Summary

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This Appendix contains detailed information on unpublished and principal methods and results, including pharmacoeconomic evaluations, on already published systematic reviews and meta-analysis.

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:

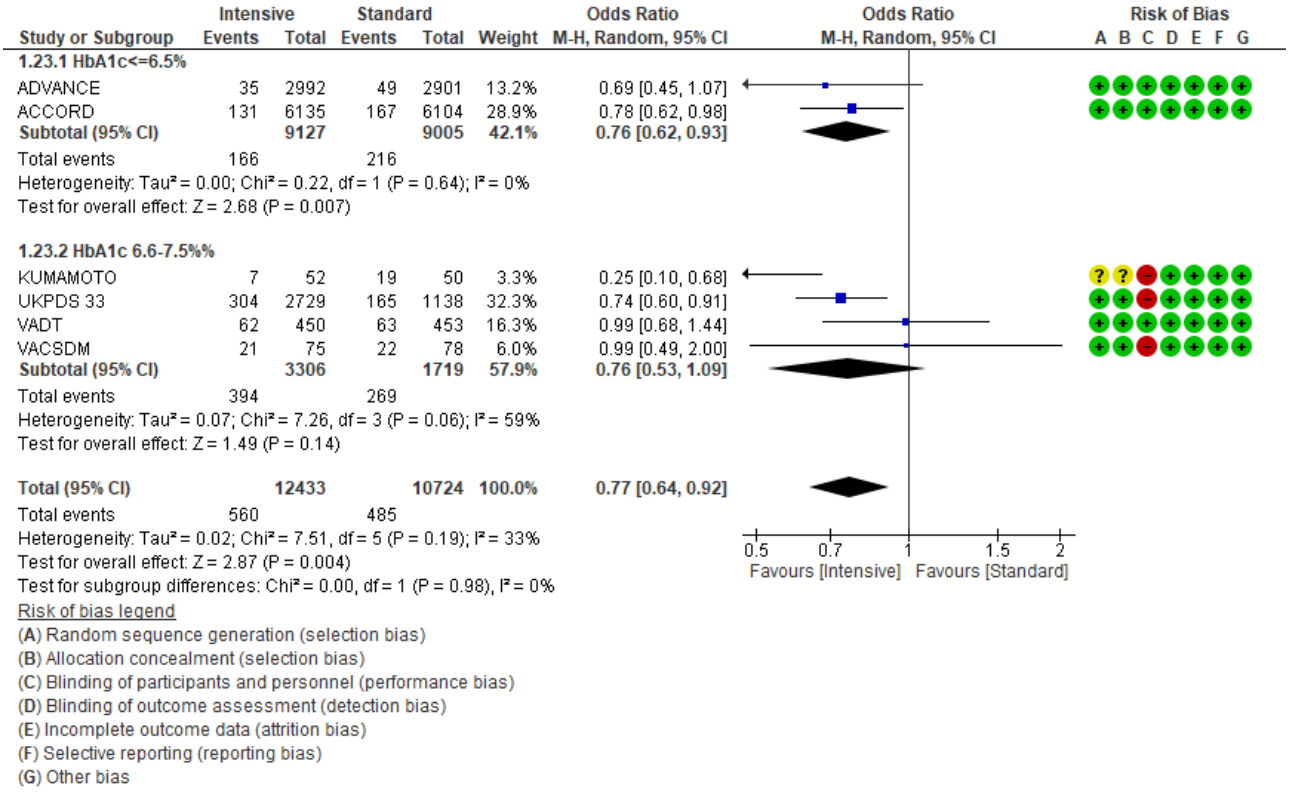
1) duration of treatment ≥2 years
2) between-group HbA1c difference ≥0.5% (≥ 6 mmol/mol)
3) primary or secondary endpoints, including at least one of the following events: MACE or microvascular complications.

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.

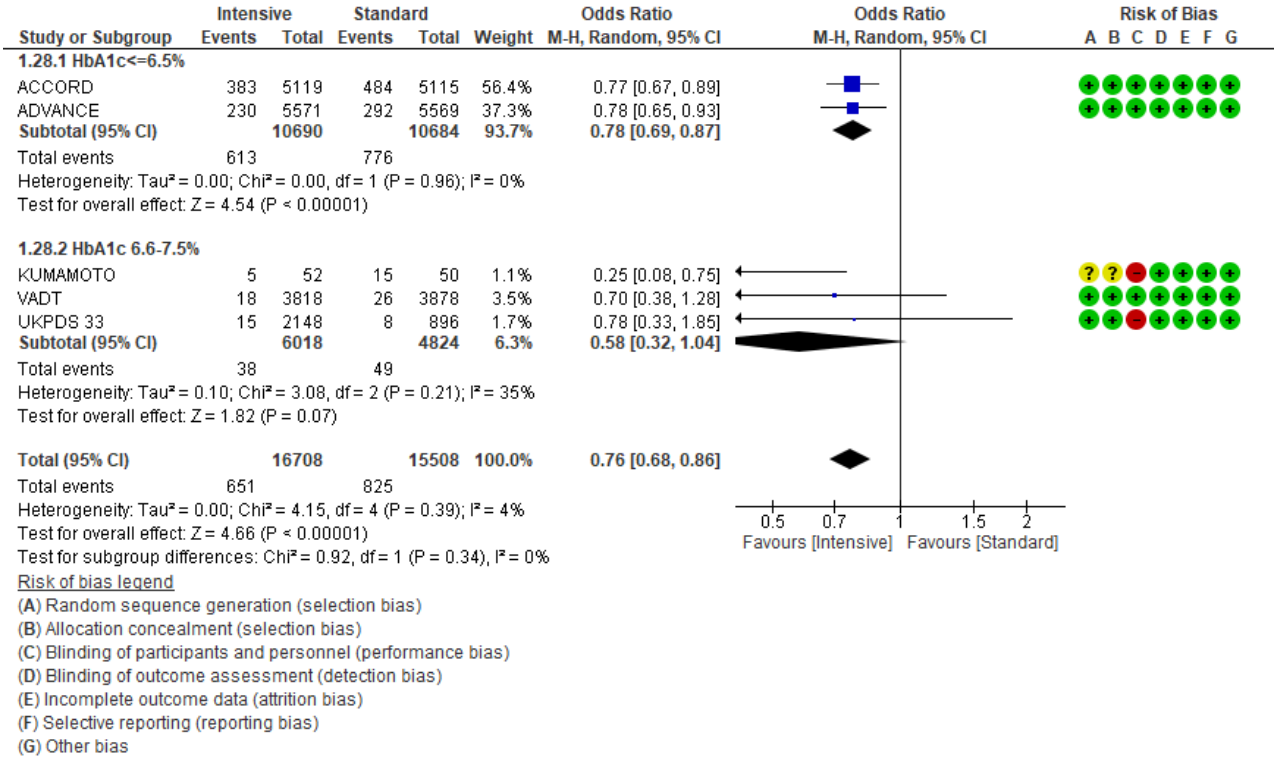
The systematic review has already been published; for complete search string, list and characteristics of included studies, and assessment of publication bias, please see the related publication[1].

