont	ol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI	ABCDEFG
Teupe 1991	0	50	0	50		Not estimable		????
Gregorio 1999	0	89	0	85		Not estimable		
UKPDS 34	11	342	17	411	35.6%	0.77 [0.36, 1.67]		$\bullet \bullet ? \bullet \bullet \bullet \bullet$
Hong 2013	9	156	10	148	26.8%	0.84 [0.33, 2.14]		
Kooy 2009	1	196	1	194	3.7%	0.99 [0.06, 15.94]		
Kahn 2006	19	1454	9	1441	34.0%	2.11 [0.95, 4.67]		$\bullet \bullet \bullet \bullet \bullet \bullet \bullet \bullet$
Total (95% CI)		2287		2329	100.0%	1.12 [0.65, 1.92]	+	
Total events	40		37					
Heterogeneity: Tau ² =	= 0.06; Ch	i ² = 3.6	8, df = 3 (P = 0.3	0); l ² = 19	%	0.01 0.1 1 10 100	ł
Test for overall effect	Z = 0.42	(P = 0.6	8)			1	avours (experimental) Favours (control)	,
Risk of bias legend								
(A) Random sequen	ce genera	tion (se	election b	ias)				
(B) Allocation concea	alment (se	lection	bias)					
(C) Blinding of partici	pants and	l perso	nnel (per	forman	ce bias)			
(D) Blinding of outcor	me asses	sment	(detection	n bias)				
(E) Incomplete outco	me data (a	attrition	bias)					

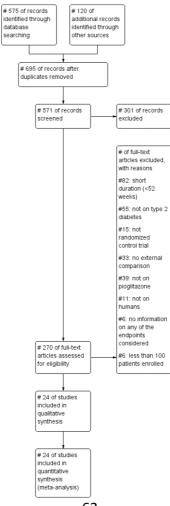
(F) Selective reporting (reporting bias)

(G) Other bias

5.4.2. Pioglitazone

The systematic review has already been submitted to a medical journal. A Medline and Embase search was conducted up to June, 1st, 2021.

5.4.2.1. Trial flow summary



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5.4.2.2. MACE, mortality, and hospitalization for heart failure

Forest plot for trials comparing the effects of pioglitazone and other glucose-lowering agents/placebo on MACE (Panel A), all-cause mortality (Panel B), and heart failure (Panel C).

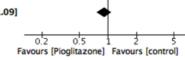
Α

	Pioglita	zone	Conti	ol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
Bolli 2009	2	281	0	295	0.2%	5.29 [0.25, 110.59]		
Bosi 2011	3	399	2	404	0.6%	1.52 [0.25, 9.16]		$\bullet \bullet ? \bullet \bullet \bullet \bullet$
Nissen 2008	13	273	11	270	2.7%	1.18 [0.52, 2.68]		
Vaccaro 2017	83	1493	74	1535	17.6%	1.16 [0.84, 1.60]	- +-	••••
Giles 2010	13	149	13	151	2.8%	1.01 [0.45, 2.27]		???++++
Mazzone 2006	2	228	2	230	0.5%	1.01 [0.14, 7.22]		
Yamasaki 2010	7	293	7	294	1.6%	1.00 [0.35, 2.90]		? • • • • ? •
Yoshii 2014	9	234	10	237	2.2%	0.91 [0.36, 2.28]		?? 🔴 🛨 🖶 🛨
Lee 2013	7	60	8	61	1.5%	0.88 [0.30, 2.59]		????++++
Dormandy 2005	301	2605	358	2633	67.7%	0.83 [0.70, 0.98]		
Henry 2014	9	1055	3	172	1.0%	0.48 [0.13, 1.81]		
Takagi 2009	6	48	15	49	1.7%	0.32 [0.11, 0.92]		??●•••
Total (95% CI)		7118		6331	100.0%	0.89 [0.78, 1.02]	•	
Total events	455		503					
Heterogeneity: Tau ² =	: 0.00; Chi	² = 10.0	0, df = 11	(P = 0.	.53); I ² = 0	%		-
Test for overall effect:							0.1 0.2 0.5 1 2 5 10 avours [Pioglitazone] Favours [control]	I

В

	Discling		Cont			Odda Batia	Odds Ratio	Risk of Bias
Study or Subaroun	Pioglita Events	Total	Cont		Weight	Odds Ratio		
Study or Subgroup					-	M-H, Random, 95% CI	M-H, Random, 95% CI	
Schernthaner 2004	3	597	2	597	1.0%	1.50 [0.25, 9.02]		
Giles 2010	2	149	2	151	0.8%	1.01 [0.14, 7.29]		— ***
Charbonnel 2005	2	313	2	317	0.8%	1.01 [0.14, 7.24]		
Dormandy 2005	177	2605	186	2633	69.8%			
Vaccaro 2017	50	1493	55		20.9%	0.93 [0.63, 1.38]		••••
Charbonnel 2004	4	624	5	626	1.8%	0.80 [0.21, 3.00]		????@@@@
Nissen 2008	2	273	3	270	1.0%	0.66 [0.11, 3.96]	·	
Henry 2014	4	1055	1	172	0.7%	0.65 [0.07, 5.86]	• • • •	- 6666666
Yoshii 2014	1	234	2	237	0.5%	0.50 [0.05, 5.60]	• • •	- ?? 🔴 🗣 🗣 🗣
Bolli 2009	0	281	1	295	0.3%	0.35 [0.01, 8.60]	· · · · · · · · · · · · · · · · · · ·	\rightarrow GGGGGGG
Bosi 2011	0	399	1	404	0.3%	0.34 [0.01, 8.29]	· · · · · · · · · · · · · · · · · · ·	
Mazzone 2006	0	228	1	230	0.3%	0.33 [0.01, 8.26]	• • • • • • • • • • • • • • • • • • • •	
Lee 2013	0	60	1	61	0.3%	0.33 [0.01, 8.35]	· · · · · · · · · · · · · · · · · · ·	
Jain 2006	0	251	2	251	0.3%	0.20 [0.01, 4.15]	← → →	
Matthews 2005	0	317	2	313	0.3%	0.20 [0.01, 4.10]	← − − −	667666
Tolman 2009	1	1051	6	1046	0.7%	0.17 [0.02, 1.37]	·	
Tan 2004	0	109	0	91		Not estimable		?? • • • • •
Yamanouchi 2005	0	38	0	37		Not estimable		
Derosa 2009	0	66	0	69		Not estimable		
Abe 2010	0	21	0	22		Not estimable		??@@@@
Tan 2004a	0	123	0	121		Not estimable		444444
Takagi 2009	0	48	0	49		Not estimable		? ? • • • • •
Total (95% CI)		10335		9527	100.0%	0.91 [0.76, 1.09]	•	
Total events	246		272					
Heterogeneity: Tau ² =		i² = 6.9		L5 (P =	0.96); I ²	= 0%		

*1*0), ſı. Test for overall effect: Z = 1.01 (P = 0.31)



Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias) (F) Selective reporting (reporting bias)

С

	Pioglita	zone	Contr	rol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
Bosi 2011	0	399	0	404		Not estimable		
Bolli 2009	0	281	0	295		Not estimable		
Mazzone 2006	1	228	0	230	0.8%	3.04 [0.12, 75.01]		\rightarrow
Henry 2014	1	1055	0	172	0.8%	0.49 [0.02, 12.10]	←	→ ••••• •••
Takagi 2009	1	48	2	49	1.5%	0.50 [0.04, 5.70]	←	?? 🛑 🖶 🖶 🖶
Nissen 2008	5	273	4	270	4.8%	1.24 [0.33, 4.67]		
Vaccaro 2017	12	1493	19	1535	14.7%	0.65 [0.31, 1.34]		••••
Dormandy 2005	209	2605	153	2633	77.3%	1.41 [1.14, 1.75]		
Total (95% CI)		6382		5588	100.0%	1.23 [0.91, 1.65]	•	
Total events	229		178					
Heterogeneity: Tau ² =	0.02; Chi	² = 5.34	, df = 5 (F	e = 0.38); I ² = 6%			t
Test for overall effect:	Z=1.37 (P = 0.17	7)				0.1 0.2 0.5 1 2 5 1 Favours [Pioglitazone] Favours [control]	10

<u>Risk of bias legend</u> (A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias) (F) Selective reporting (reporting bias)

5.4.2.3. Trials' characteristics

Baseline characteristics of the trials included in the meta-analysis

First author (reference)	MACE within endpoints	Pioglit. (n)	Comparator (molecule)	Comparator (n)	Trial duration (months)	MA	CE*		cause tality	Heart failure*	
						Piogli.	Comp.	Piogli.	Comp.	Piogli.	Comp.
Bolli 2009 ⁴²	NO	281	Vildagliptin	295	52	-	-	1	1	0	0
Bosi 2011 ⁴³	NO	399	Alogliptin	404	52	-	-	1	1	0	0
Charbonnel 2004 ⁴⁴	NO	626	Gliclazide	624	52	-	-	4	4	-	-
Charbonnel 2005 ⁴⁵	NO	313	Gliclazide	317	104	-	-	2	2	-	-
Derosa 2009 ⁴⁶	NO	66	Glimepiride	69	65	-	-	0	0	-	-
Dormandy 200547	YES	2605	Placebo	2633	150	301	358	186	186	209	153
Giles 2010 ⁴⁸	YES	149	Glyburide	151	52	13	13	2	2	NR	NR
Henry 2014 ⁴⁹	NO	1,096	Sitagliptin	186	54	-	-	4	1	-	-
Home 2015 ⁵⁰	NO	288	Placebo	116	156	-	-	3	1	-	-
Khaloo 2019 ⁵¹	NO	125	Sitagliptin	125	52	-	-	0	0	-	-
Jain 2006 ⁵²	NO	251	Glyburide	251	56	-	-	0	0	-	-
Lee 2013 ⁵³	YES	60	Placebo	61	52	7	8	1	1	NR	NR
Matthews 2005 ⁵⁴	NO	313	Gliclazide	317	52	-	-	0	0	-	-
Mazzone 2006 ⁵⁵	YES	228	Glimepiride	230	72	2	2	1	1	1	0

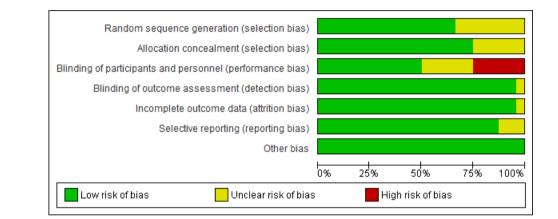
Appendix

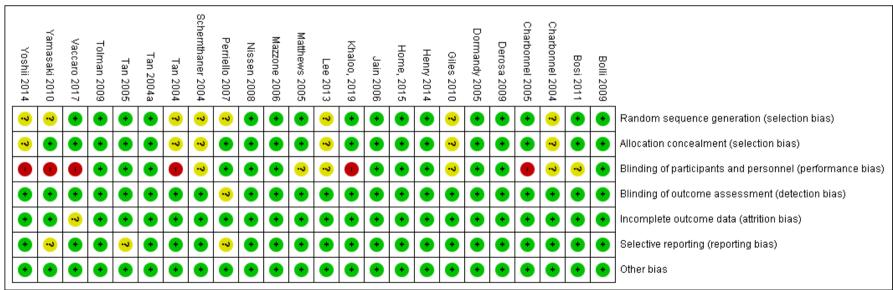
Nissen 2008 ⁵⁶	YES	273	Glimepiride	270	78	13	11	3	3	5	4
Shernthaner 2004 ⁵⁷	NO	597	Metformina	597	52	-	-	2	2	-	-
Tan 2004 ⁵⁸	NO	109	Glyburide	91	52	-	-	0	0	-	-
Tan 2004 ⁵⁹	NO	123	Glimepiride	121	52	-	-	0	0	-	-
Tolman 2009 ⁶⁰	NO	1046	Glyburide	1051	144	-	-	1	1	-	-
Vaccaro 2017 ⁶¹	YES	1493	Sulfaniluree	1535	248	83	74	55	55	12	19
Yamasaki 2010 ⁶²	YES	89	None	97	52	NR	NR	NR	NR	NR	NR
Yoshii 2014 ⁶³	YES	234	Multiple	237	96	9	10	2	2	NR	NR

* Data are reported only for trials with MACE within their principal/secondary endpoints; MACE: Major Cardiovascular Events; Piogl.: Pioglitazone; Comp.: Comparator.

5.4.2.4. Risk of bias

Graph and summary: review authors' judgements about each risk of bias item.





5.4.3. Insulin secretagogues

The systematic review has already been published; for complete search string, list and characteristics of included studies, and assessment of publication bias, please see the related publication ⁶⁴

Forest plot for trials comparing the effects of insulin secretagogues and other glucose-lowering agents/placebo on MACE (Panel A), all-cause mortality (Panel B), and heart failure (Panel C).

Α

	SU		Compa	rator		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	ABCDEFG
Foley 2009	8	546	16	546	3.4%	0.49 [0.21, 1.16]		????
Ferrannini 2009	б	1393	11	1396	2.6%	0.54 [0.20, 1.48]		
ADOPT	26	1441	46	1454	8.4%	0.56 [0.35, 0.91]	_ _	~~~ ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
Filozof 2012	4	513	5	494	1.5%	0.77 [0.21, 2.88]		
UKPDS	270	1234	409	1807	21.3%	0.96 [0.80, 1.14]	-	
CHICAGO	2	228	2	230	0.7%	1.01 [0.14, 7.22]	•	
Giles 2010	13	149	13	151	3.8%	1.01 [0.45, 2.27]		???9999
CAROLINA	362	3010	356	3023	22.3%	1.02 [0.88, 1.20]	+	666666
TOSCAIT	83	1493	74	1535	13.8%	1.16 [0.84, 1.60]	- -	
PERISCOPE	13	273	11	270	3.7%	1.18 [0.52, 2.68]		
Goke 2013	5	430	4	428	1.5%	1.25 [0.33, 4.68]		
Del Prato 2014	11	874	14	1665	3.9%	1.50 [0.68, 3.33]		667666
SPREAD-DIMCAD	52	148	39	156	8.2%	1.63 [0.99, 2.67]		6666666
Gallwitz 2012	26	775	12	775	4.9%	2.21 [1.11, 4.41]		
Total (95% CI)		12507		13930	100.0%	1.03 [0.87, 1.22]		
Total events	881		1012				ſ	
Heterogeneity: Tau ² =	= 0.03; Ch	$i^2 = 20.$	66. df =	13 (P =	0.08); I ²	= 37%		+
Test for overall effect	,						0.2 0.5 1 2	5
	0.5 (·· · · ·	,				Favours SU Favours comp	arator

В

	SU		Compa			Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI	ABCDEFG
LEAD-2	0	200	1	200	0.1%	0.33 [0.01, 8.19]	• • •	\rightarrow \bullet
CHICAGO	0	228	1	230	0.1%	0.33 [0.01, 8.26]	•	
Goke 2013	2	430	4	428	0.4%	0.50 [0.09, 2.72]	• • • • •	
PERISCOPE	2	273	3	270	0.3%	0.66 [0.11, 3.96]	•	
CANTATA-SU	2	473	3	485	0.3%	0.68 [0.11, 4.10]	1 10 10	
Tan 1977	1	18	4	60	0.2%	0.82 [0.09, 7.87]	• •	
TOSCAIT	50	1493	55	1535	7.1%	0.93 [0.63, 1.38]		
Filozof 2010	1	513	1	494	0.1%	0.96 [0.06, 15.44]	• •	
EMPA-REG H2H-SU	8	3120	8	3076	1.1%	0.99 [0.37, 2.63]		
GENERATION	1	360	1	360	0.1%	1.00 [0.06, 16.05]	•	
Gallwitz 2012	4	775	4	776	0.6%	1.00 [0.25, 4.02]	2	
EUREXA	5	487	5	490	0.7%	1.01 [0.29, 3.50]	· · · · · · · · · · · · · · · · · · ·	
ADOPT	31	1441	31	1454	4.3%	1.01 [0.61, 1.67]		
Charbonnel 2005	2	313	2	317	0.3%	1.01 [0.14, 7.24]	• +	
Giles 2010	2	149	2	151	0.3%	1.01 [0.14, 7.29]	•	
UKPDS	257	1234	424	2109	35.9%	1.05 [0.88, 1.24]		
CAROLINA	336	3010	308	3023	40.5%	1.11 [0.94, 1.30]		
QUARTET (EC405)	5	626	4	624	0.6%	1.25 [0.33, 4.67]		- ??.?
Ferrannini 2009	3	1393	2	1396	0.3%	1.50 [0.25, 9.02]		
Foley 2009	9	546	6	546	1.0%	1.51 [0.53, 4.27]		- ???
Del Prato 2014	5	874	6	1665	0.8%	1.59 [0.48, 5.23]		
HARMONY-3	3	317	2	417	0.3%	1.98 [0.33, 11.94]	. <u> </u>	
VERTIS SU	2	437	1	440	0.2%	2.02 [0.18, 22.34]	• .	
Clarke 1977	6	109	3	107	0.5%	2.02 [0.49, 8.29]		
Ariona Ferreira 2013 (a)	6	211	3	212	0.6%	2.04 [0.50, 8.26]		
SPREAD-DIMCAD	14	148	7	156	1.2%	2.22 [0.87, 5.67]		$\rightarrow \bullet \bullet \bullet \bullet \bullet \bullet \bullet \bullet$
Arjona Ferreira 2013	7	64	3	65	0.6%	2.54 [0.63, 10.29]		
START-J TRIAL	1	143	0	127	0.1%	2.68 [0.11, 66.48]	•	
Jain 2006	2	251	0	251	0.1%	5.04 [0.24, 105.51]		
QUARTET	2	313	0	317	0.1%	5.10 [0.24, 106.58]		
LEAD-3	1	248	0	498	0.1%	6.04 [0.25, 148.86]		
Tolman 2009	6	1046	1	1051	0.2%	6.06 [0.73, 50.40]		
DIANA	3	101	1	201	0.2%	6.12 [0.63, 59.62]		
Nauck 2011	3	401	0	400	0.1%	7.04 [0.36, 136.64]		
Seck 2011	8	588	1	584	0.2%	8.04 [1.00, 64.50]		
Nauck 2014	4	802	0	800	0.1%	9.02 [0.48, 167.86]	10000	\rightarrow
Total (95% CI)		23135		25315	100.0%	1.11 [1.00, 1.23]	•	
Total events	794		897					
Heterogeneity: Tau² = 0.0 Test for overall effect: Z =			= 35 (P =	0.88); I ^z	= 0%		0.2 0.5 1 2 Favours SU Favours com	5 parator

С

	SU		Compa	rator		Odds Ratio	Odds Ratio Risk	of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI A B C	DEFG
Foley 2009	4	546	0	546	1.5%	9.07 [0.49, 168.80]		
HARMONY-3	1	307	0	404	1.2%	3.96 [0.16, 97.52]		•••
CHICAGO	1	228	0	230	1.2%	3.04 [0.12, 75.01]		
UKPDS	48	1234	56	1807	32.4%	1.27 [0.85, 1.87]		
PERISCOPE	5	273	4	270	6.5%	1.24 [0.33, 4.67]		
SPREAD-DIMCAD	10	148	9	146	11.7%	1.10 [0.43, 2.80]		
Ferrannini 2009	2	1393	2	1396	3.2%	1.00 [0.14, 7.12]		
Goke 2013	1	430	1	428	1.6%	1.00 [0.06, 15.96]		
TOSCA.IT	12	1493	19	1535	16.8%	0.65 [0.31, 1.34]		
CAROLINA	12	3010	19	3023	16.8%	0.63 [0.31, 1.31]		
ADOPT	3	1441	12	1454	7.0%	0.25 [0.07, 0.89]		
Del Prato 2014	0	874	0	1665		Not estimable	•••	
Total (95% CI)		11377		12904	100.0%	0.92 [0.64, 1.32]	+	
Total events	99		122					
Heterogeneity: Tau ² =	= 0.06; Chi ^a	= 12.3	5, df = 10	(P = 0.2)	6); I ^z = 19	1%		
Test for overall effect	: Z = 0.45 (P = 0.65	5)	1	8		0.2 0.5 1 2 5 Favours SU Favours comparator	

Risk of bias legend (A) Random sequence generation (selection bias) (B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias) (E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

5.4.4. DiPeptidil Dipeptidasi-4 inhibitors

The systematic review has already been published; for complete search string, list and characteristics of included studies, and assessment of publication bias, please see the related publication⁶⁵.