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.

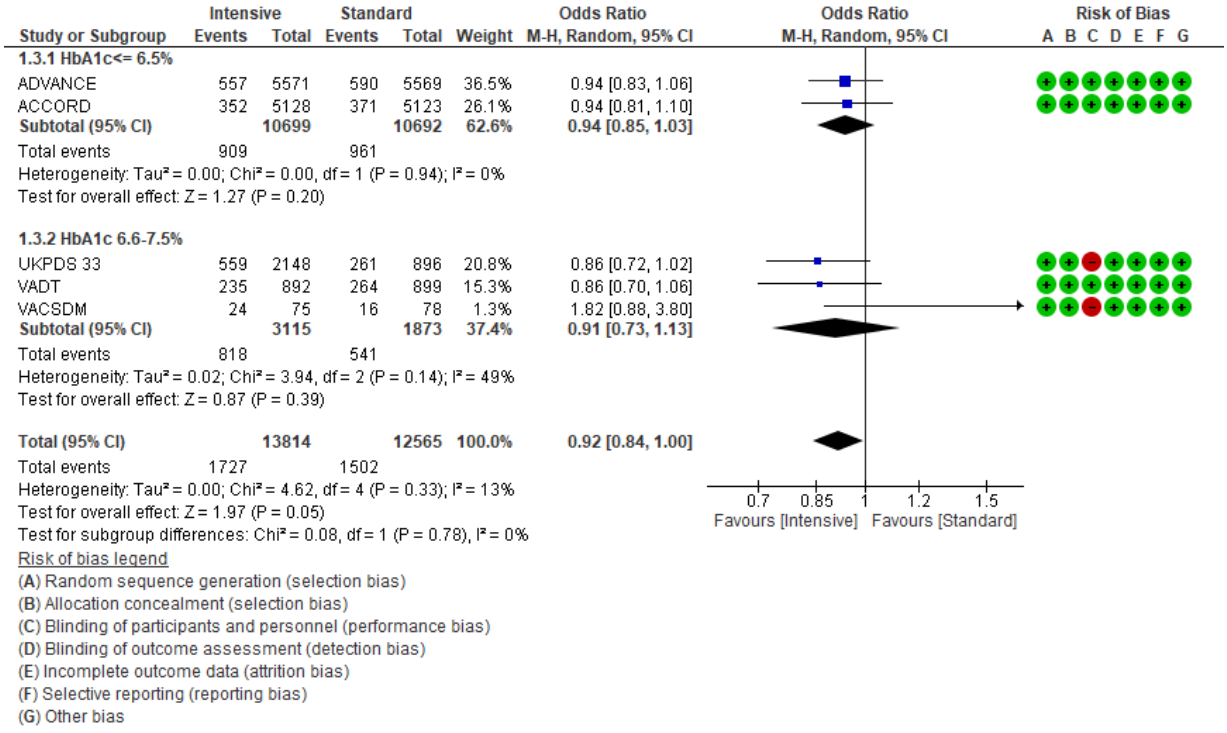


Forest plot for trials comparing the effects of intensive glycemic control (using drugs associated with hypoglycemia) and standard care on renal adverse events.