Forest plot for trials comparing the effects of DPP-4i and other glucose-lowering agents/placebo on MACE (Panel A), all-cause mortality (Panel B), and heart failure (Panel C).

Α

	Dpp	4i	Cont	rol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	ABCDEFG
Ahren 2014 (101)	0	302	0	710		Not estimable		9999999
McMurray 2018 (39)	0	128	0	126		Not estimable		
dita 2016 (26)	0	83	0	82		Not estimable		
errannini 2009 (156)	0	1396	0	1393		Not estimable		
Arturi 2017 (37)	0	10	0	10		Not estimable		
Aita 2016 (34)	0	172	2	169	0.0%	0.19 [0.01, 4.08]	←	\rightarrow
Del Prato 2014 (41)	14	1665	11	874	0.5%	0.67 [0.30, 1.47]	←	? • ? • • •
Goke 2013 (83)	3	428	4	430	0.2%	0.75 [0.17, 3.38]	+	\rightarrow 0000000
Rosenstock 2019 (38)	356	3023	362	3010	14.1%	0.98 [0.84, 1.14]		9999999
White 2013 (27)	315	2701	316	2679	12.4%	0.99 [0.84, 1.17]		9999999
Dyama 2016 (35)	4	222	4	220	0.2%	0.99 [0.24, 4.01]	•	\rightarrow
Scirica 2013 (32)	613	8280	609	8212	25.2%	1.00 [0.89, 1.12]		0000000
Green 2015 (33)	745	7332	746	7339	29.8%	1.00 [0.90, 1.11]	+	0000000
Rosenstock 2019 (29)	434	3494	420	3485	16.7%	1.04 [0.90, 1.19]	-	0000000
Rosenstock 2019 (30)	4	467	7	931	0.2%	1.14 [0.33, 3.92]	•	\rightarrow 0000000
(ki-Jarvinen 2013 (72)	8	631	б	630	0.3%	1.34 [0.46, 3.87]	•	→ ??●●●●
Foley 2009	16	546	8	546	0.5%	2.03 [0.86, 4.78]		→ ?♀?♀♀♀
Fotal (95% CI)		30880		30846	100.0%	1.00 [0.94, 1.06]	◆	
Fotal events	2512		2495					
leterogeneity: Tau ² = 0.	00; Chi ² =	= 5.55, (df = 11 (f	= 0.90	(); $ ^2 = 0\%$	5	07 085 1 12 15	
est for overall effect: Z	= 0.05 (P	= 0.96)			-		0.7 0.85 1 1.2 1.5 avours [experimental] Favours [control]	

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias) (G) Other bias

В

tudy or Subgroup CT01186562	Events		Events	Total	weight	M-H, Random, 95% CI	M-H, Randon	1, 3076 UI	ABCDEFO
	0	54	0	29		Not estimable			2220202
eng 2017	0	36	0	36		Not estimable			
rturi 2017 (37)	0	10	0	10		Not estimable			0000000
CT00374907	0	20	0	16		Not estimable			??? • ? • ?
erosa 2013	0	228	0	225		Not estimable			
erosa 2010 (124)	0	75	0	76		Not estimable			
oley 2011 (162)	0	29	0	30		Not estimable			
erosa 2013a	0	91	0	87		Not estimable			
obs 2013 (136)	0	181	0	97		Not estimable			
ita 2016 (34)	0	172	0	169		Not estimable			
aku 2019 (63)	0	213	0	214		Not estimable			
olli 2009 (159)	0	295	0	281		Not estimable			
oon 2012 (147)	0	261	0	259		Not estimable			
osenstock 2013 (42)	0	222	0	219		Not estimable			???•• • •
ei Cas 2017 (153)	0	40	0	24		Not estimable			
errannini 2013 (108)	0	56	0	332		Not estimable			? • ? • • • •
eck 2011 (118)	1	588	8	584	0.1%	0.12 [0.02, 0.98]			
hacra 2011 (86)	1	501	4	267	0.1%	0.13 [0.01, 1.18]			
chernthaner 2013 (105)	0	378	2	377	0.0%	0.20 [0.01, 4.15]			
oses 2016 (141)	0	213	2	214	0.0%	0.20 [0.01, 4.17]	•		
futzner 2011 (95)	1	320	5	328	0.1%	0.20 [0.02, 1.74]		-	
ewin 2015 (52)	1	402	3	265	0.1%	0.22 [0.02, 2.10]		-	00?000
(Illiams-Herman 2010 Study 1 (126)	0	179	3	364	0.1%	0.29 [0.01, 5.60]			
erauchi 2017 (115)	0	143	1	127	0.0%	0.29 [0.01, 7.28]			??●•••
íilliams-Herman 2010 Study 2 (126)	2	372	3	176	0.1%	0.31 [0.05, 1.88]		-	
cherbaum 2008 (168)	0	156	1	150	0.0%	0.32 [0.01, 7.88]			??? •••
ita 2016 (26)	0	83	1	82	0.0%	0.33 [0.01, 8.10]			
hren 2014 (101)	1	302	7	710	0.1%	0.33 [0.04, 2.72]			
atthaei 2015 (92)	0	153	1	162	0.0%	0.35 [0.01, 8.67]			
rjona 2013 (116)	3	64	7	65	0.2%	0.41 [0.10, 1.65]			
auck 2014 Study 2 (103)	0	492	1	606	0.0%	0.41 [0.02, 10.08]			
chweizer 2007	2	526	2	254	0.1%	0.48 [0.07, 3.43]			
rjona 2013 (119)	3	211	6	212	0.2%	0.50 [0.12, 2.01]		_	
el Prato 2014 (41)	6	1665	5	874	0.3%	0.63 [0.19, 2.07]		-	? • ? • • • •
oley 2009	6	546	9	546	0.4%	0.66 [0.23, 1.88]		-	? • ? • • • •
errannini 2009 (156)	2	1396	3	1393	0.1%	0.66 [0.11, 3.98]			
owicki 2011 (98)	3	85	4	85	0.2%	0.74 [0.16, 3.41]			
/hite 2013 (27)	153	2701	173	2679	8.8%	0.87 [0.69, 1.09]	-		
osenstock 2019 (38)	308	3023	336	3010	16.6%	0.90 [0.77, 1.06]	-		
ilozof 2010 (155)	1	513	1	494	0.1%	0.96 [0.06, 15.44]			
osenstock 2019 (29)	367	3494	373	3485	19.1%	0.98 [0.84, 1.14]	+		
ki-Jarvinen 2013 (72)	5	631	5	630	0.3%	1.00 [0.29, 3.47]			?? ••••
allwitz 2012 (53)	4	776	4	775	0.2%	1.00 [0.25, 4.01]			
chernthaner 2015 (84)	1	360	1	360	0.1%	1.00 [0.06, 16.05]			
eiter 2014 (102)	4	253	4	254	0.2%	1.00 [0.25, 4.06]			
reen 2015 (33)	547	7332	537	7339	29.0%	1.02 [0.90, 1.16]	+		
cirica 2013 (32)	420	8280	378	8212	21.8%	1.11 [0.96, 1.28]	-		
yama 2016 (35)	3	222	2	220	0.1%	1.49 [0.25, 9.02]			
osenstock 2019 (30)	3	467	4	931	0.2%	1.50 [0.33, 6.72]			000000
hren 2017 (149)	3	407	3	818	0.2%	2.02 [0.41, 10.04]	-+		
oke 2013 (83)	4	428	2	430	0.2%	2.02 [0.37, 11.08]	-+		
ollander 2011 (91)	2	381	ō	184	0.0%	2.43 [0.12, 50.89]			?
avalle-Gonzalez 2013 (104)	1	366	1	918	0.1%	2.51 [0.16, 40.27]			
cMurray 2018 (39)	11	128	4	126	0.3%	2.87 [0.89, 9.26]	+		
enry 2014 (131)	7	1252	1	515	0.1%	2.89 [0.35, 23.55]			
osi 2011 (44)	1	404	o	399	0.0%	2.97 [0.12, 73.13]			
ratley 2010 (121)	2	219	1	446	0.1%	4.10 [0.37, 45.48]	+	· · · · ·	220000
otal (95% CI)		42395		42170	100.0%	0.98 [0.92, 1.05]			
otal events	1879		1908				1		
eterogeneity: Tau ² = 0.00; Chi ² = 36.74		P = 0.62					0.01 0.1 1	10 100	

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias) (D) Blinding of outcome assessment (detection bias) (E) Incomplete outcome data (attrition bias) (F) Selective reporting (reporting bias) (G) Other bias

С

	Dpp4	4i	Cont	rol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
Arturi 2017 (37)	0	10	0	10		Not estimable		
Mita 2016 (26)	0	83	0	82		Not estimable		
Del Prato 2014 (41)	0	1665	0	874		Not estimable		? • ? • • • •
Foley 2009	0	546	8	546	0.2%	0.06 [0.00, 1.01]	<	? • ? • • • •
Mita 2016 (34)	0	172	0	169		Not estimable		
Oyama 2016 (35)	2	222	4	220	0.5%	0.49 [0.09, 2.71]		
Ahren 2014 (101)	0	302	1	710	0.1%	0.78 [0.03, 19.25]	• • • • • • • • • • • • • • • • • • •	→ ••••• •••
Rosenstock 2019 (29)	209	3494	226	3485	21.5%	0.92 [0.76, 1.11]		
Green 2015 (33)	228	7332	229	7339	22.5%	1.00 [0.83, 1.20]	+	
Ferrannini 2009 (156)	2	1396	2	1393	0.4%	1.00 [0.14, 7.09]		$\bullet \bullet \bullet \bullet \bullet \bullet \bullet \bullet$
Yki-Jarvinen 2013 (72)	4	631	4	630	0.8%	1.00 [0.25, 4.01]		??●••••
Goke 2013 (83)	1	428	1	430	0.2%	1.00 [0.06, 16.11]	· · · · · · · · · · · · · · · · · · ·	→ ●●●●●●
McMurray 2018 (39)	23	128	22	126	3.3%	1.04 [0.54, 1.97]		$\bullet \bullet \bullet \bullet \bullet \bullet \bullet \bullet$
White 2013 (27)	106	2701	89	2679	13.0%	1.19 [0.89, 1.58]	+	
Rosenstock 2019 (38)	112	3023	92	3010	13.5%	1.22 [0.92, 1.62]	+	
Scirica 2013 (32)	289	8280	228	8212	23.8%	1.27 [1.06, 1.51]		$\bullet \bullet \bullet \bullet \bullet \bullet \bullet \bullet$
Rosenstock 2019 (30)	3	467	1	931	0.3%	6.01 [0.62, 57.96]		→ ● ●●●●●●●
Total (95% CI)		30880		30846	100.0%	1.09 [0.96, 1.23]	◆	
Total events	979		907					
Heterogeneity: Tau ² = 0.0	1; Chi ² = 1	14.85, d	f = 12 (P	= 0.25);	l² = 19%			ι 0
Test for overall effect: Z =	1.34 (P =	0.18)				-	0.1 0.2 0.5 1 2 5 1 avours [experimental] Favours [control]	U

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias) (F) Selective reporting (reporting bias) (G) Other bias

5.4.5. Glucagon-Like Peptide-1 receptor agonists

The systematic review has already been published; for complete search string, list and characteristics of included studies, and assessment of publication bias, please see the related publication⁶⁶.

Forest plot for trials comparing the effects of GLP-1RA and other glucose-lowering agents/placebo on MACE (Panel A), all-cause mortality (Panel B), and heart failure (Panel C).

Α

	GLP.1	RA	Cont	trol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	ABCDEFG
Rosenstock 2019 (69)	14	1397	2	467	0.1%	2.35 [0.53, 10.39] ←		9999999
Tuttle 2018 (70)	8	383	4	194	0.2%	1.01 [0.30, 3.41] ←		
Gough 2015 (65)	1	414	1	413	0.0%	1.00 [0.06, 16.00] ←		
ELIXA (31)	389	3034	397	3034	14.2%	0.98 [0.84, 1.13]	_	6666766
EXSCEL (34)	839	7356	905	7396	31.9%	0.92 [0.84, 1.02]		6666766
REWIND (5)	594	4949	663	4952	22.8%	0.88 [0.78, 0.99]		6666666
LEADER (32)	608	4668	694	4672	23.2%	0.86 [0.76, 0.97]	_ _	0000000
PIONEER-6 (30)	61	1591	76	1592	2.7%	0.80 [0.56, 1.12] -		0000000
SUSTAIN-6 (33)	108	1648	146	1649	4.8%	0.72 [0.56, 0.94] -		0000000
Arturi 2017 (64)	0	10	0	10		Not estimable		
Total (95% CI)		25450		24379	100.0%	0.89 [0.84, 0.94]	•	
Total events	2622		2888				-	
Heterogeneity: $Tau^2 = 0$.00; Chi ²	= 7.00.	df = 8 (l	P = 0.54); $ ^2 = 0\%$			
Test for overall effect: Z	,	,					0.7 0.85 1 1.2 1.5 GLP-1 RA Favours [control]	

В

	Experim		Cont			Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events		Events		Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl	ABCDEFG
Arturi 2017 (64)	0	10	0	10		Not estimable		•••••••
Derosa 2013 (52)	0	86	0	85		Not estimable		
Gough 2015 (65)	0	414	0	413		Not estimable		
Jaiswal 2015 (56)	0	22	0	24		Not estimable		
Miyagawa 2015 (43)	0	281	0	70		Not estimable		
Bunck 2009 (55)	0	36	0	33		Not estimable		
de Wit 2014 (60)	0	26	-	24		Not estimable		
Derosa 2010 (49)	0	63	0	65 49		Not estimable		
Derosa 2011 (51)	0	52 34	0	49		Not estimable Not estimable		
Liang 2013 (50) Umpierrez 2014 (44)	0	269	0	268		Not estimable		
Sathyanarayana 2011 (48)	0	209	0	200		Not estimable		
	0	271	3	115	0.1%		· · · · · · · · · · · · · · · · · · ·	
Home 2015 (37) Weinstock 2015 (45)	1	606	2	177	0.1%	0.06 [0.00, 1.16] 0.14 [0.01, 1.60]		
Garber 2011 (66)	o i	498	1	248	0.2%	0.17 [0.01, 4.08]	•	
Pratley 2011 (63)	1	490	2	240	0.1%	0.25 [0.02, 2.75]		
Kaku 2018 (67)	1	480	1	121	0.2%	0.25 [0.02, 4.03]		
Blonde 2015 (46)	2	588	3	296	0.1%	0.33 [0.06, 2.01]		
Giorgino 2015 (47)	1	275	2	262	0.3%	0.47 [0.04, 5.26]		
Weissman 2014 (41)	3	504	3	202	0.2%	0.48 [0.10, 2.37]		
PIONEER-6 (30)	23	1591	45	1592	3.2%	0.50 [0.30, 0.84]		
Tuttle 2018 (70)	20	383		194	0.8%	0.75 [0.26, 2.15]		
LEADER (32)	381	4668	447	4672	21.7%	0.84 [0.73, 0.97]	-	
EXSCEL (34)	507	7356	584	7396	24.9%	0.86 [0.76, 0.98]	_	
REWIND (5)	536	4949	592	4952	24.8%	0.89 [0.79, 1.01]	-	
Gallwitz 2012 (53)	5	490	5	487	0.6%	0.99 [0.29, 3.45]		
Rosenstock 2019 (69)	ğ	1397	3	467	0.5%	1.00 [0.27, 3.72]		
Diamant 2014 (58)	1	233	1	234	0.1%	1.00 [0.06, 16.15]		
SUSTAIN-6 (33)	62	1648	60	1649	5.9%	1.04 [0.72, 1.49]	+	
ELIXA (31)	223	3034	211	3034	15.2%	1.06 [0.87, 1.29]	+	
Nauck 2007 (54)	2	253	1	248	0.2%	1.97 [0.18, 21.84]		
Inagaki 2012 (59)	1	215	0	212	0.1%	2.97 [0.12, 73.37]		
NCT01648582	1	263	0	263	0.1%	3.01 [0.12, 74.26]		?? 🛑 🖶 🖶 🖶
Davies 2015 (61)	1	211	0	212	0.1%	3.03 [0.12, 74.76]		
Jabbour 2018 (57)	3	231	1	233	0.2%	3.05 [0.32, 29.56]		
Nauck 2009 (62)	2	482	0	363	0.1%	3.78 [0.18, 79.03]		
Nauck 2016 (38)	4	200	0	101	0.1%	4.65 [0.25, 87.20]		
Ahren 2014 (36)	3	302	1	710	0.2%	7.11 [0.74, 68.66]		?••••
Total (95% CI)		32872		29787	100.0%	0.89 [0.81, 0.97]	•	
Total events	1782		1974					
Heterogeneity: Tau ² = 0.01; 0 Test for overall effect: Z = 2.5			5 (P = 0.2	29); I ² = 1	2%		0.01 0.1 1 10 10 GLP-1 RA Favours [control	

С

	Experim	ental	Cont	rol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
Arturi 2017 (64)	0	10	0	22		Not estimable		
Gough 2015 (65)	0	414	1	413	0.1%	0.33 [0.01, 8.17]	· · · · · · · · · · · · · · · · · · ·	
Rosenstock 2019 (69)	5	1397	3	467	0.4%	0.56 [0.13, 2.33]		
Tuttle 2018 (70)	7	383	5	194	0.7%	0.70 [0.22, 2.25]		
PIONEER-6 (30)	21	1591	24	1592	2.6%	0.87 [0.48, 1.58]		
LEADER (32)	218	4668	248	4672	25.8%	0.87 [0.73, 1.05]	-	
REWIND (5)	213	4949	226	4952	24.5%	0.94 [0.78, 1.14]	-	
EXSCEL (34)	219	7356	231	7396	25.5%	0.95 [0.79, 1.15]	+	$\bullet \bullet \bullet \bullet \bullet ? \bullet \bullet$
ELIXA (31)	127	3034	122	3034	14.0%	1.04 [0.81, 1.34]	+	$\bullet \bullet \bullet \bullet \bullet ? \bullet \bullet$
SUSTAIN-6 (33)	59	1648	54	1649	6.4%	1.10 [0.75, 1.60]		$\bullet \bullet \bullet \bullet \bullet \bullet \bullet \bullet$
Total (95% CI)		25450		24391	100.0%	0.94 [0.86, 1.04]	•	
Total events	869		914					
Heterogeneity: Tau ² = 0.1	00; Chi ² =	3.11. df:	= 8 (P = 0	.93); l ² =	:0%			
Test for overall effect: Z =				/1 -				
		,					GLP-1 RA Favours [control]	

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias) (E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

5.4.6. Sodium-Glucose Transporter-2 inhibitors

The systematic review has already been published; for complete search string, list and characteristics of included studies, and assessment of publication bias, please see the related publication⁶⁷.

Forest plot for trials comparing the effects of SGLT-2i and other glucose-lowering agents/placebo on MACE (Panel A), all-cause mortality (Panel B), and heart failure (Panel C).