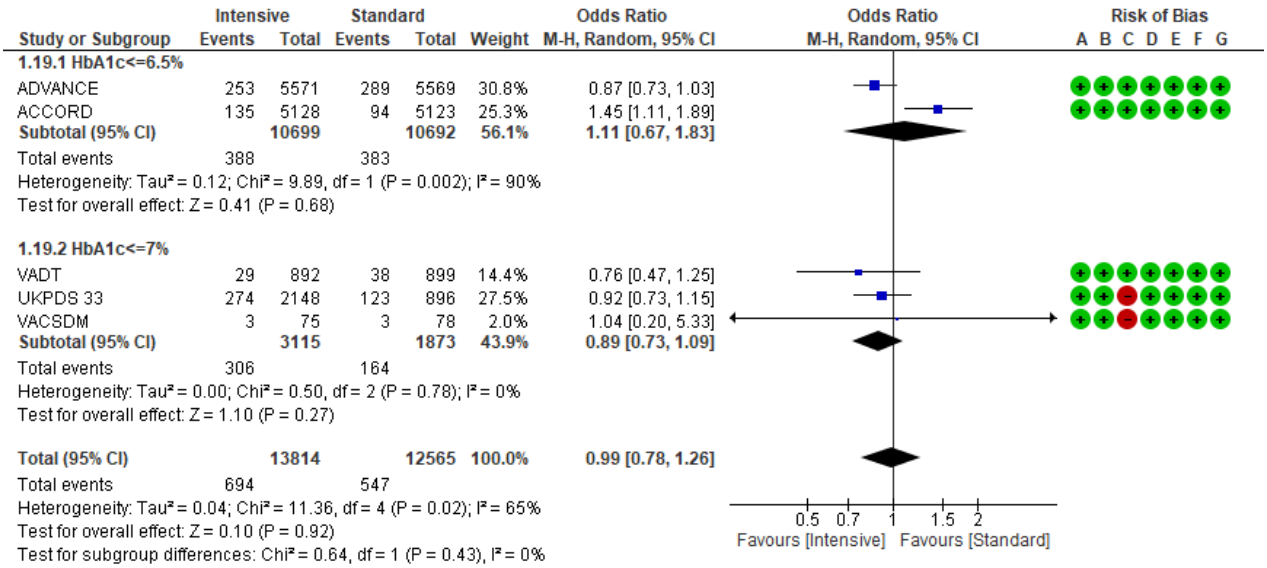


1.1.2. MACE

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

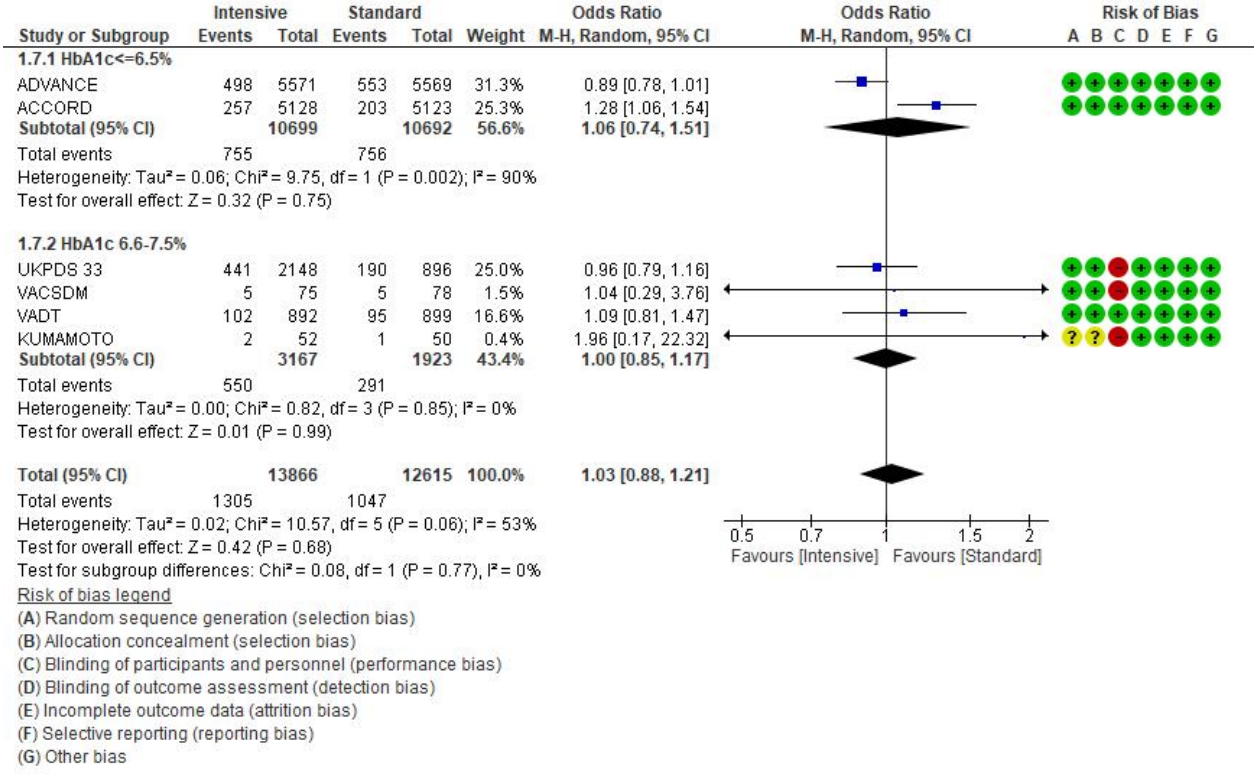


Forest plot for trials comparing the effects of intensive glycemic control (using drugs associated with hypoglycemia) and standard care on cardiovascular mortality.



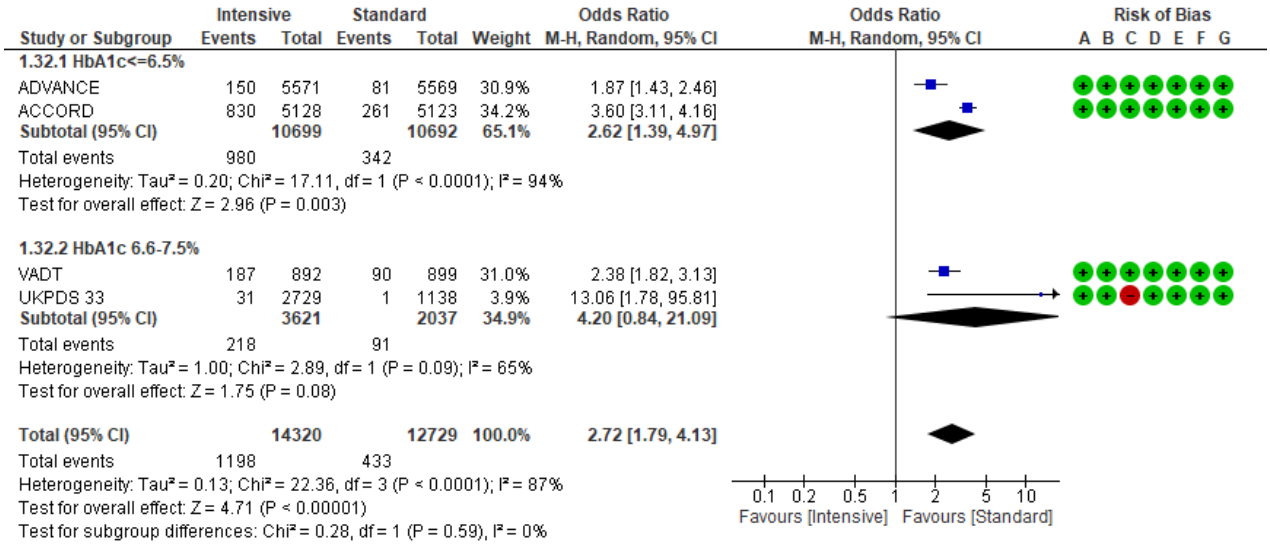
1.1.3. All-cause mortality

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.



1.1.5. GRADE evidence table

Certainty assessment							Summary of findings				
							Study event 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 in controls	Risk difference with the intervention
MACE											
For HbA1c ≤48 mmol/mol (6.5%)											
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)
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	*19 fewer per 1.000* (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	*4 more per 1.000* (from 17 fewer to 32 more)
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	*0 fewer per 1.000* (from 20 fewer to 21 more)

Certainty assessment							Summary of findings				
							Study event 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
Cardiovascular mortality											
For HbA1c ≤48 mmol/mol (6.5%)											
21391 (2 RCTs)	serious[a]	serious[b]	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	*4 more per 1000* (from 12 fewer to 28 more)
For HbA1c 48-58 mmol/mol (6.6-7.5%)											
4988 (3 RCTs)	serious[a]	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	*9 fewer per 1000* (from 22 fewer to 7 more)
Eye adverse events											
For HbA1c ≤48 mmol/mol (6.5%)											
18132 (2 RCTs)	serious[a]	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 fewer)
For HbA1c 48-58 mmol/mol (6.6-7.5%)											
5025 (4 RCTs)	serious[a]	serious[b]	not serious	not serious	none	⨁⨁◯◯ LOW	269/1719 (15.6%)	394/3306 (11.9%)	OR 0.76 (0.53 to 1.09)	156 per 1000	**33 fewer per 1000** (from 67 fewer to 12 more)

Certainty assessment							Summary of findings				
							Study event 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
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	⊕⊕◯◯ LOW	49/4824 (1.0%)	38/6018 (0.6%)	OR 0.58 (0.32 to 1.04)	10 per 1000	*4 fewer per 1000* (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	*119 more per 1000* (from 7 fewer to 45 2 more)

CI: 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:

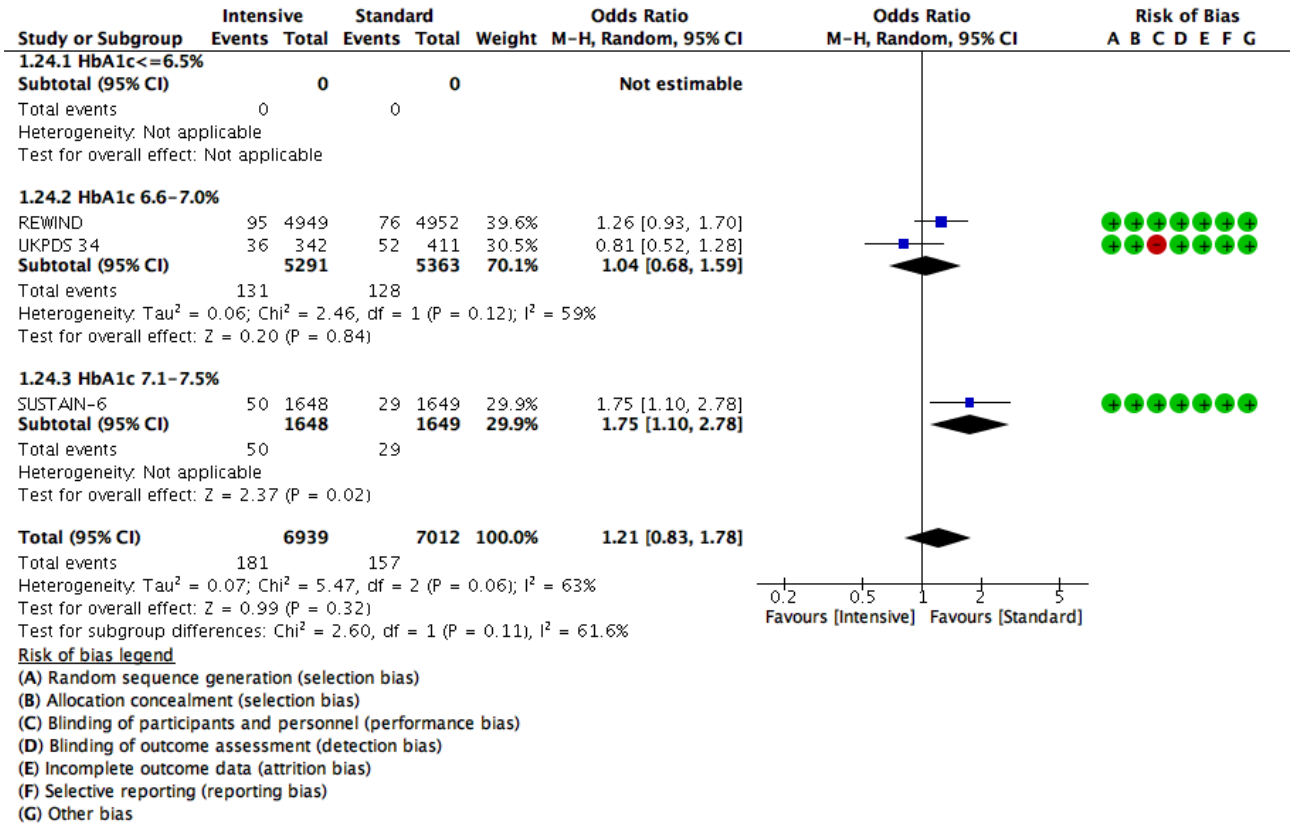
1) duration of treatment ≥2 years
2) between-group HbA1c difference ≥0.5% (≥ 6 mmol/mol)
3) primary or secondary endpoints, including at least one of the following events: MACE or microvascular complications.

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.

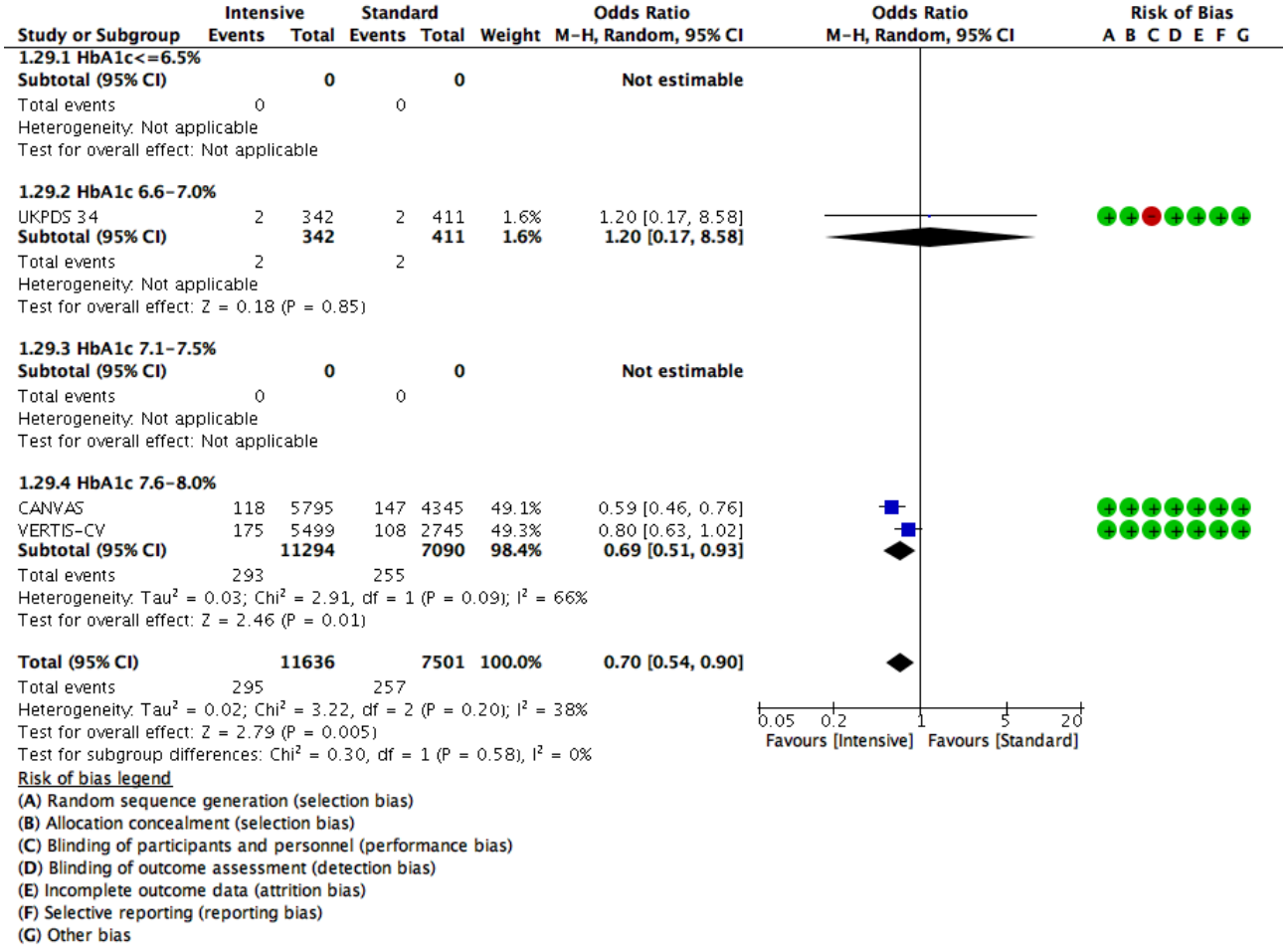
The systematic review has already been published; for complete search string, list and characteristics of included studies, and assessment of publication bias, please see the related publication [1].