Α

	SGLT-2 inh	ibitors	Compar	ators		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
Jabbour 2018	1	228	0	227	0.1%	3.00 [0.12, 74.03]		\rightarrow
Neal 2017	355	5795	311	4347	23.2%	0.85 [0.72, 0.99]		
Wiviott 2018	756	8582	803	8578	53.0%	0.94 [0.84, 1.04]		
Zinman 2015	490	4687	282	2333	23.7%	0.85 [0.73, 0.99]		
Total (95% CI)		19292		15485	100.0%	0.89 [0.83, 0.96]	•	
Total events	1602		1396					
Heterogeneity: Tau ² =	= 0.00; Chi ^z =	2.14, df=	3 (P = 0.)	54); I² = I	0%			
Test for overall effect	Z = 2.90 (P =	0.004)					0.1 0.2 0.5 1 2 5 Favours [SGLT-2i] Favours [contro	10 I]

В

	SGLT-2 inh	ibitors	Compar			Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
3olinder 2014	0	175	0	80		Not estimable		
Araki 2015	0	273	0	63		Not estimable		•••?••
Merker 2015	0	311	0	301		Not estimable		
Dagogo-Jack 2018	0	153	0	153		Not estimable		
Ferrannini 2013	0	588	0	112		Not estimable		
Wilding 2014	0	156	0	156		Not estimable		
Nauck 2014	0	406	4	408	0.1%	0.11 [0.01, 2.06]	< <u>←</u>	
NCT01242215	0	77	1	36	0.1%	0.15 [0.01, 3.84]	•	???++???
Mathieau 2016	0	160	1	160	0.1%	0.33 [0.01, 8.19]		????++++
Bailey 2013	0	135	1	137	0.1%	0.34 [0.01, 8.32]		
Roden 2015	0	327	1	333	0.1%	0.34 [0.01, 8.34]		
Rosenstock 2015 (a)	0	233	1	255	0.1%	0.36 [0.01, 8.96]		
Lavalle-Gonzalez 2013	1	735	2	549	0.1%	0.37 [0.03, 4.12]		
Zinman 2015	269	4687	194	2333	21.8%	0.67 [0.55, 0.81]	-	
Neal 2017	228	5795	193	4347	20.8%	0.88 [0.72, 1.07]	+	
/Viviott 2018	529	8582	570	8578	53.5%	0.92 [0.82, 1.04]	•	
Kohan 2014	5	170	5	168	0.5%	0.99 [0.28, 3.48]		
Yale 2013	2	179	1	90	0.1%	1.01 [0.09, 11.24]		
Ridderstråle 2018	8	765	8	780	0.8%	1.02 [0.38, 2.73]		
Leiter 2014	5	480	4	482	0.5%	1.26 [0.34, 4.71]	<u> </u>	
Leiter 2015	6	968	2	482	0.3%	1.50 [0.30, 7.44]		
Jabbour 2018	3	461	1	230	0.2%	1.50 [0.16, 14.50]		
Barnett 2014	2	149	1	147	0.1%	1.99 [0.18, 22.15]		
Schernthaner 2013	2	377	1	378	0.1%	2.01 [0.18, 22.27]		
DeFronzo 2015	1	134	0	128	0.1%	2.89 [0.12, 71.54]		- •••••••
Lewin 2015	1	137	0	135	0.1%	2.98 [0.12, 73.75]		
Rosenstock 2014	1	189	0	188	0.1%	3.00 [0.12, 74.11]		
Bailey 2015	1	137	0	147	0.1%	3.24 [0.13, 80.25]		
Kovacs 2015	4	246	1	241	0.2%	3.97 [0.44, 35.75]		- ••?•••
Bode 2015	2	472	0	474	0.1%	5.04 [0.24, 105.31]		── → ●●●●? ●●
Hollander 2018	6	888	0	437	0.1%	6.44 [0.36, 114.66]		\longrightarrow
Total (95% CI)		28545		22508	100.0%	0.86 [0.79, 0.94]	•	
Total events	1076		992					
Heterogeneity: Tau² = 0.00 Test for overall effect: Z = 3			4 (P = 0.5	8); I² = 0	%			100

С

	SGLT-2 inh	ibitors	Compar	ators		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
Jabbour 2018	0	228	0	227		Not estimable		
Neal 2017	74	5795	84	4347	18.5%	0.66 [0.48, 0.90]		
Wiviott 2018	212	8582	286	8578	56.5%	0.73 [0.61, 0.88]		
Zinman 2015	126	4687	95	2333	25.0%	0.65 [0.50, 0.85]	+	
Total (95% CI)		19292		15485	100.0%	0.70 [0.61, 0.80]	•	
Total events	412		465					
Heterogeneity: Tau ² =	0.00; Chi ² =	0.71, df=	2 (P = 0.1)	70); I^z = I	0%			
Test for overall effect:	Z = 5.20 (P <	0.00001)				0.01 0.1 1 10 Favours [SGLT-2i] Favours [contr	100 ol]

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias) (D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

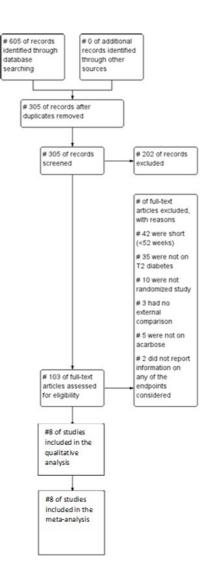
(F) Selective reporting (reporting bias)

(G) Other bias

5.4.7. Alpha-glucosidase inhibitors

The systematic review has already been submitted to a medical journal. A Medline and EMBASE search was conducted up to April 1st, 2020.

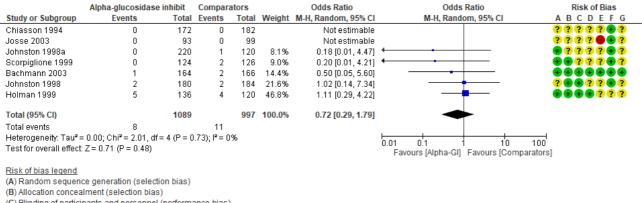
5.4.7.1. Trial flow summary



5.4.7.2. MACE

Forest plot for trials comparing the effects of pioglitazone and other glucose-lowering agents/placebo on MACE (Panel A), all-cause mortality (Panel B), and heart failure (Panel C).

Α



(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias) (F) Selective reporting (reporting bias)

(F) Selective re (G) Other bias

В

No available data on this endpoint.

С

No available data on this endpoint.

5.4.7.3. Trials' characteristics

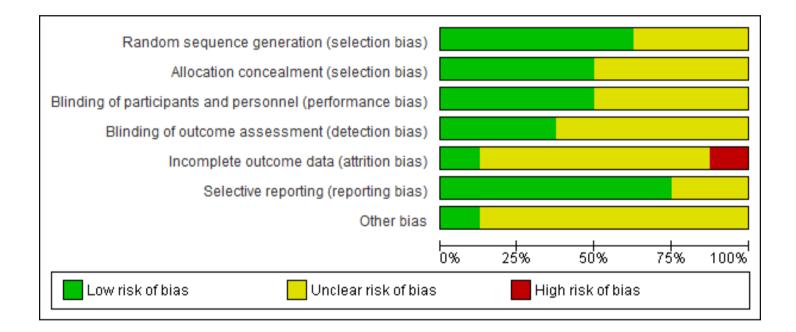
Baseline characteristics of the trials included in the meta-analysis

First author (ref.)	Investigational drug	Comparator	Trial duration	# patients	Mean Age	MA	CE	All-ca morta		-	art ure
	(ID)	(C)	(weeks)	(ID/C)	(years)				-		
						ID	С	ID	С	IC	С
Hasche 1999 ⁶⁸	Acarbose	Placebo	104	35/33	59	NR	NR	0	0	NR	NR
Chiasson 1994 69	Acarbose	Placebo	52	172/182	57	NR	NR	0	0	NR	NR
Josse 2003 ⁷⁰	Acarbose	Placebo	52	93/99	70	NR	NR	0	0	NR	NR
Johnston 1998 71	Miglitol	Placebo	52	180/92	67	NR	NR	2	0	NR	NR
		Glibenclamide	52	180/92	67	NR	NR	2	2	NR	NR
Johnston 1998 ⁷²	Miglitol	Placebo	52	220/120	53	NR	NR	0	1	NR	NR
Scorpiglione 1999 73	Acarbose	Placebo	52	124/126	63	NR	NR	0	2	NR	NR
Holman 1999 ⁷⁴	Acarbose	Placebo	156	136/120	60	NR	NR	5	4	NR	NR
Bachmann 2003 ⁷⁵	Acarbose	Placebo	78	164/166	63	NR	NR	1	2	NR	NR

NR, not reported; ID, investigational drug; C, comparator

5.4.7.4. Risk of bias

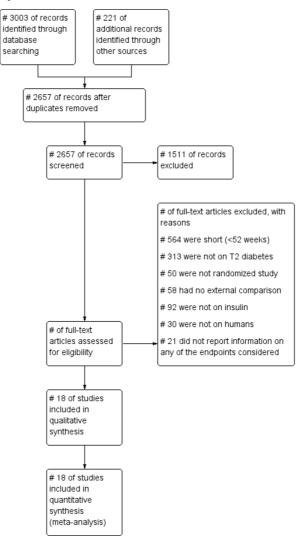
Graph and summary: review authors' judgements about each risk of bias item.



5.4.8. Insulin

The systematic review is in preparation.

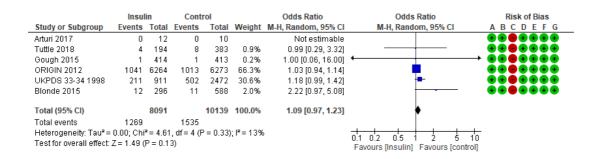
5.4.8.1. Trial flow summary



5.4.8.2. MACE, mortality, and hospitalization for heart failure

Forest plot for trials comparing the effects of insulin and other glucose-lowering agents/placebo on MACE (Panel A), all-cause mortality (Panel B), and heart failure (Panel C).

Α



В

	Insu		Cont			Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events		Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl	ABCDEFG
Ko 2006	0	56	0	56		Not estimable		?? 🛑 🖶 🖶 🖶
Klein 1991	0	25	0	25		Not estimable		?? 🗧 🖶 🖶 🖶
Weng 2008	0	261	0	121		Not estimable		
Jaiswal 2015	0	24	0	22		Not estimable		?? 🛑 🖶 🖶 🛨
Gough 2015	0	414	0	413		Not estimable		
Bunck 2009	0	33	0	36		Not estimable		
Arturi 2017	0	12	0	10		Not estimable		
NCT01648582	0	263	1	263	0.1%	0.33 [0.01, 8.19]	· · · · · · · · · · · · · · · · · · ·	?? 🛑 🖶 🖶 🖶
nagaki 2012	0	212	1	215	0.1%	0.34 [0.01, 8.31]	•	
Nauck 2007	1	248	2	253	0.1%	0.51 [0.05, 5.64]	•	
ORIGIN 2012	951	6264	965	6273	77.8%	0.98 [0.89, 1.09]		
Lingvay 2009	1	29	1	29	0.1%	1.00 [0.06, 16.79]	•	→ ••••••••
Diamant 2014	1	233	1	234	0.1%	1.00 [0.06, 16.15]	•	→ €€€€€ €
UKPDS 33-34 1998	184	911	497	2472	20.6%	1.01 [0.83, 1.22]	+	
Tuttle 2018	6	194	9	383	0.7%	1.33 [0.47, 3.78]		
Giorgino 2015	2	262	1	275	0.1%	2.11 [0.19, 23.38]		→ ++++ +++++
Alvarsson 2010	2	23	1	26	0.1%	2.38 [0.20, 28.14]		→ ??●•••
Blonde 2015	3	296	2	588	0.2%	3.00 [0.50, 18.05]		→ •••• ••••
Total (95% CI)		9760		11694	100.0%	0.99 [0.91, 1.08]	•	
Total events	1151		1481					
Heterogeneity: Tau ² =	0.00; Chi	2 = 3.84	l, df = 10	(P = 0.96	5); I ² = 0%	5		 10
Test for overall effect:	•						0.1 0.2 0.5 1 2 5 Favours (Insulin) Favours (contro	10

С

	Insu	in	Cont	rol		Odds Ratio	Odds Ratio	Risk of Bias	
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% Cl	ABCDEFG			
Arturi 2017	0	12	0	10		Not estimable			
Gough 2015	5	414	7	413	1.6%	0.71 [0.22, 2.25]			
UKPDS 33-34 1998	25	911	77	2472	10.4%	0.88 [0.56, 1.39]			
ORIGIN 2012	310	6264	343	6273	87.4%	0.90 [0.77, 1.05]			
Blonde 2015	1	296	2	588	0.4%	0.99 [0.09, 11.00]			
Tuttle 2018	1	194	0	383	0.2%	5.95 [0.24, 146.63]		\rightarrow	
Total (95% CI)		8091		10139	100.0%	0.90 [0.78, 1.04]	•		
Total events	342		429						
Heterogeneity: Tau ² =	0.00; Chi	² = 1.51	l, df = 4 (F	^o = 0.82)	; I² = 0%			100	
Test for overall effect:	Z=1.43 (P = 0.1	5)				0.01 0.1 1 10 Favours [Insulin] Favours [cont	100 rol]	

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias) (F) Selective reporting (reporting bias)

(G) Other bias

5.4.8.3. Trials' characteristics

Baseline characteristics of the trials included in the meta-analysis

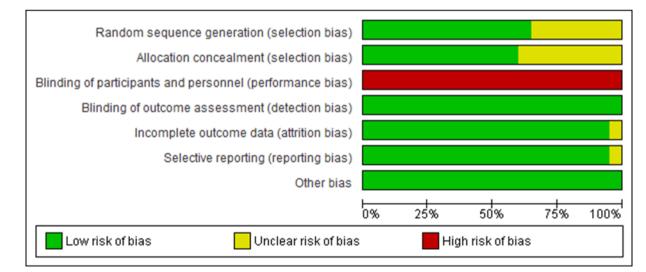
Study Name	Investigationa	Comparator	Trial duration	Pati	ients	Age	MA	CE	ALL-C	AUSE	HEA	ART
(Reference)	l drug		(weeks)	(ID)/C)	(years)			MORT	ALITY	FAIL	URE
				ID	С		ID	С	ID	С	IC	С
Alvarsson2008 ⁷⁶	Human Insulin	Glibenclamide	330	23	26	53	NR	NR	2	1	NR	NR
Arturi 2017 ⁷⁷	Glargine	Sitagliptin	52	12	10	60	0	0	0	0	0	0
Blonde 2015 ⁷⁸	Glargine	Dulaglutide	52	296	588	60	12	11	3	2	1	2
Bunck 2009 ⁷⁹	Glargine	Exenatide	52	33	36	58	0	0	0	0	NR	NR
Diamant 2014 ⁸⁰	Glargine	Exenatide LAR	156	233	234	58	NR	NR	1	1	NR	NR
Giorgino 2015 ⁸¹	Glargine	Dulaglutide	78	262	275	57	NR	NR	2	1	NR	NR
Gough 2015 ⁸²	Degludec	Liraglutide	52	414	413	55	1	1	0	0	5	7
Inagaki 2012 ⁸³	Glargine	Exenatide LAR	52	212	215	57	NR	NR	0	1	NR	NR
jaiswal 2015 ⁸⁴	Glargine	Exenatide	78	24	22	52	NR	NR	0	0	NR	NR
Klein 1991 ⁸⁵	NPH	Metformin	52	25	25	67	0	2	0	0	NR	NR
Ko 2006 ⁸⁶	NPH	Rosiglitazone	52	56	56	58	0	1	0	0	NR	NR
Lingvay 2009 ⁸⁷	BiAsp	Pioglitazone+Glibenclamide	156	29	29	45	NR	NR	1	1	NR	NR
Nauck 2007	BiAsp	Exenatide	52	248	253	58	NR	NR	1	2	NR	NR
NCT01648582	Glargine	Dulaglutide	52	263	263	55	NR	NR	0	1	NR	NR
ORIGIN 2012 ⁸⁸	Glargine	OAD	322	6264	6273	63	1041	1013	951	965	310	34
												3
Tuttle 2018 ⁸⁹	Glargine	Dulaglutide	52	194	383	65	4	8	6	9	1	0
UKPDS 1998 ^{90,91}	Human Insulin	Met+SU	572	911	2472	54	211	502	184	497	25	77
Weng 2008 ⁹²	Human insulin	Gliclazide e/o Metf	52	261	121	51	0	0	0	0	NR	NR

NR, not reported; ID, investigational drug; C, comparator

5.4.8.4. Risk of bias

Graph and summary: review authors' judgements about each risk of bias item.

Weng 2008	UKPDS 33-34 1998	Tuttle 2018	ORIGIN 2012	NCT01648582	Nauck 2007	Lingvay 2009	Li 2009	Ko 2006	Klein 1991	Jaiswal 2015	Inagaki 2012	Gough 2015	Giorgino 2015	Diamant 2014	Bunck 2009	Blonde 2015	Birkeland 1994	Arturi 2017	Alvarsson 2010	
•	•	•	•	••	•	•	••	••	••	•	•	•	•	•	•	•	?	•	••	Random sequence generation (selection bias)
•	•	•	•	~	•	•	~	••	••	••	•	•	•	•	••	•	?	•	•	Allocation concealment (selection bias)
					•	•														Blinding of participants and personnel (performance bias)
•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	Blinding of outcome assessment (detection bias)
•	•	•	•	•	•	•	••	•	•	•	•	•	•	•	•	•	•	•	•	Incomplete outcome data (attrition bias)
•	•	•	•	•	•	•	••	•	•	•	•	•	•	•	•	•	•	•	•	Selective reporting (reporting bias)
•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	Other bias



5.4.9 Grade of evidence

5.4.9.1 Grade of evidence common to all questions

Certainty a	ssessment						Summa	ary of findi	ings		
Participants	Disk of hiss	Inconsistency	Indirectness	Improvision	Publication	Overall	Relative	e effect	Anticipa	ted absolute	effects
(studies) Follow up	Risk of bias	Inconsistency	mairectness	Imprecision	bias	certainty of evidence	(95%	6, CI)	Control	Inter	vention
medium/lon	-term HbA1c										
41,730 (68 RCTs)	not serious	serious ^b	not serious	not serious	none	⊕⊕⊕⊖ MODERATE	-	-	-	-	-
Severe hypo	glycemia								·		
41,730 (68 RCTs)	not serious	serious ^b	not serious	not serious	none	⊕⊕⊕⊖ MODERATE	-	-	-	-	-
Quality of life							· · · · ·		1		
1760 (4 RCTs	not serious	not serious	not serious	serious ^d	none	⊕⊕⊕⊖ MODERATE	-	-	-	-	-

5.4.9.2 Grade of evidence in patients without cardiovascular events.

Certainty a	assessmen	t					Summary of	findings			
Participants	Risk of				Publication	Overall	Study ever	nt rates (%)	Relative effect (95% Cl)	Anticip	pated absolute effects
(studies) Follow up	bias	Inconsistency	Indirectness	Imprecision	bias	certainty of evidence	With Standard care	With Intensive glycemic control		Risk with placebo	Risk difference with intervention
MACE Metformin											
1,057 (2 RCTs)	not serious	not serious	serious ^c	serious ^d	very strong association	⊕⊕ ⊖⊖ LOW	123/559 (22.0%)	62/498 (12.4%)	OR 0.52 (0.37;0.73)	220 per 1.000	92 lower per 1.000 (from 126 to 49 lower)
Pioglitazone			· · ·		1				L		
13,499 (12 RCTs)	not serious	not serious	serious ^c	not serious	none	⊕⊕⊕ MODERATE	503/6331 (7.9%)	455/7118 (6.4%)	OR 0.89 (0.78;1.02)	79 per 1.000	8 lower per 1.000 (from 16 lower to 1 higher)
Insulin secret	agogues		1					I		1	
26,779 (14 RCTs)	not serious	not serious	serious ^c	not serious	none	ODERATE	1012/13930 (7.3%)	881/12507 (7.0%)	OR 1.03 (0.87;1.22)	76 per 1.000	3 higher per 1.000 (from 6 lower to 15 higher)
DPP-4i		-	ıl		- I	1	- I			ı I	
61,726 (17 RCTs)	not serious	not serious	serious ^c	not serious	none	⊕⊕⊕ MODERATE	2512/30846 (8.1%)	2495/30880 (8.1%)	OR 1.00 (0.94;1.06)	81 per 1.000	0 lower per 1.000 (from 5 lower to 4 higher)

GLP-1 RA

GLP-1 KA											
49,829 (10 RCTs)	not serious	not serious	serious ^c	not serious	strong association	⊕⊕⊕ MODERATE	2888/24379 (11.8%)	2622/25450 (10.3%)	OR 0.89 (0.84;0.94)	118 per 1.000	12 lower per 1.000 (from 17 to 6 lower)
SGLT-2i											
34,777 (4 RCTs)	not serious	not serious	serious ^c	not serious	strong association	MODERATE	1396/15485 (8.3%)	1602/19292 (8.3%)	OR 0.89 (0.83 ;0.96)	90 per 1.000	9 lower per 1.000 (from 14 to 3 lower)
Alfa glucosido	ase inhibitors									-	-
-	-	-	-	-	-	-	-	-	-	-	-
Insulin									•		•
18,230 (6 RCTs)	seriousª	not serious	serious ^c	not serious	none	⊕⊕⊕ MODERATE	1535/10139 (15.1%)	1269/8091 (15.7%)	OR 1.09 (0.97;1.23)	151 per 1.000	11 lower per 1.000 (from 4 low er to 29 hig her

ALL-CAUSE MORTALITY

Metformin

9,210 (13 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH	148/4993 (3.0%)	107/4217 (2.5%)	OR 0.80 (0.60;1.07)	54 per 1.000	13 lower per 1.000 (from 22 lower to 2 higher)
--------------------	----------------	----------------	----------------	----------------	------	---------------------	--------------------	--------------------	------------------------	-----------------	--

Pioa	litazone
i iogi	TCGLOTIC.