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.

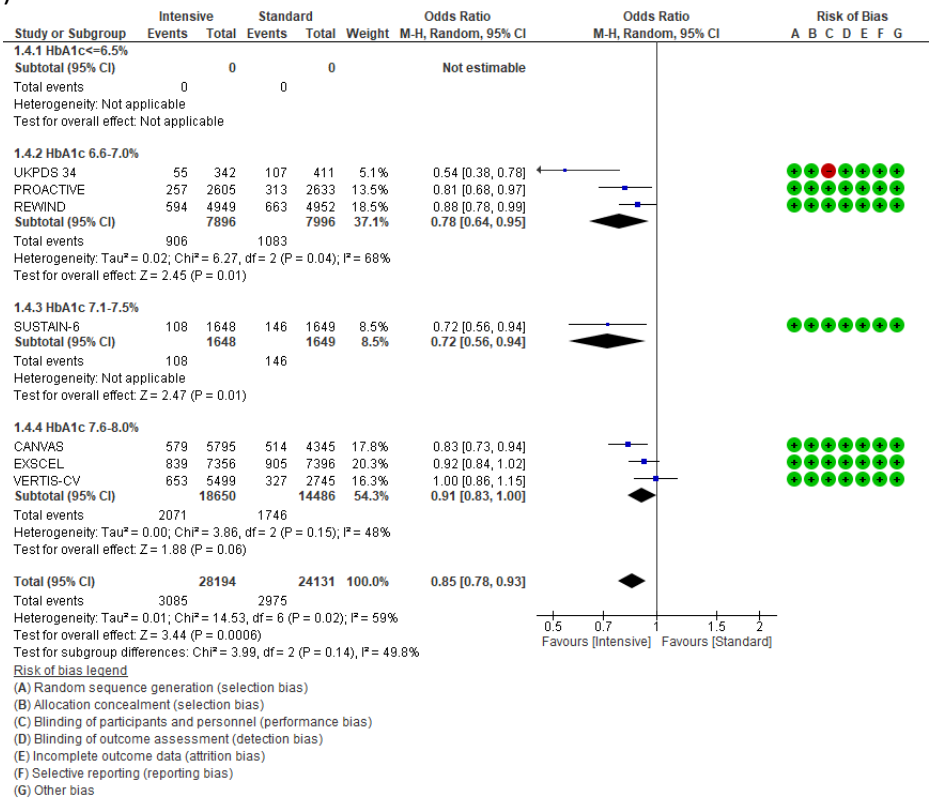


Forest plot for trials comparing the effects of intensive glycemic control (using drugs associated with hypoglycemia) and standard care on renal adverse events.