Pioglitazone											
19.862 (22 RCTs)	not serious	not serious	not serious	not serious	Probably publication bias	⊕⊕⊕ ⊖ MODERATE	272/9527 (2.9%)	246/10335 (2.4%)	OR 0.91 (0.76;1.09)	29 per 1.000	3 lower per 1.000 (from 7 lower to 2 higher)
Insulin secret	tagogues	1		· · · · · · · · · · · · · · · · · · ·			1				1
50.539 (46 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH	897/26351 (3.4%)	794/24188 (3.3%)	OR 1.11 (1.00;1.23)	54 per 1.000	4 higher per 1.000 (from 0 to 8 higher)
DPP-4i		-	-			-					-
84.565 (57 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH	1908/42170 (4.5%)	1879/42395 (4.4%)	OR 0.98 (0.92;1.05)	66 per 1.000	2 lower per 1.000 (from 12 lower to 8 higher)
GLP-1 RA											
62659 (38 RCTs)	not serious	not serious	serious ^c	not serious	strong association	⊕⊕⊕ MODERATE	1974/29787 (4.5%)	1782/32872 (4.4%)	OR 0.89 (0.81;0.97)	66 per 1.000	7 lower per 1.000 (from 12 to 2 lower)
SGLT-2i		·	-			•			·		·
51053 (31 RCTs)	not serious	not serious	serious ^c	not serious	strong association	⊕⊕⊕ MODERATE	992/22508 (4.4%)	1076/28545 (3.8%)	OR 0.86 (0.79;0.94)	44 per 1.000	6 lower per 1.000 (from 9 to 3 lower)

Alpha-glucosidase inhibitors

1756 (6 RCTs) Insulin	seriousª	not serious	not serious	serious ^d	none	000 LOW	9/831 (1.1%)	7/925 (0.8%)	OR 0.76 (0.28;2.05)	11 per 1.000	3 lower per 1.000 (from 8 lower to 11 higher)
21454 (18 RCTs)	seriousª	not serious	not serious	not serious	none	OODERATE	1481/11694 (12.7%)	1151/9760 (11.8%)	OR 0.99 (0.91;1.08)	127 per 1.000	1 lower per 1.000 (from 10 lower to 9 higher)

HOSPITALIZATION FOR HEART FAILURE

Metformin

4.616 (6 RCTs)	not serious	not serious	serious ^c	not serious	none	⊕⊕⊕ MODERATE	37/2329 (1.6%)	40/2287 (1.7%)	OR 1.12 (0.65;1.92)	16 per 1.000	2 higher per 1.000 (from 6 lower to 14 higher)
Pioglitazone 11.970 (8 RCTs))	not serious	not serious	serious ^c	not serious	Probably publication bias	⊕⊕⊕ ○ MODERATE	178/5588 (3.2%)	229/6382 (3.6%)	OR 1.23 (0.91;1.65)	32 per 1.000	7 higher per 1.000 (from 3 lower to 20 higher)

Insulin secretagogues

24.281 (12 RCTs)	not serious	not serious	serious ^c	not serious	none	⊕⊕⊕ MODERATE	122/12094 (0.9%)	99/11377 (0.9%)	OR 0.92 (0.64;1.32)	9 per 1.000	1 lower per 1.000 (from 3 lower to 3 higher)
DPP-4i					1				<u> </u>		
61.726 (17 RCTs))	not serious	not serious	serious ^c	not serious	none	⊕⊕⊕ ○ MODERATE	907/30846 (2.9%)	979/30880 (3.2%)	OR 1.09 (0.96;1.23)	29 per 1.000	3 higher per 1.000 (from 1 lower to 7 higher)
GLP-1 RA				_	-			_	· ·		
49.847 (10 RCTs)	not serious	not serious	serious ^c	not serious	associazione forte	⊕⊕⊕ MODERATE	914/24391 (3.7%)	869/25450 (3.4%)	OR 0.94 (0.86;1.04)	37 per 1.000	2 lower per 1.000 (from 5 lower to 1 higher)
SGLT-2i	-		1		1			1			
34.777 (4 RCTs)	not serious	not serious	serious ^c	not serious	very strong association	⊕⊕⊕ ⊖ MODERATE	465/15485 (3.0%)	412/19292 (2.1%)	OR 0.70 (0.61;0.80)	30 per 1.000	9 lower per 1.000 (from 11 to 6 lower)
Alfa-glucosid	ase inhibitors		1		1						
-	-	-	-	-	-	-	-	-	-	-	-
Insulin			1								
21.454 (18 RCTs)	serious ^a	not serious	serious ^c	not serious	none	⊕⊕⊕ ⊖ MODERATE	1481/11694 (12.7%)	1151/9760 (11.8%)	OR 0.99 (0.91;1.08)	127 per 1.000	1 lower per 1.000 (from 10 lower to 9 higher)

Cl: Confidence interval; **OR:** Odds Ratio; **Explanations** a. *Open-label study; b. High/*Moderate heterogeneity; c. Indirect evidences; d. Limited sample size.

5.4.9.3 Grade of evidence in patients with previous cardiovascular events (with or without heart failure).

Certainty a	ssessmen	t					Summary of	findings			
Participants	Risk of				Publication	Overall	Study ever	nt rates (%)	Relative effect (95% CI)	Anticip	pated absolute effects
(studies) Follow up	bias	Inconsistency	Indirectness	Imprecision	bias	certainty of evidence	With Standard care	With Intensive glycemic control		Risk with placebo	Risk difference with intervention
MACE Metformin											
1,057 (2 RCTs)	not serious	not serious	not serious	serious ^d	very strong association	DD MODERATE	123/559 (22.0%)	62/498 (12.4%)	OR 0.52 (0.37;0.73)	220 per 1.000	92 lower per 1.000 (from 126 to 49 lower)
Pioglitazone		1	1		·	ſ					
13,499 (12 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH	503/6331 (7.9%)	455/7118 (6.4%)	OR 0.89 (0.78;1.02)	79 per 1.000	8 lower per 1.000 (from 16 lower to 1 higher)
Insulin secreto	igogues		1 1					1		11	
26,779 (14 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH	1012/13930 (7.3%)	881/12507 (7.0%)	OR 1.03 (0.87;1.22)	76 per 1.000	3 higher per 1.000 (from 6 lower to 15 higher)
DPP-4i			· ·		·	1	-	· · · · · · · · · · · · · · · · · · ·		· · ·	
61,726 (17 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH	2512/30846 (8.1%)	2495/30880 (8.1%)	OR 1.00 (0.94;1.06)	81 per 1.000	0 lower per 1.000 (from 5 lower to 4 higher)

GLP-1 RA

OLP-I NA											
49,829 (10 RCTs)	not serious	not serious	not serious	not serious	strong association	⊕⊕⊕⊕ HIGH	2888/24379 (11.8%)	2622/25450 (10.3%)	OR 0.89 (0.84;0.94)	118 per 1.000	12 lower per 1.000 (from 17 to 6 lower)
SGLT-2i											
34,777 (4 RCTs)	not serious	not serious	not serious	not serious	strong association	⊕⊕⊕⊕ HIGH	1396/15485 (8.3%)	1602/19292 (8.3%)	OR 0.89 (0.83 ;0.96)	90 per 1.000	9 lower per 1.000 (from 14 to 3 lower)
Alfa glucosid	ase inhibitors									-	
-	-	-	-	-	-	-	-	-	-	-	-
Insulin				1				1			
18,230 (6 RCTs)	seriousª	not serious	not serious	not serious	none	ODERATE	1535/10139 (15.1%)	1269/8091 (15.7%)	OR 1.09 (0.97;1.23)	151 per 1.000	11 lower per 1.000 (from 4 low er to 29 hig her

ALL-CAUSE MORTALITY

Metformin

9,210 (13 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH	148/4993 (3.0%)	107/4217 (2.5%)	OR 0.80 (0.60;1.07)	54 per 1.000	13 lower per 1.000 (from 22 lower to 2 higher)
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Pioglitazone

Pioglitazone											
19.862 (22 RCTs)	not serious	not serious	not serious	not serious	Probably publication bias	⊕⊕⊕ ⊖ MODERATE	272/9527 (2.9%)	246/10335 (2.4%)	OR 0.91 (0.76;1.09)	29 per 1.000	3 lower per 1.000 (from 7 lower to 2 higher)
Insulin secret	tagogues										
50.539 (46 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH	897/26351 (3.4%)	794/24188 (3.3%)	OR 1.11 (1.00;1.23)	54 per 1.000	4 higher per 1.000 (from 0 to 8 higher)
DPP-4i					1						
84.565 (57 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH	1908/42170 (4.5%)	1879/42395 (4.4%)	OR 0.98 (0.92;1.05)	66 per 1.000	2 lower per 1.000 (from 12 lower to 8 higher)
GLP-1 RA											
62659 (38 RCTs)	not serious	not serious	not serious	not serious	strong association	⊕⊕⊕⊕ HIGH	1974/29787 (4.5%)	1782/32872 (4.4%)	OR 0.89 (0.81;0.97)	66 per 1.000	7 lower per 1.000 (from 12 to 2 lower)
SGLT-2i	-	-	-	-		-	-	-			
51053 (31 RCTs)	not serious	not serious	not serious	not serious	strong association	⊕⊕⊕⊕ HIGH	992/22508 (4.4%)	1076/28545 (3.8%)	OR 0.86 (0.79;0.94)	44 per 1.000	6 lower per 1.000 (from 9 to 3 lower)

Alpha-glucosidase inhibitors

1756 (6 RCTs) Insulin	very seriousª	not serious	not serious	serious ^d	none		9/831 (1.1%)	7/925 (0.8%)	OR 0.76 (0.28;2.05)	11 per 1.000	3 lower per 1.000 (from 8 lower to 11 higher)
21454 (18 RCTs)	seriousª	not serious	not serious	not serious	none	OODERATE	1481/11694 (12.7%)	1151/9760 (11.8%)	OR 0.99 (0.91;1.08)	127 per 1.000	1 lower per 1.000 (from 10 lower to 9 higher)

HOSPITALIZATION FOR HEART FAILURE

Metformin

4.616 not (6 RCTs) seriou	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH	37/2329 (1.6%)	40/2287 (1.7%)	OR 1.12 (0.65;1.92)	16 per 1.000	2 higher per 1.000 (from 6 lower to 1 higher)
Pioglitazone										lower

Tiogintazoni	-										
11.970 (8 RCTs))	not serious	not serious	not serious	not serious	Probably publication bias	⊕⊕⊕⊕ HIGH	178/5588 (3.2%)	229/6382 (3.6%)	OR 1.23 (0.91;1.65)	32 per 1.000	7 higher per 1.000 (from 3 lower to 20 higher)

Insulin secretagogues

24.281 (12 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH	122/12094 (0.9%)	99/11377 (0.9%)	OR 0.92 (0.64;1.32)	9 per 1.000	1 lower per 1.000 (from 3 lower to 3 higher)
DPP-4i			•				•				•
61.726 (17 RCTs))	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH	907/30846 (2.9%)	979/30880 (3.2%)	OR 1.09 (0.96;1.23)	29 per 1.000	3 higher per 1.000 (from 1 lower to 7 higher)
GLP-1 RA								_	ч н -		
49.847 (10 RCTs)	not serious	not serious	not serious	not serious	associazione forte	⊕⊕⊕⊕ HIGH	914/24391 (3.7%)	869/25450 (3.4%)	OR 0.94 (0.86;1.04)	37 per 1.000	2 lower per 1.000 (from 5 lower to 1 higher)
SGLT-2i				-	-						
34.777 (4 RCTs)	not serious	not serious	not serious	not serious	very strong association	⊕⊕⊕⊕ HIGH	465/15485 (3.0%)	412/19292 (2.1%)	OR 0.70 (0.61;0.80)	30 per 1.000	9 lower per 1.000 (from 11 to 6 lower)
Alfa-glucosia	lase inhibitors		I	1	1		1	T		I	
1.756 (6 RCTs)	very serious ^a	not serious	not serious	serious ^d	none	⊕⊕⊖⊖ LOW	9/831 (1.1%)	7/925 (0.8%)	OR 0.76 (0.28;2.05)	11 per 1.000	3 lower per 1.000 (from 8 lower to 11 higher)

Insulin

21.454 (18 RCTs)	serious ^a	not serious	not serious	not serious	none	⊕⊕⊕ MODERATE	1481/11694 (12.7%)	1151/9760 (11.8%)	OR 0.99 (0.91;1.08)	127 per 1.000	1 lower per 1.000 (from 10 lower to 9 higher)
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Cl: Confidence interval; OR: Odds Ratio; Explanations a. Open-label study; b. High/Moderate heterogeneity; c. Indirect evidences; d. Limited sample size.

5.4.10. Pharmacoeconomic evidence

Author	Country	Intervention	Type of analysis	Incremental cost	Incremental cost (QALY)	Incremental cost per QALY gained	Authors' conclusions
Johnston R 2017 ⁹³	UK, National healthcare perspective	Different available drugs for patients who cannot take metformin: empagliflozin, canagliflozin, dapagliflozin, sitagliptin, pioglitazone, gliclazide, repaglinide	Cost-utility, lifetime (40 yrs)	Pioglitazone is the cheapest alternative, glicazide and sitagliptin had higher costs vs pioglitazone, canagliflozin, empagliflozin and higher costs vs pioglitazone, sitagliptin and glicazide; flozins slightly increased QALY vs gliptins, pioglitazone nd SU	Glicazide and sitagliptin had lower QALY (vs pioglitazone), canagliflozin, empagliflozin and dapaglifozin had higher QALYs (vs pioglitazone, sitagliptin and glicazide); flozins increased costs vs gliptins, pioglitazone nd SU	Pioglitazone is the cheapest alternative and both glicazide and sitagliptin are dominated by it having lower QALYs and higher costs. Canagliflozin, empagliflozina and dapaglifozin had higher QALYs and costs (vs pioglitazone) but they showed ICURs higher than common accepted WTP, they are indeed cost- effective compared with sitagliptin and glicazide for WTP well below standard tresholds; flozins ere cost-effective vs both gliptins and pioglitazone for WTP <20,000 £/QALYs, while vs SU ICUR were above conventional thresholds; repaglinide could be cost-effective as	Dapagliflozin, canagliflozin and empagliflozin in monotherapy do not appear cost-effective compared with gliclazide, pioglitazone or repaglinide, but may be competitive against sitagliptin

Appendix

						compared to gliclazide if we incorporate into the model the possible effects of drugs on BMI, on the other hand with this hypothesis other strategies are dominated and canagliflozin suggested ICUR over conventional WTP	
Shyangdan D 2011 ⁹⁴	UK, National healthcare perspective	Liraglutide vs different available drugs for patients who cannot take metformin (glargine, sitagliptin and exenatide)	Cost-utility, lifetime (40 yrs)	Liraglutide increased QALY as compared with alternatives lowering blood glucose and avoiding weight gain and hypoglycaemia	Csost were also higher for liraglutide vs alternatives	ICUR was £15,130 per QALY for liraglutide 1.8 mg compared with glargine, £10,054 per QALY for liraglutide 1.8 mg compared with exenatide, £10,465 per QALY for liraglutide 1.8 mg compared with sitagliptin and £9851 per QALY for liraglutide 1.2 mg compared with sitagliptin	Liraglutide may be a cost-effective option for T2DM patients not achieving good glicaemic control with metformin
Geng J 2015 ⁹⁵	Different healthcare systems, 2013 US\$	DPP-4i vs insulin, thiazolidinediones, sulfonylureas	Cost-utility	DPP-4i increased QALYs vs SU; DPP-4i generally increased QALYs vs TDZs; similarly vs insulin	DPP-4i also increased costs vs SU; vs both TDZs and insulin the impact on costs varied depending on the context	ICUR suggested DPP- 4i could be cost- effective as compared to SU in different contexts, not in Canada; when compared to TDZs ICURs largely varied anyway in most cases DPP-4i dominated or were	Whether add-on DPP-4 inhibitor therapy is cost- effective compared with thiazolidinediones remains uncertain. DPP-4 inhibitors may be an attractive treatment option from a payer perspective. High-quality cost-effectiveness analyses that utilize

Appendix

						cost-effective; compared to insulin DPP-4i were cost- effective or even dominant	long-term follow-up data and have no conflicts of interests are still needed
Hong D 2019 ⁹⁶	Different healthcare systems, 2013 US\$	GLP-1, SGLT-2, DPP-4i vs other agents	Cost-utility	When compared to insulin the impact on QALYs largely varied; vs TDZs newer drugs increased QALYs, similarly vs SU	Compared to insulin the impact on costs largely varied; vs TDZs newe drugs increased costs; results were quite similar vs SU	Compared to insulin ICUR suggested different results in different contexts and according to the different analyses; ICURs values suggested the cost- effectivenes of newer drugs vs TDZs, results were also generally positive vs	Newer antidiabetic medications in most of the reviewed studies were found to be cost effective, compared with insulin, TZDs, and sulfonylureas
Bruhn 2016 ⁸	US Healthcare payer , 2014 US dollar	Albiglutide vs insulin lispro (both combined with ins. Glargine); Albiglutide vs insulin glargine; Albiglutide vs Sitagliptin	Cost-utility (50 years)	Albiglutide increased costs as compared to insulin lispro of about \$4,332; Albiglutide increased costs as compared to insulin glargine by \$2,597; Albiglutine incresed costs compared to sitagliptin of +\$2,223	Albiglutide improved both life expectancy vs insulin lispro of +0.099 and QALYs of about +0.099; Albiglutide modestly improved life expectancy and QALY vs insulin glargine (+0.017 and +0.033 respectively) and reduced diabetes- related complications; Albiglutide increased both life expectancy of +0.11 compared to sitagliptin and QALY by +0.101 reducing diabetes-related complications	SU ICER for albiglutide vs insulin lispro was \$43,541 per QALY; ICER for albiglutide vs insulin glargine was \$79,166 per QALY; ICER vs sitagliptin aws \$22,094 per QALY	At a WTP of \$100,000 per QALY albiglutide was cost-effective vs all comparators; at a WTP of \$50,000 per QALY albiglutide was cost- effective vs sitagliptin and insulin ispro

Tzanetakos 2017 ⁹⁷	Greek thirdy payer, Euro 2016	Exenatide vs Insulin Glargine; Exanatide vs Liraglutide	Cost-utility (40 years)	Exenatide increased direct health costs vs insulin glargine of €2,061; Exenatide slightly incresed costs vs Liraglutide (+€110)	Exenatide increased both life expectancy and QALY vs Insulin glargine of +0.003 and +0.458 respectively reducing the risk of events; Compared to Liraglutide, Exenatide increased both life expectancy and QALY of +0.004 and +0.039 reducing the risk of cerebrovascular events and cardiovascular complications.	ICER for exenatide vs insulin glargine was €4,499 per QALY; ICER vs Liraglutide was €2,827 per QALY	Exenatide is a cost- effective option for T2DM poorly controlled with OAD when compared to insulin glargine at various WTP, similary when comparing exenatide to Liraglutide and considering a WTP >=€20,000 per QALY
Hunt 2017 ⁹⁸	Italy NHS, Euro 2015	Liraglutide vs lixisenatide	Cost-utility (lifetime)	Liraglutide was associated with marginally higher lifetime costs (€243)	Liraglutide increased both life expectancy and QALY (+0.11 and +0.12 respectively) reducing and/or delaying diabetes- related complications	The ICER for Liraglutide vs lixisenatide was €2,001 per QALY	Liraglutide had a probability of 77.2% of beingcost-effective at the commonly quoted WTP threshold of €30,000 per QALY
Kvapil 2017 ⁹⁹	Czech republic public payer perspective , 2016 CZK	IdegLira vs BBT	Cost-effectiveness and cost-utility (50 years)	IDegLira also resulted in higher costs, +107,829CZK	IDegLira reduced and/or delayed onset of diabetes related complications thus increasing both life expectancy by +0.10 and QALY by +0.31	ICER was CZK 1,043,842 per LY and ICUR was CZK 345,052 per QALY	IDegLira is likely to be cost- effective versus BBI at the commonly accepted WTP threshold in the Czech Republic of CZK 1,100,000 per QALY gained.
Gu 2017 ¹²	China healthcare payer perspective, 2014 Chinese Yuan	Exenatide vs Insulin glargine	Cost-utility (40 years)	Exenatide was associated with lower costs because of lower drug costs and reduced costs of events, - 177,706 Y	Exenatide resulted in both higher QALY (+1.94) and increased LY (+0.03)	Exenatide was dominant	Exenatide was a superior therapy (with higher total QALY benefits gained but lower total costs) to insulin glargine

Appendix

							offering an effective third-line therapy for the management of T2DM. The cost-effectiveness results remained stable in the sensitivity analyses.
Davies 2016 ¹⁰⁰	United Kingdom (NHS)	IDegLira vs Basal Insulin+Liraglutide	Cost-utility (40yrs)	Compared with both Basal Insulin+Liraglutine and IGlar+3xIAsp and Up- titrated IGlar, increasing	Compared with both Basal Insulin+Liraglutine and	Compared with both Basal Insulin+Liraglutine	IDegLira was higly cost- effective (of even dominant) highly cost-
	2015 GBP	IDegLira vs IGlar+3xIAsp		QALYs of +0.123, +0.414 and +0.237 respectively.	IGlar+3xlAsp, IDegLira reduced overall healthcare costs (- £971 and -£1,698) because of avoided-	and IGlar+3xlAsp, IDegLira was dominant increasing QALYs and reducing overall healthcare.	effective treatment option vs. current insulin intensification options for type 2 diabetes
		IDegLira vs Up-titrated IGlar			diabets-related complications.	Compared with up-	patients uncontrolled on basal insulin from the UK NHS perspective
					Compared with up- titrated IGlar, IDegLira increased costs (+£1,441) because of higher acquisition price.	titrated IGlar, IDegLira showed an ICER of £6,090 per QALY. Results remained consisten at sensitivity analyses.	
Kousoulakou 2017 ¹⁰¹	Greek Social Insurance funds perspective, Euro 2014	Vildagliptin vs glimepiride	Cost-effectiveness and cost-utility (lifetime)	The addition of vildagliptin to metformin increased pharmaceutical cost compared with the addition of glimepiride to metformin that were offset by a decrease in the associated comorbidity and adverse event costs, resulting in a lower total cost for glimepiride -€74	Vildagliptin was also associated withincreased LY (+0.11) and increased QALY (+0.11)	Vildagliptin was dominant	Vildagliptin as add-on treatment to metformin in the management of T2DM in Greece appears to be dominant versus glimepiride in terms of both cost per LY and cost per QALY gained.

Hunt 2017 ¹⁰²	The Netherlands, health payer perspective Treatment costs correct as of April 2016, other costs expressed in 2015 EUR	IDegLira vs IGlar U100+3x IAsp (basal-bolus Therapy) Patients received IgDegLira for the first five years of the analysis, after they are switched to basal-bolus therapy. Patient receiving basal bolus terapy remain it for the duration of their lifetime	Cost-utility analysis (lifetime, 50 years)	Mean cost per patient in IDegLira group was €4679 lower than basal-bolus therapy. Discounted direct costs (€) IDegLira vs bolus: 58.014 vs 62.62 The pharmacy cost over the first 5 years of the anlysis was lower in IdDegLira.	IDegLira vs basal bolus Discountd life expencanty (years) 16.74 vs 16.49 QALYs 10.61 vs 10.18	IDegLira was dominant	IDegLira was less costly and more effective. IDegLira was an effective alternative for patients with diabetes uncontrolled on basal insulin reducing the risk of hypoglycemia and weight gain resepct to basal bolus therapy.
Mezquita-Raya 2017 ¹⁰³	Spain NHS, Euro 2015	Liraglutide vs Lixisenatide (both for 3 yrs then insulin) in add-on to met	Cost-effectiveness and cost-utility (lifetime)	Liraglitide increased costs (+€454) because of higher drug costs in the first 3 years that were partially offset by reduced diabetes complications	Liraglutide increased both LY (+0.12) and QALY (+013) bacuse of a reduced cumulative incidence of diabetes- related complications	ICER was €4,493 per LY and ICUR €4,113 per QALY for Liraglitide vs lixisenatide	Liraglutide is likely to be a cost-effective add-on therapy to metformin for Spanish patients with type 2 diabetes at commonly accepted WTP. Sensitivity analyses showed that the ICER would increase to €37,282 per QALY gained if the HbA1c difference between the two treatments were to be abolished

Ericsson 2017 ¹⁰⁴	Sweden Societal perspective, SEK 2013	IDegLira vs different treatment intensification strategies (added to met?)	Cost-utility (40 years)	IDegLira strongly reduced costs vs insulin+NPH/glargine insulin (-€47,200 and - €115,200 respectively). Costs were also slightly loer for IDegLira vs Liraglutide+insulin glargine (-€3,500). On the contrary when compared with Liraglitide+NPH insulin, insulin glargine and NPH insulin liraglutide resulted in higher costs (+€24,000, +€27,700, +€68,400 respectively)	IDegLira increased QALy as compared to insuling glargine, NPH insulin (+0.97 for both), insulin aspart+insulin glargine, insulin aspart+NPH insulin (+2.14 for both) and liraglutide+insulin glargine, liraglutide+NPH insulin (0.40 for both)	IDegLira was dominant vs insulin aspart+insulin glargine, insulin aspart+NPH insulin and liraglutide+insulin glargine. ICUR values for IDegLira were €28,400 per QALY when compared to insulin glargine, €70,100 per QALY vs NPH insulin and €60,000 per QALY vs Liraglutide+NPH insulin	IDegLira may be cost effective for the treatment of patients with T2DM that is uncontrolled with basal insulin therapy in Sweden; IDegLira was either cost effective, with an ICER of SEK70,000 or lower (vs. basal insulin up- titration or vs. adding GLP1 to basal insulin), or both more effective and cost saving (vs. basal bolus regimens)
Zhang 2016 ¹⁰⁵	China 2012 RMB societal perspective	Oral Meformin plus liragludine vs metformin plus exenatide. Patients were followed up for 52 weeks	Cost-effectiveness (30 years)	Total cost of liraglutide treatment amount to 407,582 RMB vs 412,065 in exanatide group (difference 4,483). The cost of cardiovascular diseases iwas higher in exenatide group (+6,073 RMB).	Liraglutide vs Exenatide (30 years) <i>Life expectancy (years)</i> 14.506 vs 14.369 <i>QALYs</i> 10.018 vs 9.630	ICER for Liraglutide vs Exenatide -11,550 RMB/QALys	Liraglutide results superior to exenatide. The study shows that once-a-day injection of Liraglutide is uperior to twice-a-day injection of Exenatide in terms of costs and effectiveness. This is the first study related to long term effectivess and cost- effectiveness of Metformin combined with Liraglutude or Exenatide based on diabetes model on Chinese population.

Gu 2016 ¹⁰⁶	China/2015 Chinese Yuan healthcare perspective	Dapagliflozin vs Acarbose as monotherapy. The study uses the Cardiff Diabetes Model.	Cost-effectiveness (40 years)	Dapagliflozin vs Acarbose Discounted costs accumulated over 40 years ¥161,010.05 vs ¥ 169,449.46	Dapagliflozin was associated with a mean incremental benefit of 0.25 QALYs and a lower cost of ¥ 8,439 versus acarbose arm. Cost saving: ¥ 33,786 per QALY gained	Dapagliflozin dominates acarbose	The model shows that Dapagliflozin has lower incidences of cardiovascular events, hypoglycemia and mortality. Dapagliflozin has lower costs and higher QALY gained for patient over a 40 year time horizon.
Hunt 2017 ¹¹	USA, healthcare perspective	IDegLira versus Insulin glargine U100 with re-education and up-titration of the dose for treatment of patients failing to acheicve glycemic control on basal insulin.	Cost-effectiveness (lifetime, 50 years)	IDegLira vs insulin glargine Total Annual treatment costs \$10,280.24 vs \$6733.53 (based on wholesale acquisation costs derived from DUAL V trial) Meand direct cost per patient cost of IDegLira was \$16,970 higher than insulin glargine (increasedacquistion cost of IDegLira over first 5 years of analysis). IDeglLira impacts on the decrease of cardiovascular complications (mean cost saving for patient of \$527) and ulcer/amputation/neuropa tiy complications (cost saving of \$369 per patient)	IDegLira wasassociate with an ICER of \$63,678 per QALY gained vs insulin glargine. ICER (life expencantcy): \$96,039 per life year gained.	IDegLira was cost- effective	IDegLira improves the long term clinical outcomes for patients with diabetes 2 not achieving the glycemic control on basal insulin compared to re- eductaion and up- tritation of the dose of insulinglargine U100.

Vega-Hernandez 2017 ¹⁰⁷	UK, national payer perspective GBP 2016	Liraglutide 1.2 and 1.8 mg/day versus Dapagliflozin 10 mg as a part a dual and a triple antidiabetic therapy.	Cost-effectiveness (lifetime)	Dual therapy: liraglutide vs dapagliflozin <i>liraglutide 1.2 mg</i> -higher treatment costs -lower complication costs -lower total costs Lower costs are associated with lower incidence of complications. <i>liraglutide 1.8 mg</i> -higher total costs -higher treatment costs -lower complication costs	Dual therapy: <i>liraglutide 1.2 mg</i> -higher QALYs -increase of life expenctancy <i>liraglutide 1.8 mg</i> -higher life expectancy and QALYs Triple Therapy: liraglutide 1.2 mg vs dapagliflozin: QALY gain of 0.064 liraglutide 1.8 mg vs dapagliflozin: QALY gain of 0.067	Liraglutide 1.2 mg was dominant in the majority of sensitivity analysis. Liraglutide 1.8 mg is cost-effectiveness across the majority of analysis.	Liraglutide 1.2 mg and 1.8 mg are cost- effectivess respect to dapagliflozin in dual and triple therapy.
Hunt 2017 ¹⁰	UK, NHS healthcare payer perspective, 2015£	Liraglutide 1.8 mg versus lixesenatide 20 µg admistres once daily in patients failing to achieve glycaemic control on metfromin monotherapy.	Cost-effectiveness (20-10 years)	Base case Liraglutide 1.8 mg vs Lixisenatide 20 µg Discounted costs (£): mean direct costs 37,158 vs 36,174 *The increased cost is due to the higher acquistion cost of liraglutide over the first 3 years of the analysis. These costs are offset by reduced costs of complications.	Liraglutide vs Lixisenatide <i>Discounted life</i> <i>expectancy (years)</i> 13.54 vs 13.45 <i>QALYs</i> 8.87 vs 9.76	ICER : life expectancy £10,351 per life-year gained ICER: QALYS £8901 per QALY gained Liraglutide 1.8 mg is cost-effectiveness in UK setting.	Liraglutide 1.8 mg results cost-effectiveness respect to lixisenatide in treatment of patients failing to ahcieve the glycaemin controls on metformin monotherapy. Liraglutide improves life expectancy and the quality-adjsuted life expectancy.
Hunt 2017 ¹¹	USA, healthcare perspective 2015 US dollars	IDegLira versus Liraglutide added to basal insulin.	Cost-effectiveness (20-10 years)	Base case IDegLira vs Liraglutide <i>Discounted direct costs (\$)</i> 206,385 vs 223,072 (- 17,687) Cost savings are due to lower acquisition cost of IDegLIra vs Liraglutide added to basal insulin over firts 5	IDegLIra vs Liraglutide Discounted life expectancy (years) 14.0 vs 14.02 Discounted QALYs 8,94 vs 8,91	ICER (life expectancy): IDegLira is dominant ICER (QALYs): IDegLira is dominant	IDegLira results dominant compared to Liraglutide added to basal insulin for patiens failing to achieve the glycemic control on basal insulin. IDegLira reduces the diabetes-related

Appendix

				year of the analysis. Lower acquisition costs are due to lower dose of liraglutide received as part of IDegLira. Furthermore, avoided diabeters-related complications.			complications over patient's lifetime.
Roussel 2016 ¹⁰⁸	France, healthcare perspective, 2013€	Liraglutide vs Sitagliptin Liraglutide vs Glimepiride	Cost-effectiveness (5,10,20 years)		Liraglutide vs Sitagliptin Undiscounted life expectancy (years) 23.46 vs 23.05 Discounted life expectancy (years) 15.62 vs 15.43 QALYs 10.09 vs 9.84 Liraglutide vs Glimepiride Undiscounted life expectancy (years) 23.48 vs 23.16 Discounted life expectancy (years) 15.63 vs 15.47 QALYs 10.25 vs 10.02	Liraglutide is associated with ICERs of €10,436 and €20,709 per QALYs gained respect to Sitagliptin and Glimepiride.	Liraglutide is cost- effectiveness respect to Sitagliptin and Glimepiride from a healthcare payer perspective.
Chuang 2016 ¹⁰⁹	UK, NHS perspective, 2014£	Exenatide QW vs Dulaglutide 1.5 mg QW Exenatide QW vs Liraglutide 1.2 mg QD (once-daily) Exenatide QW vs Liraglutide 1.8 mg QD Exenatide QW Lixisenatide 20 µg QD In adults inadequately controlled on	Cost-effectiveness (lifetime)	Base case Total lifetime costs (per patient) Exenatide: €19,930 Dulaglutide 1.5 mg QW: €19,903 Liraglutide 1.2 mg QD: €19,827 Liraglutide 1.8 mg QD: €22,016	Base case QALYs (per patient) Exenatide: 11.279 Dulaglutide 1.5 mg QW: 11.233 Liraglutide 1.2 mg QD: 11.177 Liraglutide 1.8 mg QD: 11.236 Lixisenatide 20 µg QD: 11.206	Exenatide QW is cost-effective respect other treatments. Better efficacy in term od HbA1c and body weight reduction.	This is the first simulation related to the cost- effectiveness of Exenatide QW respect to newer GLP-1 Receptor Antagonist in patients non adequately controlled on metformin alone.

Appendix

		metformin alone and in whom other oral drugs are not effective, suboptimal or contraindicated.		Lixisenatide 20 µg QD: €19,192			
Gordon 2016 ¹¹⁰	Sweden, heathcare perspective, 2015€ (SEK converted in €)	Exenatide twice daily versus Insulin lispro 3 times daily in add on therapy with insulin glargine	Cost-effectiveness (lifetime, 40 years)	Base case Exenatide vs Lispro <i>Expected costs</i> 44,526 vs 43,256 <i>Discounting 0%</i> 64,850 vs 63,665 Discounting 6% 32,968 vs 31,678	Base case Exenatide vs Lispro <i>QALYs</i> 11.51 vs 10.86 Discounting 0% 15.99 vs 15.11 Discounting 6% 8.87 vs 8.37	The cost per QALY gained with Exenatide respect to LIspro is €1,971. QALY increase of +0.64 compared to Lispro over 40 years	Exenatide BID results a cost-effectiveness treatment respect to Lispro TID as add-on therapy in patients with a scarce control of basal insulin.
Tzanetakos 2016 ¹¹¹	Greece, third- party payer, 2015€	Dapagliflozin on add on to metformin versus Sulfonylureas plus metformin or DPP-4i in adjunct to metformin in patients indadeguately controlled on metformin alone.	Cost-effectiveness (lifetime, 40 years)	Base case Met+Dapa vs Met+SU Discounted total lifetime direct medical costs (€) 24,997 vs 19,855 Met+Dapa vs Met+DPP-4i Discounted total lifetime direct medical costs (€) 25,088 vs 24,332	Base case Met+Dapa vs Met-SU Discounted life expectancy (years) 14.77 vs 14.76 Discounted QALYs 12.22 vs 11.73 Met+Dapa vs Met+DPP-4i Discounted life expecatancy (years) 14.71 vs 14.70 Discounted QALYs 12.24 vs 12.19	Met+Dapa versus Met+SU ICER: 10,623€ Met+Dapa versus Met+DPP-4i ICER: 17,695€	In the probabilistic sensitivity analysis: dapa+ Met is associated with 100% or 79.7% probability of being cost-effective respect to SU+Met or DPP-4i + Met (WTP threshold of €34,000 per QALY gained. Dapagliflozin with metformin results cost- effectiveness for patients don't achieve sufficient glycemic control in the Greek setting.