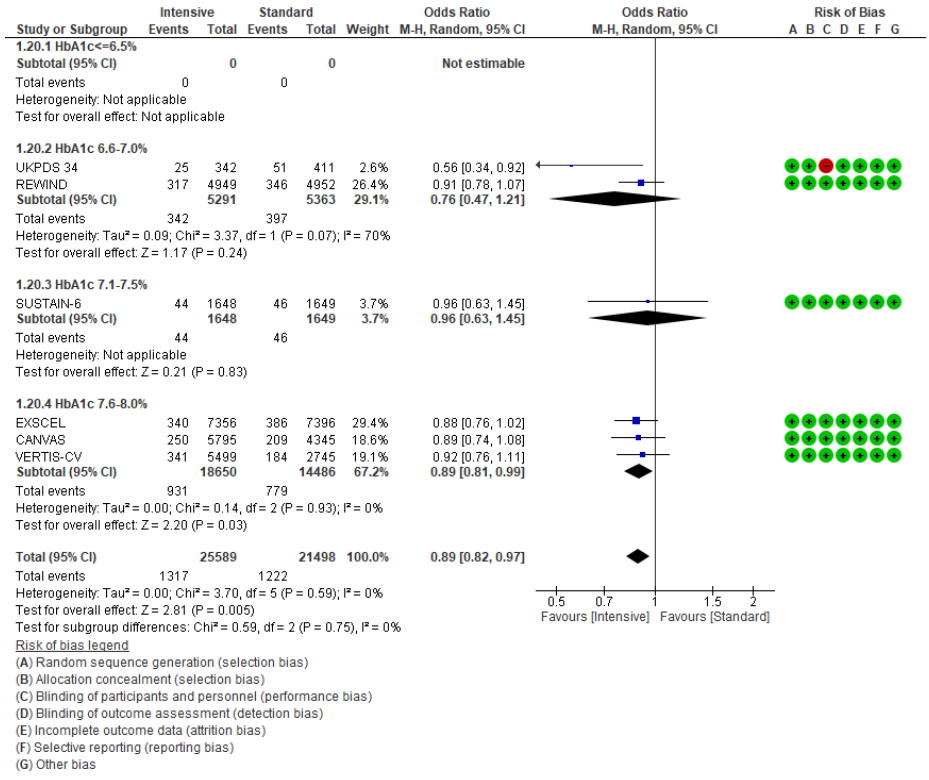


1.1.2. MACE

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

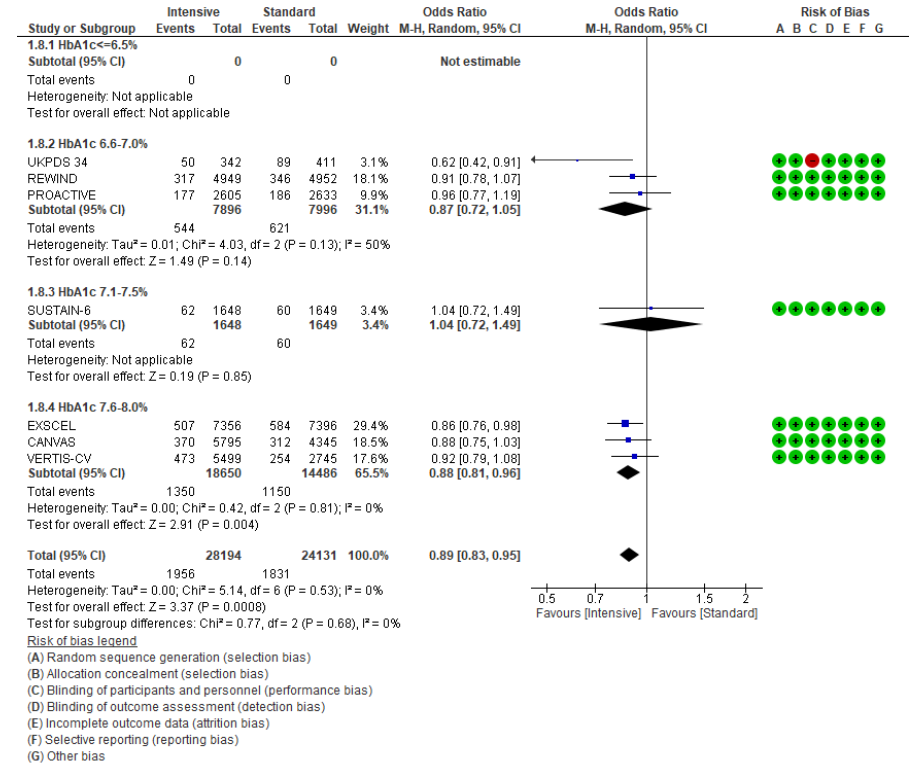


Forest plot for trials comparing the effects of intensive glycemic control (using drugs associated with hypoglycemia) and standard care on cardiovascular mortality.



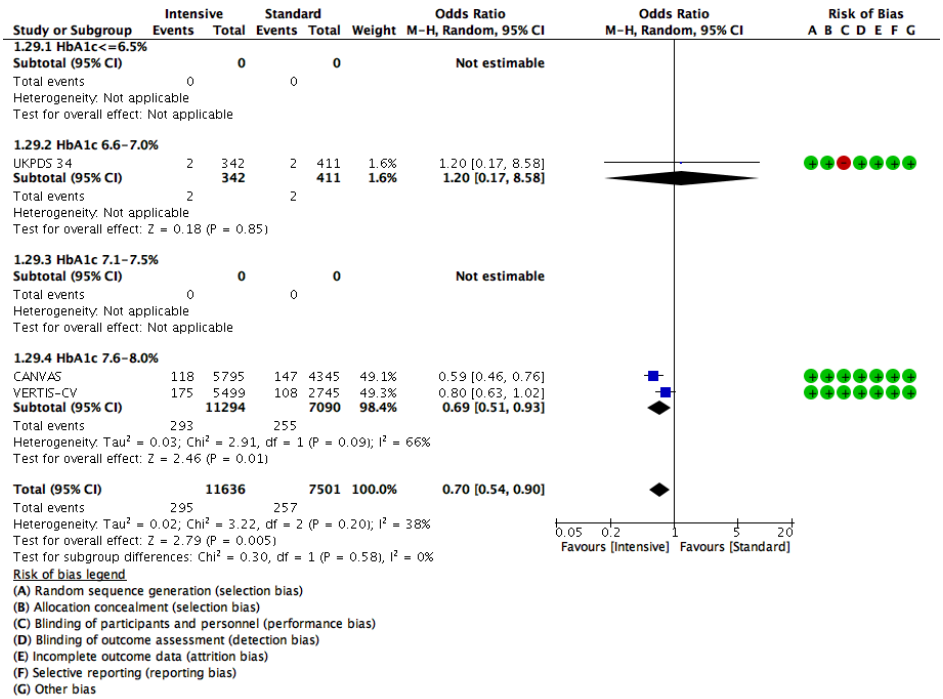
1.1.3. All-cause mortality

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.



1.1.5. GRADE evidence table

Certainty assessment							Summary of findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Standard care	With Intensive glycemic control		Risk with placebo	Risk difference with Intensive glycemic control
MACE											
For HbA1c ≤48 mmol/mol (6.5%)											
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	*5 fewer per 1000* (from 12 fewer to 2 more)
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)
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)
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)

Certainty assessment							Summary of findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							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 serious	serious[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 32 more)
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	*9 fewer per 1000* (from 21 fewer to 4 more)
For HbA1c 54-58 mmol/mol (7.1-7.5%)											
3297 (1 RCT)	not serious	serious[b]	not serious	serious[d]	none	⨁⨁◯◯ LOW	60/1649 (3.6%)	62/1648 (3.8%)	OR 1.04 (0.72 to 1.49)	36 per 1000	*1 more per 1000* (from 10 fewer to 17 more)
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 assessment							Summary of findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							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	*4 more per 1000* (from 12 fewer to2 8 more)
For HbA1c 49-53 mmol/mol (6.6-7.0%)											
10654 (2 RCTs)	not serious	serious[b]	not serious	not serious	none	⊕⊕⊕◯ MODERATE	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)
For HbA1c 54-58 mmol/mol (7.1-7.5%)											
3297 (1 RCT)	not serious	not serious	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	*1 fewer per 1000* (from 10 fewer to 1 2 more)
For HbA1c 59-64 mmol/mol (7.6-8.0%)											
33136 (3 RCTs)	not serious	not 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)

Certainty assessment							Summary of findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							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)
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	*1 more per 1000* (from 8 fewer to 14 more)
For HbA1c 54-58 mmol/mol (7.1-7.5%)											
3297 (1 RCT)	not serious	not serious	not serious	very serious[c]	strong association	⨁⨁◯◯ LOW	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 assessment							Summary of findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							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)
For HbA1c 48-53 mmol/mol (6.6-7.0%)											
753 (1 RCT)	serious[a]	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)
For HbA1c 59-64 mmol/mol (7.6-8.0%)											
18384 (2 RCTs)	not serious	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)

*CI: 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 treatment 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 €1,922 for the reference group (HbA1c>8%) and €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% (€1,044) and 16.4% (€1,249), 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.

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/instrumental 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

					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 remained stable in the sensitivity analyses.

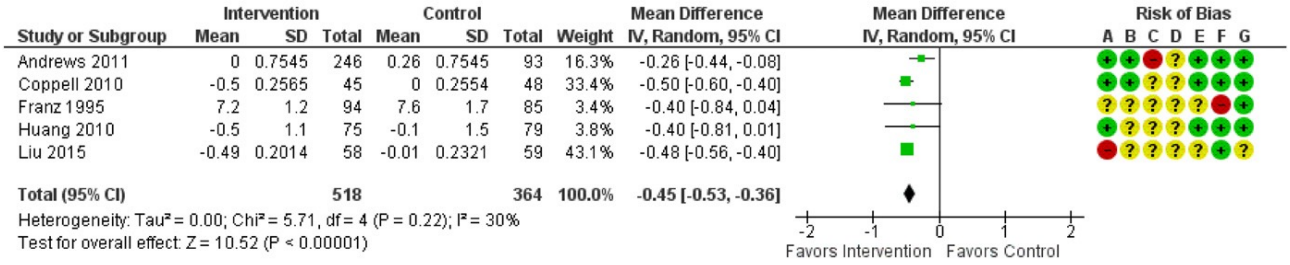
RECOMMENDATION # 2: NUTRIOTIONAL THERAPY.