Sabapathy 2016 ¹¹²	Canada, perspective of Canadian Agency for Drugs and Technologies in Health (CADTH)	Canagliflozin 300 mg vs Sitagliptin 100 mg, Canagliflozin 100 mg vs Sitagliptin 100 mg in patients with not adequately controlled with metformin plus sulfonylurea.	Cost-effectiveness (40 years)	Base case CANA 300 mg vs SITA 100 mg <i>Total costs (\$)</i> 44,680 vs 46,897 (difference -2,217) CANA 100 mg vs SITA 100 mg 45,247 vs 47,807 (difference -2,560)	Base case CANA 300 mg vs SITA 100 mg <i>LYs</i> 11.99 vs 11.76 (difference 0.23) <i>QALYs</i> 8.65 vs 8.35 (difference 0.31) CANA 100 mg vs SITA 100 mg <i>LYs</i> 12.04 vs 11.83 (difference 0.21) <i>QALYs</i> 8.64 vs 8.37(difference 0.28)	Canagliflozin (300 mg and 100 mg) is associated with cost savings and impreved quality of life versus Sitagliptin	Canagliflozin have near 100% likelihoods of being cost.effectivenss at all WTP. Sensativity analysis shows that Canagliflozin dominating Sitagliptin in each scenario
Gordon 2016 ¹¹⁰	UK National Healthcare System Perspective, £ 2015	Met+Alogliptin (DPP4i) 12.5 or 25mg vs Met+SU	Costeffectiveness and cost-utility (lifetime)	Alogliptin implied higher costs (+£1,131 for 12.5mg and +£1,012 per QALY for 25mg) because of higher cost acquisition that was partially offset by reduction in complications costs (particularly CVD complications)	Alogliptin implied both higher LE (+0.044 for 12.5mg and +0.081 for 25mg) and higher QALY (0.103 and 0.14 for 12.5mg and 25mg respectively)	ICER for alogliptin was £25,588 per LE and £12,476 for 12.5mg and 25mg respectively, similarly ICUR were £10,959 and £7,217 respectively	Alogliptin, in combination with metformincost-effective treatment alternative to SU as add-on therapy to metformin in patients with poorly managed T2DM
Gu et al. 2016 ¹⁰⁶	China health insuerance payer perspective, 2014 Chinese Yuan	Saxagliptin+Met vs Acarbose+Met	Cost-effectiveness and cost-utility (40 years)	Saxa+Met resulted in reduced costs mainly because of the beneficial effect on BMI and hypoglicemia despite higher costs for congestive HF, stroke and nephropathy	Saxa+Met resulted in both higher LY (+0.02) and QALY (0.48)	Saxa+Met was dominant	SAXA+MET was dominant over ACAR +MET, with a little QALYs gain and lower costs for Chinese patients with T2DM who were inadequately controlled following MET monotherapy

Permsuwan et al. 2016 ¹¹³	Thai National healthcare system perspective, US\$ 2014	DPP4-i monotherapy (saxagliptin, sitagliptin and vidagliptin) vs MET; DPP4-i monotherapy (saxagliptin, sitagliptin and vidagliptin) vs SU	Cost-effectiveness and cost-utility (lifetime)	All DPP4-i increased costs both as compared to MET and SU	All DPP4-i decresed QALY compared to MET, while increased QALY when compared to SU (+0.031 for all)	DPP4-i were dominated when compared to Met, while compared to SU ICURS were comprised between US\$110,215 per QALY to US\$137,456 per QALY being above the Thai threshold	DPP-4 inhibitor monotherapy was not a cost-effective treatment for elderly T2DM patients in Thailand compared to either SFU monotherapy or metformin monotherapy; efficacy in HbA1c reduction, risk of severe hypoglycemia, and cost of DPP-4 inhibitors play an important role in the findings of the study.

5.5. Basal and prandial insulin therapy

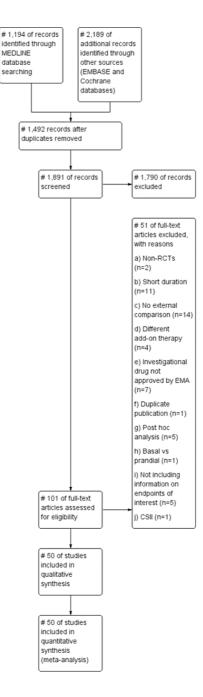
The systematic review has been already submitted to a medical journal. A Medline and EMBASE search was conducted up to January, 1st, 2020.

RCT assessing the efficacy of insulin analogues (lispro, aspart, glulisine, detemir, glargine, and degludec) in comparison with another different insulin analogue or human insulin, with duration of at least 24 weeks, enrolling participants with type 2 diabetes, aged \geq 18 years.

The primary outcome was HbA1c at 24, 52, and 104+ weeks. Secondary endpoints included:

- a) Fasting plasma glucose (FPG) at endpoint
- b) Body mass index (BMI) at endpoint
- c) Number of subjects with any, severe, and nocturnal hypoglycemia
- d) Quality of Life (QoL)

5.5.1. Trial flow summary



5.5.2. Hypoglycemia in trials with basal insulin therapy

Forest plot for trials comparing the effects of long-acting basal insulin and NPH on total (Panel A), nocturnal (Panel B), and severe (Panel C) hypoglycaemia.

Α

	Long-acting ana	logues	NPH	1		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI	ABCDEFG
1.6.1 Detemir								
Haak 2005	152	341	80	164	9.5%	0.84 [0.58, 1.23]		?
Hermansen 2006	151	236	191	237	8.8%	0.43 [0.28, 0.65]		
Fajardo 2008	43	125	95	146	7.6%	0.28 [0.17, 0.47]	<u> </u>	
Subtotal (95% CI)		702		547	25.9%	0.47 [0.25, 0.89]		
Total events	346		366					
Heterogeneity: Tau ² = 0	0.26; Chi ² = 13.06, c	If = 2 (P =	0.001); 12	= 85%				
Test for overall effect: Z	= 2.31 (P = 0.02)							
1.6.2 Glargine								
Hsia 2011	47	55	23	30	2.7%	1.79 [0.58, 5.54]		→ ??●●●●●
Yokoyama 2006	15	31	13	31	3.2%	1.30 [0.48, 3.54]		?? 🔴 🖶 🖶 🖲
Home 2015	128	352	125	349	10.6%	1.02 [0.75, 1.39]		
Fritsche 2003	330	463	173	232	9.8%	0.85 [0.59, 1.21]		
Rosenstock 2001	159	259	173	259	9.7%	0.79 [0.55, 1.13]		?
Massi Benedetti 2003	103	289	117	281	10.1%	0.78 [0.55, 1.09]		
Yki-Jarvinen 2000	71	214	87	208	9.1%	0.69 [0.46, 1.03]		
Eliaschewitz 2006	122	231	157	250	9.7%	0.66 [0.46, 0.95]		?? 🔴 🖶 🕀 😉
Fonseca 2004	24	52	29	48	4.5%	0.56 [0.25, 1.24]		? • • • • • • •
Yki-Jarvinen 2006	26	61	28	49	4.8%	0.56 [0.26, 1.19]		
Subtotal (95% CI)		2007		1737	74.1%	0.80 [0.70, 0.92]	•	
Total events	1025		925					
Heterogeneity: Tau ² = 0).00; Chi ² = 8.61, df	= 9 (P = 0	.47); 2 =	0%				
Test for overall effect: Z	= 3.14 (P = 0.002)							
Total (95% CI)		2709		2284	100.0%	0.70 [0.57, 0.86]	•	
Total events	1371		1291					
Heterogeneity: Tau ² = 0	0.08; Chi ² = 31.23, c	f=12 (P:	= 0.002);	1ª = 629	Xó	0.2	0.5 1 2	-
Test for overall effect: Z	= 3.37 (P = 0.0007)	11				U.5 1 2 rs [Long-acting] Favours [NPH]	*
Test for subgroup differ			= 0.11). [² = 60.8	196	Favou	is [Long-acting] Favours [NPH]	

В

	Long-acting anal		NPH			Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
1.8.1 Detemir								
Haak 2005	52	341	38	164	9.8%	0.60 [0.37, 0.95]		? • • • ? • •
Hermansen 2006	71	236	112	237	11.1%	0.48 [0.33, 0.70]		
Fajardo 2008	37	125	102	146	9.0%	0.18 [0.11, 0.31]		
Subtotal (95% CI)		702		547	29.9%	0.38 [0.20, 0.73]		
Total events	160		252					
Heterogeneity: Tau ² = 0		= 2 (P = 1	0.002); I²	= 84%				
Test for overall effect: Z	= 2.91 (P = 0.004)							
1.8.2 Glargine								
Hsia 2011	9	55	3	30	2.6%	1.76 [0.44, 7.07]		- ?? 🛑 🖶 🕀 🗣
Home 2015	56	352	68	349	10.9%	0.78 [0.53, 1.15]		
Rosenstock 2001	81	259	104	259	11.4%	0.68 [0.47, 0.97]		? • • • • • •
Fonseca 2004	8	52	13	48	4.4%	0.49 [0.18, 1.31]		? • • • • • •
Eliaschewitz 2006	47	231	87	250	10.6%	0.48 [0.32, 0.72]		?? 🔴 🔁 🔁 🔁
Massi Benedetti 2003	35	289	68	281	10.1%	0.43 [0.28, 0.67]		
Fritsche 2003	91	463	89	232	11.5%	0.39 [0.28, 0.56]		
Yki-Jarvinen 2000	21	214	48	208	8.6%	0.36 [0.21, 0.63]		•••••
Subtotal (95% CI)		1915		1657	70.1%	0.53 [0.41, 0.67]	◆	
Total events	348		480					
Heterogeneity: Tau ² = 0).06; Chi ² = 14.14, df	= 7 (P = I	0.05); I² =	: 51%				
Test for overall effect: Z	= 5.09 (P < 0.00001)						
Total (95% CI)		2617		2204	100.0%	0.48 [0.38, 0.62]	•	
Total events	508		732				-	
Heterogeneity: Tau ² = 0	0.11; Chi ² = 29.48, df	= 10 (P =	0.001);	l ² = 669	%			
Test for overall effect: Z	= 5.77 (P < 0.00001)					0.1 0.2 0.5 1 2 5 vours [Long-acting] Favours [NPH	10
Test for subgroup differ	rences: Chi ² = 0.86,	df = 1 (P :	= 0.36), P	²= 0%		Fa		1
		-						

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	Long-acting ana		NPI			Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl	ABCDEFG
1.7.1 Detemir								
Swinnen 2010	14	478	12		23.7%	1.19 (0.55, 2.60)		
Hermansen 2006	1	236	6		3.8%	0.16 [0.02, 1.37]	← · · · · · · · · · · · · · · · · · · ·	
Subtotal (95% CI)		714		723	27.5%	0.57 [0.08, 3.83]		
Total events	15		18					
Heterogeneity: Tau ² = 1		= 1 (P = 0	.08); I² =	67%				
Test for overall effect: Z	= 0.58 (P = 0.56)							
1.7.2 Glargine								
Home 2015	3	352	1	439	3.3%	3.77 [0.39, 36.35]		+ + + + + + + + + + + + + + + + + + +
Massi Benedetti 2003	5	289	3	281	8.0%	1.63 [0.39, 6.89]	-	
Riddle 2003	9	367	7	389	15.6%	1.37 [0.51, 3.72]	+ •	
Bolli 2015	4	439	4	439	8.5%	1.00 [0.25, 4.02]		
Fritsche 2003	9	463	6	232	14.4%	0.75 [0.26, 2.12]		
Eliaschewitz 2006	6	231	11	250	15.3%	0.58 [0.21, 1.59]		?? 🗣 🗣 🗣 🗣
Fonseca 2004	0	52	1	48	1.7%	0.30 [0.01, 7.58]	·	?•••••
Betonico 2019	0	29	2	29	1.8%	0.19 [0.01, 4.06]	·	
Rosenstock 2001	1	259	6	259	3.8%	0.16 [0.02, 1.37]	• • • • • • • • • • • • • • • • • • •	?
Yki-Jarvinen 2000	0	214	0	208		Not estimable		
Yokoyama 2006	0	31	0	31		Not estimable		??●●●●
Yki-Jarvinen 2006	0	61	0	49		Not estimable		
Hsia 2011	0	55	0	~~		Not estimable		?? 🗣 🗣 🗣 🗣
Subtotal (95% CI)		2842		2684	72.5%	0.86 [0.54, 1.38]	-	
Total events	37		41					
Heterogeneity: Tau² = 0		= 8 (P = 0	.47); I² =	0%				
Test for overall effect: Z	= 0.63 (P = 0.53)							
Total (95% CI)		3556		3407	100.0%	0.87 [0.57, 1.32]	-	
Total events	52		59					
Heterogeneity: Tau ² = 0	.03; Chi ² = 10.72, dt	f = 10 (P =	= 0.38); P	²= 7%				_
Test for overall effect: Z	= 0.65 (P = 0.52)					F	avours [Long-acting] Favours [NPH]	
Test for subgroup differ	ences: Chi² = 0.17,	df = 1 (P :	= 0.68), l	²=0%			avous [cong-ading] - Lavous [NEH]	
Risk of bias legend								
(A) Random sequence	generation (selection	on bias)						

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

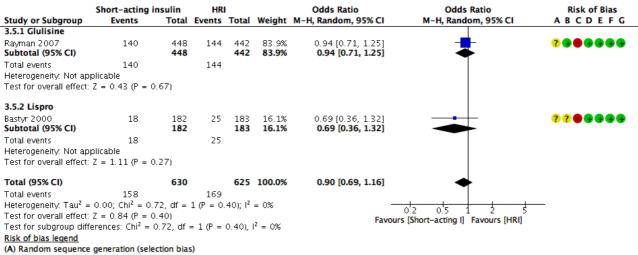
(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias) (F) Selective reporting (reporting bias) (G) Other bias

5.5.3. Hypoglycemia in trials with prandial insulin therapy

Forest plot for trials comparing the effects of long-acting basal insulin and NPH on total (Panel A), nocturnal (Panel B), and severe (Panel C) hypoglycaemia.

Α



(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

В

	Short-acting i	nsulin	HR	1		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	ABCDEFG
3.6.1 Glulisine								
Dayley 2004	93	435	108	441	57.2%	0.84 [0.61, 1.15]		•••••
Rayman 2007 Subtotal (95% CI)	39	448 883	63	442 883	42.8% 100.0%	0.57 [0.38, 0.88] 0.71 [0.49, 1.03]		? • • • • • •
Total events Heterogeneity: Tau² = Test for overall effect:		,	171 1 (P = 0	. 16); I ²	= 50%			
Total (95% CI)		883		883	100.0%	0.71 [0.49, 1.03]	-	
Total events	132		171				-	
Heterogeneity: Tau ² =	0.04; Chi ² = 1.	99, df =	1 (P = 0	. 16); I ²	= 50%	-	0'2 0'5 1 2 '	<u> </u>
Test for overall effect:	Z = 1.80 (P = 0)).07)				Eavou	U.2 U.S I 2 : Irs [Short-acting I] Favours [HRI]	>
Test for subgroup diff	erences: Not app	olicable				Favou	is [short-acting i] Favours [Fiki]	
Risk of bias legend								

<u>Risk of bias legend</u>

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias) (D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

С

	Experim	ental	Cont	rol		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
3.7.1 Glulisine								
Dayley 2004	6	435	5	441	56.3%	1.22 [0.37, 4.03]		
Rayman 2007	2	448	7	442	43.7%	0.28 [0.06, 1.35]		? • • • • • •
Subtotal (95% CI)		883		883	100.0%	0.64 [0.15, 2.70]		
Total events	8		12					
Heterogeneity: Tau ² =				= 0.14)); I ² = 54%	, ,		
Test for overall effect	:Z=0.61(F	P = 0.54)					
3.7.2 Lispro								
Altuntas 2003	0	20	0	20		Not estimable		?? \varTheta 🛨 🖶 🛨
Subtotal (95% CI)		20		20		Not estimable		
Total events	0		0					
Heterogeneity: Not a	pplicable							
Test for overall effect	: Not applic	able						
Total (95% CI)		903		903	100.0%	0.64 [0.15, 2.70]		
Total events	8		12					
Heterogeneity: Tau ² =	= 0.59; Chi ^a	= 2.16,	df = 1 (P	= 0.14)); I² = 54%	, -		_
Test for overall effect	:Z=0.61 (F	^o = 0.54)			Fa	vours [experimental] Favours [control]	
Test for subgroup dif	ferences: N	lot appl	icable			14	would texperimental in avours teoritroit	
Risk of bias legend								
(A) Random sequen	ce generati	on (sel	ection bia	is)				
(B) Allocation concea	alment (sel	ection b	ias)					
(C) Blinding of partici	pants and	personi	nel (perfo	rmance	e bias)			
(D) Blinding of outcor	me assess	ment (d	letection	bias)				
(E) Incomplete outeou	ma data (ai	Hritian b	ice)					

(E) Incomplete outcome data (attrition bias) (F) Selective reporting (reporting bias) (G) Other bias

5.5.4. HbA1c in trials with prandial insulin therapy

Forest plot for trials comparing the effects of short-acting basal insulin and human insulin on HbA1c at the endpoint.

	Short-ad	ting ins	sulin		HRI			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	ABCDEFG
3.2.1 Aspart										
Herrmann 2013 Subtotal (95% CI)	7.4	0.9	18 18	7	0.9	11 11	4.9% 4.9%			?? •••?••
Heterogeneity: Not ap	plicable									
Test for overall effect:	Z = 1.16 (P = 0.25	5)							
3.2.2 Lispro										
Altuntas 2003	6.7	2.2	20	7.5	0.9	20	2.2%	-0.80 [-1.84, 0.24] ←		??
Anderson 1997	8.2	1.2	145	8.4	1.2	150	17.3%	-0.20 [-0.47, 0.07]	_ +	22000
Bastyr 2000	8.5	1.3	182	8.3	1.3	183	17.7%	0.20 [-0.07, 0.47]	+	??
Subtotal (95% CI)			347			353	37.2%	-0.09 [-0.50, 0.31]		
Test for overall effect: 3.2.3 Glulisine	2 = 0.45 (P = 0.6:	>)							
Ravman 2007	7.3	1	448	7.2	0.9	442	28.7%	0.10 [-0.02, 0.22]		7
Dayley 2004 Subtotal (95% CI)	7.1	0.9	435 883		0.9		29.2%	-0.10 [-0.22, 0.02] -0.00 [-0.20, 0.20]	-	0 7 0 0000
	0.00. Chi2	E 1E		(D)	A. 7. 1.			-0.00 [-0.20, 0.20]	—	
Heterogeneity: Tau ² = Test for overall effect:				(P = 0.	.02);	1- = 813	76			
Total (95% CI)			1248			1247	100.0%	0.00 [-0.16, 0.16]		
Heterogeneity: Tau ² =	0.02; Chi ²	= 12.9	8, df =	5 (P =)	0.02)	l ² = 6	1%		-1 -05 0 05 1	_
Test for overall effect:	Z = 0.03 (P = 0.98	B)					Favours	[Short-acting I] Favours [HRI]	
Test for subgroup diff	erences: Ch	$i^2 = 1.5$	5, df =	2 (P =	0.46)	$, ^2 = 0$	%	ravours	conorc-acting ij ravours [riki]	
Risk of bias legend										
(A) Random sequence	e generation	(selection	on bias)							
(R) Allocation conceals	mant (calact	ion hine)								

(B) Allocation concealment (selection bias)
 (C) Blinding of participants and personnel (performance bias)
 (D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

5.5.5. Trials' characteristics

Baseline characteristics of the trials included in the meta-analysis

Study Name	Active Drug	Comparator	Trial	Patients	Patient	Mean age	Mean	Mean	Dur.	FPG (%)
(Pub year)	(AD)		Duration	AD	Comp.		HbA1c	BMI	Diab.	
			(weeks)			(years)	(%)	(Kg/m ²)	(years)	
Basal Insulin										
Aso 2017 ¹¹⁴	Degludec	GlargineU100	26	32	12	64.4	8.8	24.5	8	8.32
Berard 2015 ¹¹⁵	Glargine U100	NPH	24	32	34	NR	8	NR	11.5	8
Betonico 2019 ¹¹⁶	Glargine U100	NPH	52	29	29	61.5	8.75	29.5	7.5	NR
Bolli 2015 ¹¹⁷	Glargine U300	Glargine U100	24	439	439	57.7	8.54	33	NR	10.05
Bowering 2012 ¹¹⁸	Lispro Prot.	Glargine U100	24	211	212	56.3	9	27.7	19	NR
Eliashewitz 2006 ¹¹⁹	Glargine U100	NPH	26	231	250	56.6	9.15	27.25	12.7	11.05
Elisha 2016 ¹²⁰	Detemir	Glargine U100	26	16	20	59.2	8.9	32.15	14.05	11.1
Esposito 2008 ¹²¹	Lispro Prot.	Glargine U100	24	58	58	54.3	8.8	29.5	10.5	10.6
Fajardo 2008 ¹²²	Detemir	NPH	24	125	146	62	8.85	31.8	10.35	10.45
Fogelfeld 2010 ¹²³	Lispro Prot.	Detemir	36	219	210	56	8.8	30	8	NR
Fonseca 2004 ¹²⁴	Glargine U100	NPH	26	52	48	57.9	8.39	29.81	16.3	9.26
Franek 2016 ¹²⁵	Degludec	Aspart Prot.	24	197	197	58.9	8.4	31.2	9.2	10.25
Fritche 2003 ¹²⁶	Glargine U100	NPH	28	463	232	61	9.1	28.7	12.6	12.1
Fulcher 2014 ¹²⁷	Degludec	Aspart Prot.	26	224	222	58.7	8.35	29.3	9.5	8.75
Garber 2012 (Hollander 2015) ^{128,129}	Degludec	Glargine U100	24	744	248	59	8.35	32.1	9	9.2
Giugliano 2014 ¹³⁰	Lispro Prot.	Glargine U100	26	171	173	54.3	9.02	29.4	13	9.5

Appendix

Gough 2013 ¹³¹	Degludec U200	Glargine U100	78	228	228	57.5	8.25	32.3	13.5	9.6
Haak 2005 ¹³²	Detemir	NPH	48	341	164	60	7.9	30.4	NR	10.2
Hermansen 2006 ¹³³	Detemir	NPH	26	236	237	61	8.55	29	8.2	11
Hollander 2008 ¹³⁴	Detemir	Glargine U100	26	214	105	58.5	8.7	31.6	9.7	9.6
Home 2015 ¹³⁵	Glargine U100	NPH	102	352	349	57.25	8.2	29.9	NR	9.1
Hsia 2011 ¹³⁶	Glargine U100	NPH	52	55	30	52.1	9.3	31.6	13.5	9.94
Kaneko 2015 ¹³⁷	Degludec	Aspart Prot.	36	280	142	60	8.4	25.4	9.2	7.9
Liebl 2009 ¹³⁸	Detemir	Aspart Prot.	26	537	178	61	8.5	31	8.7	11.1
Massi-Benedetti 2003 ¹³⁹	Glargine U100	NPH	26	289	281	53.7	8.9	29	16.3	9.85
Pan 2007 ¹⁴⁰	Glargine U100	NPH	26	220	223	56	9	24.9	9.3	12.44
Pan 2016 ¹⁴¹	Degludec	Glargine U100	52	555	278	56.3	8.3	27.2	10.5	9.4
Philis-Tsimikas2020 ¹⁴²	Degludec	Glargine U300	24	805	804	59.2	7.6	31.6	10.1	7.95
Raskin 2009 ¹⁴³	Detemir	Glargine U100	24	254	131	55.8	8.4	32.7	7.8	9.61
Riddle 2003 ¹⁴⁴	Glargine	NPH	26	367	389	55	8.6	33.3	12.3	10.9
Riddle 2014-2015 ¹⁴⁵	Glargine U300	Glargine U100	26	404	403	60	8.16	36.6	13	8.85
Ritzel 2018 ¹⁴⁶	Glargine U300	Glargine U100	24	508	506	70.9	8.21	31.1	8.7	8.6
Rodbard 2013-2014 (Zinman 2012) ^{147,148}	Degludec	Glargine U100	52	773	257	59	8.2	31.3	15.8	9.59
Rosenstock2001 ¹⁴⁹	Glargine U100	NPH	26	259	259	59.3	8.6	30.5	15.3	9.15
Rosenstock2008 ¹⁵⁰	Detemir	Glargine U100	105	291	291	59	8.63	30.6	9	NR
Rosenstock2009 ¹⁵¹	Glargine U100	NPH	28	513	504	55.1	8.36	34.3	13.7	10.25
Rosenstock2018 ¹⁵²	Glargine U300	Degludec	52	466	463	60.5	8.64	10.6	9.1	10.33
Swinner 2009-2010 ¹⁵³	Glargine U100	Determir	260	478	486	58.4	8.7	30.1	10.7	10.5

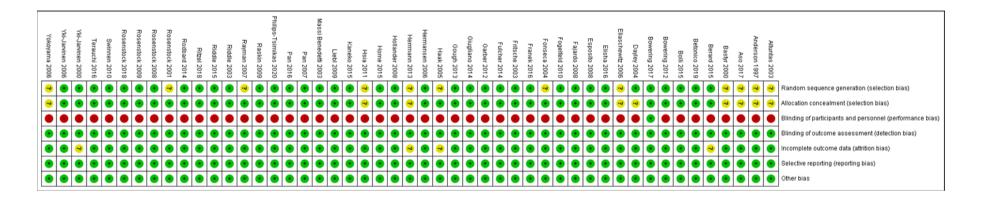
Appendix

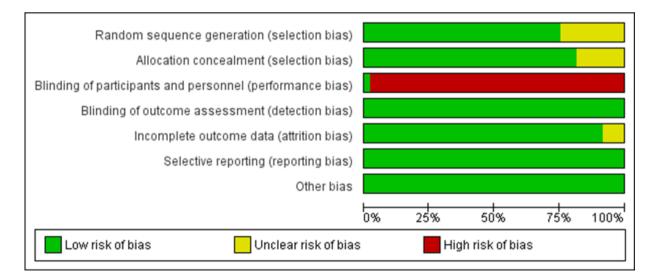
Terauchi 2016 ¹⁵⁴	Glargine U300	Glargine U100	24	121	120	61	8	25.3	10.6	7.6
Yki-Jarvinen 2000 ¹⁵⁵	Glargine U100	NPH	24	214	208	59	9	28.8	10	NR
Yki-Jarvinen 2006 ¹⁵⁶	Glargine U100	NPH	24	61	49	56.5	9.55	31.7	14	13
Yki-Jarvinen 2014 -2015 ¹⁵⁷	Glargine U300	Glargine U100	52	315	314	58.2	8.24	34.8	10	8
Yokoyama 2006 ¹⁵⁸	Glargine U100	NPH	36	31	31	61	7.1	26.2	9	8.5
Prandial Insulin										
Altuntas 2003 ¹⁵⁹	Lispro	HRI	26	20	20	55	9.5	31.5	8	NR
Anderson 1997 160	Lispro	HRI	52	145	150	56	8.8	28.4	12.2	11.6
Bastyr 2000 ¹⁶¹	Lispro	HRI	52	182	183	56	9.5	28	12.2	NR
Dailey 2004 ¹⁶²	Glulisine	HRI	48	435	441	58.3	7.55	34.55	10	NR
Herrmann 2013 ¹⁶³	Aspart	HRI	26	18	11	59	8.7	32	13	NR
Bowering 2017 ¹⁶⁴	Faster Aspart	Aspart	24	345	344	59.5	7.9	31.2	9.8	6.8
Rayman 2007 ¹⁶⁵	Glulisine	HRI	94	448	442	58	7.5	31.2	15	NR

Comp. Comparator; Dur.: duration; Diab.: diabetes.

5.5.6. Risk of bias

Graph and summary: review authors' judgements about each risk of bias item.





5.5.7.1. Grade evidence for basal insulin

Certainty ass	sessment		Sum	mary of findings	;							
						0 11	Study ever	nt rates (%)		Anticipated absolute effects		
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With Standard care	With Intensive glycemic control	Relative effect (95% CI)	Risk with placebo	Risk difference with Intensive glycemic control	
Total hypogl	ycemia											
4993 (13 RCTs)	serious ^a	serious ^b	non serious	non importante	very strong association	⊕⊕⊖⊖ LOW	1371/2284 (60.0%)	1291/2709 (47.7%)	OR 0.70 (0.57;0.86)	600 per 1000	88 lower per 1000 (da 139 a 37 lower)	
Nocturnal hy	poglycem	ia					·					
15892 (3 RCTs	seriousª	serious ^b	non serious	non serious	very strong association	⊕⊕⊖⊖ LOW	508/2204 (2 3.0%)	732/2617 (28.0%)	OR 0.48 (0.38;0.62)	230 per 1000	105 lower per 1000 (da 128 a 74 lower)	
Severe hypo	glycemia									I		
3297 (1 RCT)	seriousª	non importante	non serious	non serious	Probable publication bias	⊕⊕⊖⊖ LOW	59/3407 (1.7%)	52/3556 (1.5%)	OR 0.87 (0.57;1.32)	17 per 1000	2 lower per 1000 (da 7 lower a 5 more)	

Cl: Confidence interval; **OR:** Odds Ratio; **Explanations** a. *Open-label study; b. High/*Moderate heterogeneity; c. Indirect evidences; d. Limited sample size.

5.5.7.2. Grade evidence for prandial insulin

Certainty ass	essment		Sur	nmary of finding	S						
Participants						Quant	evidence Standard glyce	nt rates (%)		Anticipated absolute effects	
(studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	certainty of		With Intensive glycemic control	Relative effect (95% Cl)	Risk with placebo	Risk difference with Intensive glycemic control
Total hypogl	ycemia										
1255 (2 RCTs))	serious ^a	not serious	not serious	serious ^c	nessuno	⊕⊕○○ LOWER	169/625 (27.0%)	158/630 (25.1%)	OR 0.90 (0.69;1.16)	270 per 1000	20 lower per 1000 (from 67 lower to 30 more)
Nocturnal hy	poglycem	ia				L F			•	L	
1766 (2 RCTs)	serious ^a	not serious	not serious	serious ^c	nessuno	⊕⊕⊕⊖ MODERATE	171/883 (19.4%)	132/883 (14.9%)	OR 0.71 (0.49;1.03)	194 per 1000	48 lower per 1000 (from 88 lower to 5 more)
Severe hypo	glycemia										
1806 (3 RCTs)	serious ^a	serious ^b	not serious	serious ^c	nessuno	⊕○○○ VERY LOWER	12/903 (1.3%)	8/903 (0.9%)	OR 0.67 (0.27;1.63)	13 per 1000	4 lower per 1000 (from 10 lower to 8 more)

Cl: Confidence interval; OR: Odds Ratio; Explanations a. Open-label study; b. High/Moderate heterogeneity; c. Indirect evidences; d. Limited sample size.

Certainty asso	essment		Sum	Summary of findings									
Participants	Risk of bias	Inconsistency			Publication	Overall certainty of evidence	Study ever	nt rates (%)	Relative effect (95% CI)	-	d absolute ects		
(studies) Follow up			Indirectness	Imprecision	bias		With Standard care	With Intensive glycemic control		Risk with placebo	Risk difference with intervention		
HbA1c													
2495 (6 RCTs)	serious ^a	serious ^b	not serious	serious ^c	nessuno	⊕○○○ VERY LOWER	1247	1248	-	Mean endpoint HbA1c was 7.6 %	DM 0.0 % (0.11 lower a 0.11 more)		
Quality of life				•									
365 (1 RCT)	serious ^a	not serious	not serious	serious ^c	nessuno	⊕⊕○○ LOWER	-	-	-	-	-		

DM: Difference in means; Explanations a. Open-label study; b. High/Moderate heterogeneity; c. Indirect evidences; d. Limited sample size.

5.5.8. Pharmacoeconomic evaluation

Author	Country	Intervention	Type of analysis	Incremental cost	Incremental cost (QALY)	Incremental cost per QALY gained	Authors' conclusions
Insulina basale							
Permsuwan 2016 ¹⁶⁶	Thai National healthcare system perspective, US\$ 2014	Insulin glargine vs NOH insulin	Costeffectivenes s and cost-utility (50 years)	Insulin Glargine implied higher costs vs NPH insulin because of medication costs and renal complication but implied savings because of lower CV complications and hypoglicemia	Insulin Glargine also increased QALY	ICUR for insulin Glargine was US\$7,216 per QALY, ICER was US\$5,201 per LY	The result showed an incremental cost per QALY which is above the acceptable Thai threshold; findings were not consistent with those from other countries indicating which indicated that IGIar was cost effective compared with NPH insulin; this could be partly explained by big differences in medication costs
Permsuwan 2017 ¹⁶⁷	Thailand, payer's perspective, USD2015 (THB converted in USD)	IDet compared to IGlar from the payer's perspective.	Cost- effectiveness (50 years)	Base case Total costs (USD) Insulin Glargine: 66,674.03 Insulin Detemir (mixed dose): 90,417.63 Insulin Detemir (single dose): 60,645.90 Insulin Detemir (double dose): 3,587,769 THB Total costs (THB) per person Insulin detemir: 3,262,268 Insulin glargine: 2,405,599 The major cost component is	Life years Insulin Glargine:13.116 Insulin Detemir (mixed dose): 13.119 Insulin Detemir (single dose): 13.119 Insulin Detemir (doble dose): 13.119 <i>QALYS</i> Insulin Glargine: 8.908 Insulin Detemir (mixed dose): 8.921 Insulin Detemir (single dose): 8.921 Insulin Detemir (doble dose): 8.921	IDet is associated with higher costs and better QALYs respect to IGIar with an ICER of 1.7 milion USD per QALY.	IDet is not cost-effectiveness compared to IGlar treatment.

Author	Country	Intervention	Type of analysis	Incremental cost	Incremental cost (QALY)	Incremental cost per QALY gained	Authors' conclusions
				medication cost: Insulin detemir: 74,880.32 USD Insulin glargine: 51,256.10 USD The cost of complications is similar between two treatments.			
Brandle ¹⁶⁸	Switzerland Swiss Franc	Glargine U100 vs NPH insulin Observational study	Cost- effectiveness	-	Insulin glargine was associated with an improvement in quality of life (0.098 QALYs per patient) compared to NPH insulin. Insulin glargine was associated with additional life expectancy (0.05 life years gained per patient) compared to NPH insulin	Insulin glargine was associated with incremental costs of CHF 2,578 resulting in an ICER of CHF 26,271 per QALY and CHF 51,100 per LYG	The present study demonstrated that insulin glargine proved to be cost-effective with respect to accepted willingness to pay thresholds and therefore represents good value for money.
Cheng 2019 ¹⁶⁹	China <i>US Dollars</i>	Glargine U100 vs NPH insulin Literature review	Cost- effectiveness		Compared with insulin glargine, insulin degludec was associated with 0.0053 QALY at an additional cost of \$3278 in a simulated cohort.	Incremental cost- effectiveness ratio of insulin degludec over insulin glargine of \$613,443 per QALY gained.	Insulin degludec is unlikely to be costeffective compared with insulin glargine for Chinese patients with T2DM whose disease is inadequately controlled with oral antidiabetic drugs.

Author	Country	Intervention	Type of analysis	Incremental cost	Incremental cost (QALY)	Incremental cost per QALY gained	Authors' conclusions
Davies 2016 ⁶⁰	United Kingdom (NHS) 2015 GBP	IDegLira vs Basal Insulin+Liraglutide IDegLira vs IGlar+3xIAsp IDegLira vs Up- titrated IGlar	Cost-utility (40yrs)	Compared with both Basal Insulin+Liraglutine and IGlar+3xIAsp and Up-titrated IGlar, increasing QALYs of +0.123, +0.414 and +0.237 respectively.	Compared with both Basal Insulin+Liraglutine and IGlar+3xIAsp, IDegLira reduced overall healthcare costs (-£971 and -£1,698) because of avoided-diabets-related complications. Compared with up- titrated IGlar, IDegLira increased costs (+£1,441) because of higher acquisition price.	Compared with both Basal Insulin+Liraglutine and IGlar+3xIAsp, IDegLira was dominant increasing QALYs and reducing overall healthcare. Compared with up- titrated IGlar, IDegLira showed an ICER of £6,090 per QALY. Results remained consisten at sensitivity analyses.	IDegLira was higly cost-effective (of even dominant) highly cost- effective treatment option vs. current insulin intensification options for type 2 diabetes patients uncontrolled on basal insulin from the UK NHS perspective
Drummord 2018 ¹⁷⁰	United Kingdom (NHS) GBP 2016	IDegLira vs BBI	Cost-ultility (1 year)	IDegLira increased QALY of +0.0512 because of reduced hypoglycaemic events and effect on BMI change	Costs were higher for IDegLlia (+£303) because of higher acquisition costs that were partially offset by savings related with avoidance of events, as well as needle ad SMGB use	IDegLira resulted cost-effective with ICER being £5,924 per QALY and results were confirmed by sensitivity analyses	IDegLira is a cost-effective options vs BBI for the management of patients with T2DM unadequately controlled with basal insulin regimen when considering the UK NHS perspective and a WTP threshold of £20,000 per QALY.
Dempsey 2018 ⁶²	US (healthcare payer perspective) US dollars	IDegLira (intensified with BBI after 5 yrs treatment) vs BBI	Cost-ultility (lifetime)	IDegLira increased both LY by +0.02 and QALYs by +0.22 due to a small reduction and delay of onset of diabetes- related complication	IDegLira was also associated with savings of about \$3,571 (per patient over lifetime) because of lower acquisition costs and reduced incidence of complications	IDegLira was dominand and results were consistent at sensitivity analyses, only when the costs of needle, SMBG or insulin glargine were varied IDegLira resulted in	IDegLira is a dominat option vs BBI or at least a cost-effective option for T2DM unadequately controlled with basal insulin regimen when considering the US healthcare payer perspective.

Appendix

Author	Country	Intervention	Type of analysis	Incremental cost	Incremental cost (QALY)	Incremental cost per QALY gained	Authors' conclusions
						increasing costs with ICER remaining well below a WTP of \$100,000 per QALY.	
Torre 2018 ¹⁷¹	Italy NHS and Society perspective <i>Euro</i>	IDegLira vs BBI	Cost- miniminaztion	-	IDegLira increased direct health costs being €2,126.99 vs €1,568.63 for BBI. Costs' difference were reduced when considering indirect costs for hypoglycemia (€2,145.76 vs €1,711.89) and costs were equivalent when reducing IDegLira dose to 26.3U.	-	IdegLira is a important alternative to BBI allowing adequate management of T2DM patients not adequately controlled with BBI and showing also a good value for modey.
Hunt 2017 ¹⁰²	US (healthcare payer perspective) 2015 US dollar	IDegLira (intensified with BBI after 5 yrs treatment) vs liraglutide vs basal insulin	Cost- effectiveness (lifetime)	IDegLira increased both LY by +0.02 and QALYs by +0.03 due to a small reduction and delay of onset of diabetes- related complication	IDegLira was also associated with savings of about \$17,687 (per patient over lifetime) because of lower acquisition costs and reduced incidence of complications	IDegLira was dominand and results were consistent at sensitivity analyses	IDegLira is a dominat option vs Iliraglutide added to basal insulin for T2DM unadequately controlled with basal insulin regimen when considering the US healthcare payer perspective.
Insulina prandia	le						
Farshchi 2016 ¹⁷²	Iran, Dollari USA 2012	Perspective of the Society 2012 US dollar (converted from Iranian Rials)	BIAsp 30 in two doses (pre- breakfast and pre-dinner) vs NPH Reg insulin	Cost-effectiveness and cost-utility (over 6 months)	HbA1c levels decreased 2.40 \pm 1.28 % in BIAsp 30 and 2.34 \pm 1.53 % in NPH/Reg insulin groups while there was no statistically significant difference between groups (P =0.233).	Mean direct costs were 595.15 ± 30.15USD for BIAsp 30 and 726.34 ± 60.34 USD for NPH/Reg arm. Total direct medical costs in NPH/Reg insulin	BIAsp 30 showed lower ICER as a dominant alternative

Author	Country	Intervention	Type of analysis	Incremental cost	Incremental cost (QALY)	Incremental cost per QALY gained	Authors' conclusions
					Minor, major, and nocturnal hypoglycemic events were more frequent among patients in the NPH/Reg arm (P <0.05 in all cases). BIAsp 30 significantly increased QALY at 24 weeks while NPH/Reg did not.	arm were higher than BIAsp 30 group (P = 0.017), due to more admissions and longer stay in hospital. Also Costs of lost productivity were higher in NPH/Reg insulin group. Total cost was estimated to be 930.55 ± 81.43 USD for BIAsp 30 and 1101.24 ± 165.49 USD for NPH/Reg arm	

5.6. Subcutaneous insulin infusion

Considered evidence: RCT with a duration of at least 12 weeks and comparing subcutaneous insulin infusion with multiple daily insulin injections in patients with type 2 diabetes and baseline HbA1c>8.0% (64 mmol/mol).

The primary outcome of the present meta-analysis was to assess the effects of the intervention on HbA1c, hypoglycemia, and quality of life.

The systematic review has already been published; for complete search string, list and characteristics of included studies, and assessment of publication bias, please see the related publication¹⁷³. An update of this meta-analysis was performed, without retrieving any further RCT.