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 publication[13].

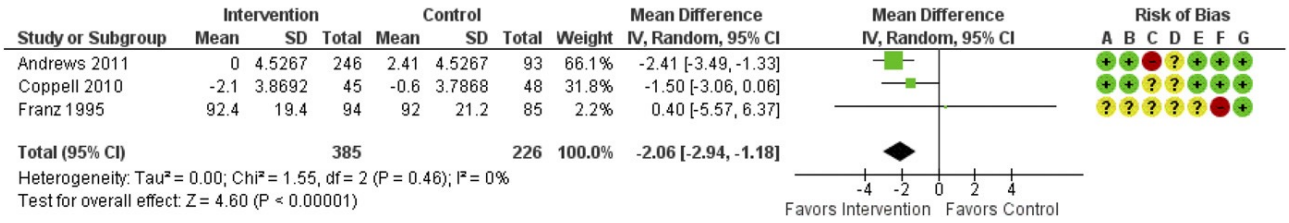
2.1.1. HbA1c

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



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.



2.1.3. GRADE evidence table

Certainty assessment							Summary of findings		
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Relative effect (95%, CI)	Anticipated absolute effects	
								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 percentage at endpoint (%)									
611 (3 RCTs)	serious[a]	serious[b]	not serious	not serious	none	⨁⨁◯◯ LOW	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 $.	NA	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%CI £1147-£1294) while the intervention group had significantly lower cost per participant than did controls for antidiabetes drugs (mean difference £120, 95%CI 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.

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:

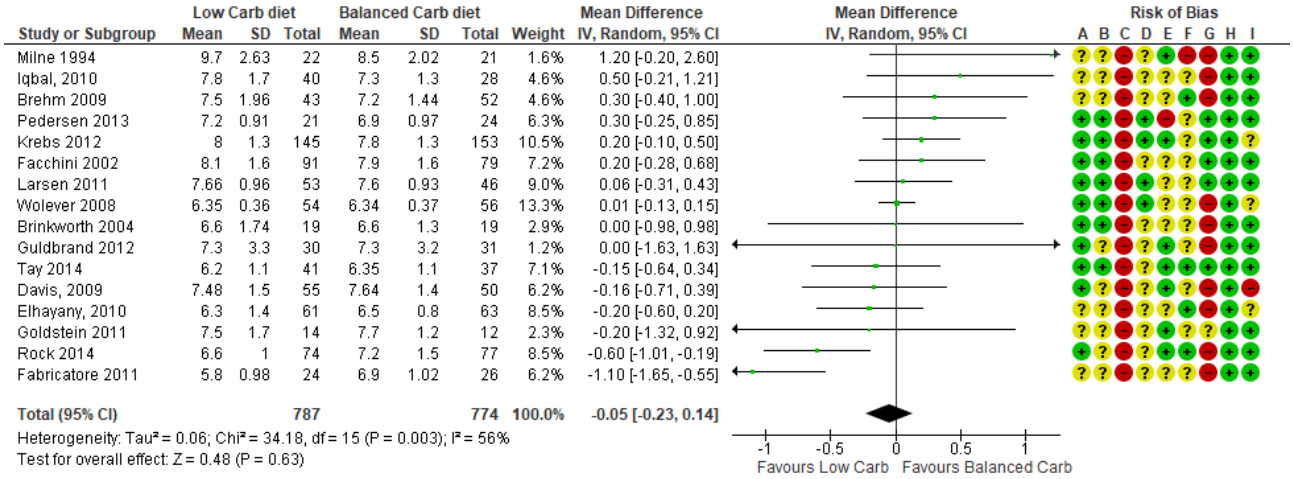
1) Difference in mean HbA1c levels, between all LC diets and balanced carbohydrate diets after 3–4, 6–8, 12, and 24 months.
2) Difference in mean creatinine levels, and mean estimated glomerular filtration rate (eGFR), between all LC diets and balanced carbohydrate diets at endpoint.
3) Difference in 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 publication[17].

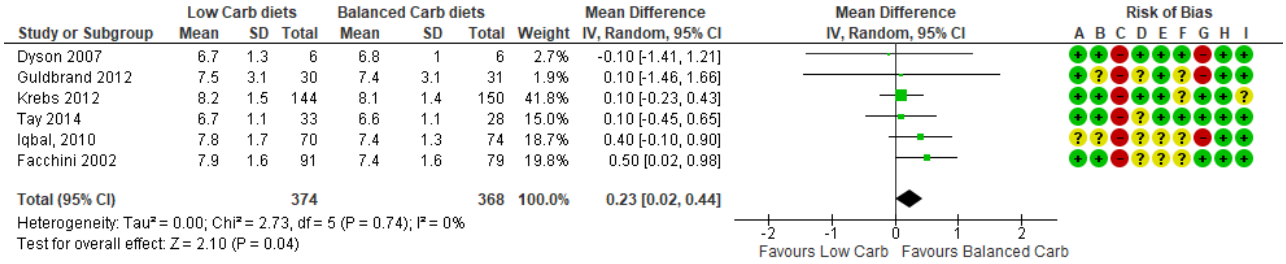
2.2.1. HbA1c

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 (%).

A



B

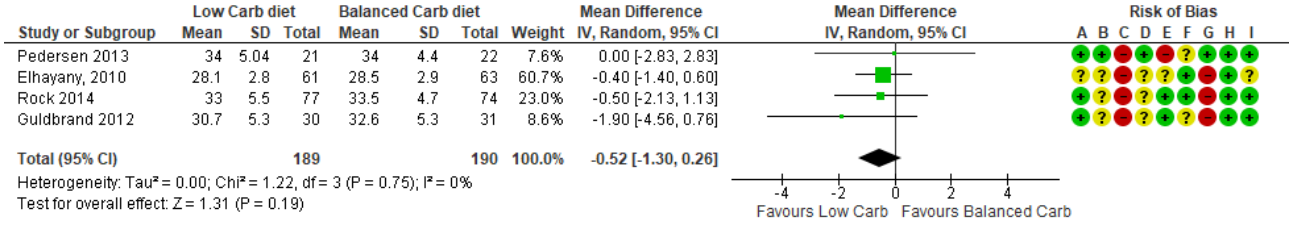


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting for weight (reporting bias)
(G) Selective reporting for renal function (reporting bias)
(H) Selective reporting (reporting bias)
(I) Other bias

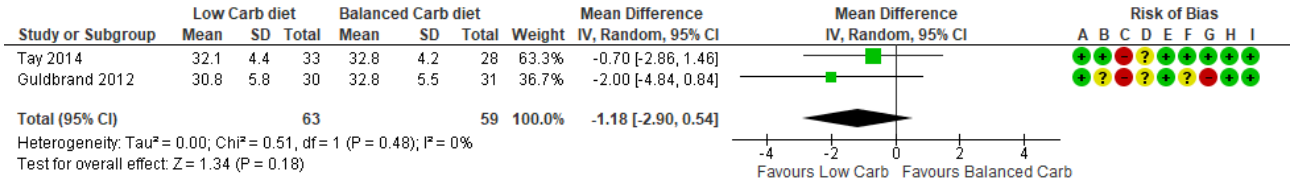
2.2.2. BMI

Forest plot for trials comparing the effects of low-carbohydrate diets and balanced diets on 12-month (panel A) and 24-month (Panel B) BMI (Kg/m^2).