5.6.1. HbA1c

Forest plot for trials comparing the effects of subcutaneous insulin infusion and multiple daily insulin injections on HbA1c (%) at endpoint.

(CSII		Co	ontro	1		Mean Difference	Mean Difference	Risk of Bias
Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	ABCDEFG
6.7	0.7	53	6.5	0.7	54	22.4%	0.20 [-0.07, 0.47]	 ∎-	
7.6	1.2	66	7.5	1.2	61	20.4%	0.10 [-0.32, 0.52]	-+	• ? • • • • •
8.4	1.2	40	8.6	1.3	40	18.3%	-0.20 [-0.75, 0.35]		?? 🗣 🗣 🗣 🗣
7.9	0.8	168	8.6	0.8	163	23.3%	-0.70 [-0.87, -0.53]	• I	
7.7	0.8	17	8.5	1.3	17	15.6%	-0.80 [-1.53, -0.07]	_ _	?? 🗧 🛨 🖶 🛨
		344			335	100.0%	-0.26 [-0.74, 0.22]	•	
= 0.25; C	hi² =	38.37, (df = 4 (F	< 0.0	00001)	, I² = 90%			
Z=1.05	5 (P =	0.29)						Favours CSII Favours Control	
	Mean 6.7 7.6 8.4 7.9 7.7 6.25; C	6.7 0.7 7.6 1.2 8.4 1.2 7.9 0.8 7.7 0.8 : 0.25; Chi ² =	Mean SD Total 6.7 0.7 53 7.6 1.2 66 8.4 1.2 40 7.9 0.8 168 7.7 0.8 17	Mean SD Total Mean 6.7 0.7 53 6.5 7.6 1.2 66 7.5 8.4 1.2 40 8.6 7.9 0.8 168 8.6 7.7 0.8 17 8.5 344 colspan="3">3.37, df = 4 (F	Mean SD Total Mean SD 6.7 0.7 53 6.5 0.7 7.6 1.2 66 7.5 1.2 8.4 1.2 40 8.6 1.3 7.9 0.8 168 8.6 0.8 7.7 0.8 17 8.5 1.3 344 sum 3.7, df = 4 (P < 0.1)	Mean SD Total Mean SD Total 6.7 0.7 53 6.5 0.7 54 7.6 1.2 66 7.5 1.2 61 8.4 1.2 40 8.6 1.3 40 7.9 0.8 168 8.6 0.8 163 7.7 0.8 17 8.5 1.3 17 344 335 c.25; Chi ² = 38.37, df = 4 (P < 0.00001)	Mean SD Total Mean SD Total Weight 6.7 0.7 53 6.5 0.7 54 22.4% 7.6 1.2 66 7.5 1.2 61 20.4% 8.4 1.2 40 8.6 1.3 40 18.3% 7.9 0.8 168 8.6 0.8 163 23.3% 7.7 0.8 17 8.5 1.3 17 15.6% 344 335 100.0% c.25; Chi ² = 38.37, df = 4 (P < 0.00001); I ² = 90%	Mean SD Total Mean SD Total Weight IV, Random, 95% CI 6.7 0.7 53 6.5 0.7 54 22.4% 0.20 [-0.07, 0.47] 7.6 1.2 66 7.5 1.2 61 20.4% 0.10 [-0.32, 0.52] 8.4 1.2 40 8.6 1.3 40 18.3% -0.20 [-0.75, 0.35] 7.9 0.8 168 8.6 0.8 163 23.3% -0.70 [-0.87, -0.53] 7.7 0.8 17 8.5 1.3 17 15.6% -0.80 [-1.53, -0.07] 344 335 100.0% -0.26 [-0.74, 0.22] c.25; Chi² = 38.37, df = 4 (P < 0.00001); P = 90%	Mean SD Total Mean SD Total Weight IV, Random, 95% CI IV, Random, 95% CI 6.7 0.7 53 6.5 0.7 54 22.4% 0.20 [-0.07, 0.47]

5.6.2. Severe hypoglycemia

Forest plot for trials comparing the effects of subcutaneous insulin infusion and multiple daily insulin injections on the risk of severe hypoglycemia.

	CSII		Control			Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events Total		Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
Wainstein 2004	3	20	2	20	32.2%	1.59 [0.24, 10.70]		??••••
Herman 2005	3	53	6	54	56.4%	0.48 [0.11, 2.03]		
Reznick 2014	0	168	1	163	11.4%	0.32 [0.01, 7.95]		
Berthe 2007	0	17	0	17		Not estimable		?? 🔴 🛨 🖶 🗣
Raskin 2003	0	66	0	61		Not estimable		
Total (95% CI)		324		315	100.0%	0.67 [0.23, 1.99]	-	
Total events	6		9					
Heterogeneity: Tau ² =	0.00; Chi	² = 1.1	9, df = 2 (P = 0.5	5); I ² = 09	6		
Test for overall effect:							0.01 0.1 1 10 1 Favours CSII Favours Contro	00

5.6.3. Quality of life

First author (year, ref.)	Quality of life
Berthe et al (2007) ¹⁷⁴	Diabetes treatment satisfaction score CSII vs MDI; MDI better
Herman et al (2005) ¹⁷⁵	DQoLc+q + SF-36 CSII vs MDI; nonsignificant
Jennings et al (1991) ¹⁷⁶	Treatment satisfaction and general well-being CSII vs MDI; nonsignificant
Raskin et al (2003) ¹⁷⁷	Diabetes treatment satisfaction score CSII vs MDI; better CSII
Reznik et al (2014) ¹⁷⁸	Treatment satisfaction and general well-being CSII vs MDI; not reported
Wainstein et al (2004) ¹⁷⁹	Not measured

Abbreviations: CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections; SMBG, self-monitoring of blood glucose; DQoL: Diabetes Quality of Life; SF: Short Form.

5.6.4. Patients' adherence

No available data.

5.6.5. GRADE evidence table

Certainty a	ssessme	nt					Summary of findings					
Participants	Risk of				Publication	Overall	Relative	effect	Anticipated absolute effects			
(studies) Follow up	bias	Inconsistency	Indirectness	Imprecision	bias	certainty of evidence	(95%, CI)		(95%, CI)		Control	Intervention
HbA1c												
679 (5 RCT)s	serious ^a	serious ^b	not serious	serious ^c	none	⊕○○○ VERY LOW	-0.26 [-0.72;0.22]		The mean HbA1c was: 8.0%	MD: -0.3% (from 0.7 lower to 0.2 more)		
Preferenza d	ei pazienti						•					
679 (5 RCTs)	serious ^a	serious ^b	not serious	serious ^c	none	⊕○○○ VERY LOW	-	-	-	-		
Qualità della	vita					•	•					
679 (5 RCTs)	serious ^a	serious⁵	not serious	serious ^c	none	⊕○○○ VERY LOW	-	-	-	-		

MD: Mean difference; a. Randomization, allocation, and blinding procedures not adequately reported for the majority of included trials; b. Presence of heterogeneity; c. Limited sample size.

Certainty ass	essment		Sur	nmary of finding	ings							
Dentisianata	Risk of bias	Inconsistency			Quorall	Study ever	it rates (%)		Antici	pated absolute effects		
Participants (studies) Follow up			Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With Stanfromrd care	With Intensive glycemic control	Relative effect (95% CI)	Risk with placebo	Risk difference with Intensive glycemic control	
Ipoglicemia t	otale											
639 (5 RCTs)	seriousª	serious ^d	not serious	serious ^c	none	⊕○○○ VERY LOW	9/315 (2.9%)	6/324 (1.9%)	OR 0.67 (0.23 to 1.99)	29 per 1000	88 lower per 1000 (from 139 a 37 lower)	

OR: Odds Ratio; **CI:** Confidence interval; a. Randomization, allocation, and blinding procedures not adequately reported for the majority of included trials; b. Presence of heterogeneity; c. Limited sample size.

5.6.6. Pharmacoeconomic evaluations

The search for pharmaeconomic studies has been performed including glycemic control as key-word; the study selection has been conducted considering the time horizon of the analysis, the target population, and excluding data deriving from drugs manufacturers. **Search string:** (economic or cost or cost-effectiveness) and drugs and (glycemic control type 2 diabetes). Filters: in the last 10 years. (up to December, 1st, 2020).

Author	Country	Intervention	Type of analysis	Incremental cost	Incremental cost (QALY)	Incremental cost per QALY gained	Authors' conclusions
No studi retrieveo							

RECOMMENDATION # 6: GLUCOSE MONITORING.

6.1. Structured glucose monitoring

Considered evidence: RCT with a duration of at least 24 weeks, enrolling patients with non-insulintreated type 2 diabetes, comparing structured with no structured glucose monitoring. The principal endpoint was the effect of these two interventions on endpoint HbA1c.

The systematic review has already been published; for complete search string, list and characteristics of included studies, and assessment of publication bias, please see the related publication¹⁸⁰. An update of this meta-analysis was performed, without retrieving any further RCT.

6.1.1. HbA1c

Forest plot for trials comparing the effects of structured with no structured glucose monitoring on HbA1c (%) at endpoint.

	Ex	perimen	tal		Control		Mean Difference		
Study	Total	Mean	SD	Total	Mean	SD	i 1	MD	95% Cl
Duran SanCarlos, 2010	99	-0.50	1.03	62	0.00	0.96		-0.50	[-0.81; -0.19]
Polonsky, 2011	21	-1.20	0.41	13	-0.90	0.36		-0.30	[-0.56; -0.04]
Bosi, 2013	501	-0.39	0.78	523	-0.27	0.79	-	-0.12	[-0.22; -0.02]
Random effects model	621			598			-	-0.27	[-0.49; -0.04]
Heterogeneity: I-squared=67.8	% [0%; 9	90.7%], ta	u-squared	t=0.026, Q=	=6.2, df=2,	p=0.0449			
							-0.5 0 0.5		
					Fa	+ avours str	ructured SMBG Favours	unstructi	ured SMBG

6.1.2. GRADE evidence table

Certainty a	(studies) RISK OT Inconsistency Indirectness Imprecision Publication bias							Summary of findings			
Participants	Risk of					Overall certainty	Relative effect	Anticipated absolute effects			
(studies) Follow up	bias	Inconsistency	Indirectness	Imprecision	Publication bias	of evidence	(95%, CI)	Control	Intervention		

HbA1c (%)

1219 (3 RCTs)	seriousª	serious ^b	not serious	serious ^c	none	⊕○○○ VERY LOW	-0.27 [-0.49;-0.04]	-	MD: 0.27% lower (from 0.49 to 0.04 lower)
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CI: Confidence interval; **MD:** Mean difference; a. Randomization, allocation, and blinding procedures not adequately reported for the majority of included trials; b. Limited sample size; c. Funnel plot showing possible publication bias, confirmed by Egger's test.

6.1.3. Pharmacoeconomic evaluations

The search for pharmaeconomic studies has been performed including glycemic control as key-word; the study selection has been conducted considering the time horizon of the analysis, the target population, and excluding data deriving from drugs manufacturers. **Search**: self-monitoring blood glucose and "type 2 diabetes" and (economic or cost or cost-effectiveness). Filters: in the last 10 years (up to December, 1st, 2020).

Author	Country	Intervention	Type of analysis	Incremental cost	Incremental cost (QALY)	Incremental cost per QALY gained	Authors' conclusions
Aghili 2012 ¹⁸¹	Iranian healthcare payer, USD 2010	Structured SMBG	Cost consequences, over a 6-months time horizon	Total costs per patient varied between USD 451.98 when considering patients treated in the public sector with insurance coverage to USD 730.74 for patients treated in the private sector	HbA1c improved significantly at 6- months from baseline (10.2 vs 8.5)	-	Structured SMBG results in significant improvement of glycemic status. Moreover, it is more cost saving in public sector with insurance coverage
Fritzen 2019 ¹⁸²	France, Germany, Italy, Spain and United Kingdom, Euro 2018	Glucose meter with color range indicator (CRI) vs glucose meter with CRI combined with a mobile app	Cost-consequences, 10 year	In France estimated cost-saving per patient/year ranged from	T2DM participants experienced HbA1c reduction of 0.63% in the meter only group 0.92% in the meter+ app group; this was associated with a reduction of fatal MI in the next 10 years of 2.0% in the meter only group and of 2.3% in the meter + app group	-	Combining the glucose meter with CRI with telemedical features has the potential to reduce costs for European health care systems

QALY: Quality Adjusted Life Years.

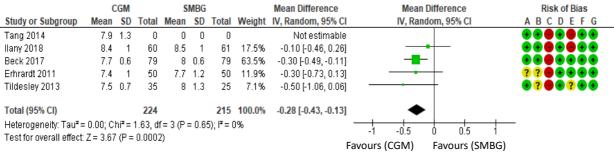
6.2. Structured glucose monitoring

Considered evidence: RCT with a duration of at least 12 weeks, enrolling patients with non-insulintreated type 2 diabetes, comparing continuous glucose monitoring with self-monitoring blood glucose. The principal endpoint was the effect of these two interventions on endpoint HbA1c and the risk of severe hypoglycemia. Secondary endpoint were the patients' preference and quality of life.

The systematic review has already been published; for complete search string, list and characteristics of included studies, and assessment of publication bias, please see the related publication¹⁷³. An update of this meta-analysis was performed, without retrieving any further RCT.

6.2.1. HbA1c

Forest plot for trials comparing the effects of continuous glucose monitoring with self-monitoring blood glucose on HbA1c (%) at endpoint.



Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

6.2.2. Severe hypoglycemia

No severe hypoglycemia was observed in available RCT

6.2.3. Patients' preference

No available data for this issue.

6.2.4. GRADE evidence table

Certainty a	ssessme	ent					Summary of findings				
Participants	Risk of	Inconsistence	In dimentioners	Incomerciations	Dublication bios	Overall certainty	Relative effect	Antici	pated absolute effects		
(studies) Follow up	bias	Inconsistency	Indirectness	Imprecision	Publication bias	of evidence	(95%, CI)	Control	Intervention		
HbA1c (%)											
436 (5 RCTs)	serious ^a	serious ^b	not serious	serious ^c	none	⊕○○○ VERY LOW	-0.28 [-0.43;-0.13]	-	MD 0.28% lower (from 0.43 to 0.13 lower)		
Qualità della	a vita			· · · · ·							
436 (5 RCTs)	serious ^a	serious ^b	not serious	serious ^c	none	⊕○○○ VERY LOW	-	-	-		
Ipoglicemia	Ipoglicemia severa (RR)										
250 (3 RCTs)	serious ^a	serious ^b	not serious	serious ^c	none	⊕○○○ VERY LOW	Nessun evento	_	-		

CI: Confidence interval; **MD:** Mean difference; a. Randomization, allocation, and blinding procedures not adequately reported for the majority of included trials; b. Presence of heterogeneity; c. Limited sample size.

6.2.5. Pharmacoeconomic evaluations

The search for pharmaeconomic studies has been performed including glycemic control as key-word; the study selection has been conducted considering the time horizon of the analysis, the target population, and excluding data deriving from drugs manufacturers. **Search**: self-monitoring blood glucose and "type 2 diabetes" and (economic or cost or cost-effectiveness) Filters: in the last 10 years (up to December, 1st, 2020).

Author	Country	Intervention	Type of analysis	Incremental cost	Incremental cost (QALY)	Incremental cost per QALY gained	Authors' conclusions
Healthcare Improvement Scotland, 2018 ¹⁸³	Scottish NHS, GBP 2007	Flash Glucose Monitoring vs SMBG	Cost utility analysis over a lifetime perspective	Costs increased by €4,916 with Flash Glucose Monitoring being €10,450 vs €5,535 for SMBG	QALYs incresed from 5.04 to 6.14 for Flash Glucose Monitoring	ICER was € 4,498 per QALY gained	Flash Glucose Monitoring resulted cost effective for people with T2 DM who are insulin users and self-monitor their blood glucose levels.
Bilir 2018 ¹⁸⁴	Swedish societal perspective, SEK 2016	Flash Glucose Monitoring vs SMBG	Cost- effectiveness and cost-utility analysis over a lifetime horizon (40 years)	Costs were SEK 1,630,586 for flash glusocse monitoring and SEK 1,459,394 for SMBG with a cost increase of SEK 171,192 with flash glucose monitoring	LY were 14. with flash glusocse monitoring and 14.34 for SMBG with a difference of -0.010 for flash glucose monitoring, QALYs were 6.21 for flash glusocse monitoring and 5.65 for SMBG with an increment of 0.560	ICUR was SEK 306,082 per QALY	Flash monitoring system is associated with a modest impact on diabetes-related costs, and can be considered cost-effective compared to current standard of care for glucose monitoring (SMBG). Although SMBG is less costly overall (flash monitoring improves QALYs for patients, leading to a favourable cost- effectiveness ratio of just over SEK300,000/QALY
Fonda 2016 ¹⁸⁵	US third- party payer perspective, USD 2011	Real-time continuous glucose monitoring (RT- CGM) vs SMBG	Cost- effectiveness and cost-utility analysis, over a life time horizon	Per patient costs were \$66 094 and \$65 441 for RT-CGM and SMBG respectively, with a cost increase of \$653 per patient with RT-CGM	Life expectancy (LE) and Quality Adjusted Life Expectancy (QALE) were10.62 and 6.03 for, versus 10.52 and 5.96 for SMBG; incremental LE and QALE were 0.10 and 0.07, respectively	The incremental cost-effectiveness ratios were \$6293 per LY gained and \$8898 per QALY gained	RT-CGM is a cost-effective disease management option in the US for people with type 2 diabetes not on prandial insulin
García-Lorenzo 2018 ¹⁸⁶	Spanish NHS, Euro 2017	Real time continuous glucose	Cost-utility analysis, over a lifetime horizon	Mean incremental cost per T2DM patient by using RT-CGM compared	Mean incremental QALY per T2DM patient gain by using RT-CGM was	ICER was €180,533 per QALY in T2DM patients	RT-CGM does not appear to be cost-effective for glucose

Author	Country	Intervention	Type of analysis	Incremental cost	Incremental cost (QALY)	Incremental cost per QALY gained	Authors' conclusions
		monitoring (RT- CGM) vs SMBG		with SMBG was estimated at €49,172	estimated at 0.27 QALYs per patient		monitoring in DM patients in Spain from the NHS perspective
Hellmund 2018 ¹⁸⁷	UK NHS, £ 2016-2017	Flash Glucose Monitoring vs SMBG	Cost- consequences	The total annual cost for the flash monitoring system was £1,235 per patient vs £1,426 for a patient using routine SMBG resulting in a reduction of £191 per patient per year for the flash monitoring system compared with SMBG	-	-	From a UK NHS perspective, for patients with T2DM using intensive insulin, flash monitoring is potentially cost- saving compared with routine SMBG irrespective of testing frequency
Sierra 2018 ¹⁸⁸	US societal perspective, USD 2015	Professional Continuous glucose monitoring vs other devices	Cost analysis	In the baseline period, mean total costs for the Pro CGM cohort were \$23,021 per patient per year compared to the control cohort average cost per patient per year of \$21,502; for the year following the index date, Pro CGM patient mean total cost increased to \$26,525, and the control cohort mean costs increased to \$23,736 per patient per year on average. This resulted in a non-statistically significant "difference- in-difference" of growth of total cost of \$1,270 per patient per year higher for the users of professional CGM (p = .08). On the other	-	-	Economic benefits were observed for patients who utilized professional CGM more than once within a 1-year period or who used it during a change of diabetes therapy

Author	Country	Intervention	Type of analysis	Incremental cost	Incremental cost (QALY)	Incremental cost per QALY gained	Authors' conclusions
				hand patients using professional CGM more than once per year had a -\$3,376 difference in the growth of total costs (p = .05); patients who used professional CGM while changing their diabetes treatment regimen also had a difference of -\$3,327 in growth of total costs (p = .0023)			

QALY: Quality Adjusted Life Years.

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