A



B



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 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 assessment							Summary of findings		
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Relative effect (95%, CI)	Anticipated absolute effects	
								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 mesi									
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 mesi									
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)	serious[a]	serious[b]	non serious	serious[c]	none	⨁◯◯◯ VERY LOW	- 1.18 [-2.90; 0.54]	-	MD 1.18 Kg/m^2 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	-	-	-	-	-	-	-

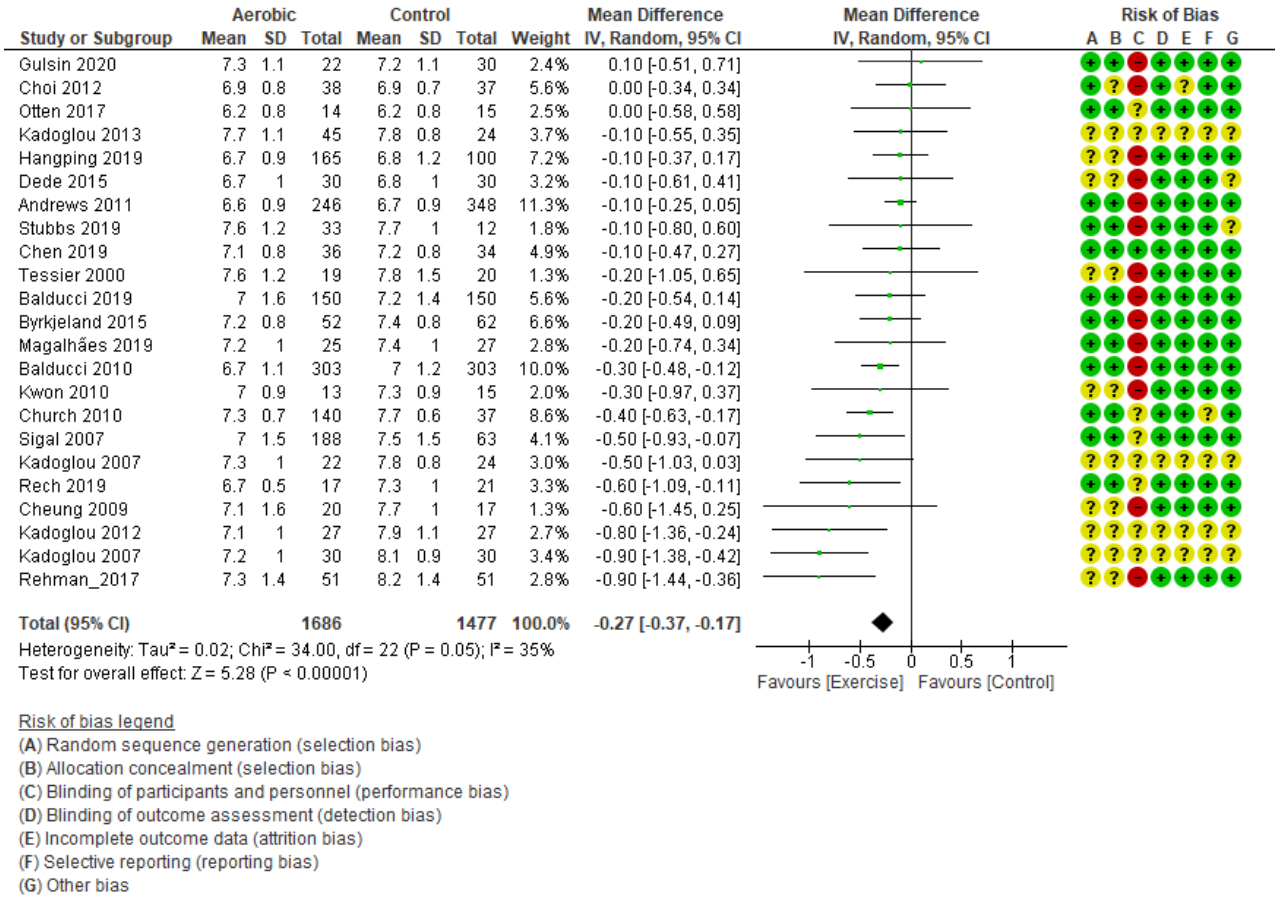
RECOMMENDATION # 3: PHYSICAL EXERCISE.

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 publication[18].

3.1.1. HbA1c

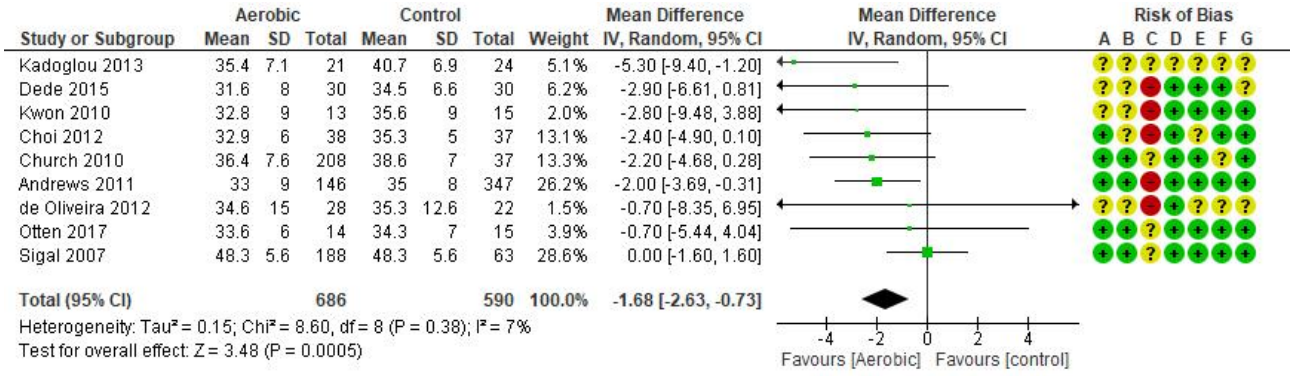
Forest plot for trials comparing the effects of regular physical exercise and no intervention on HbA1c (%) at endpoint.



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

3.1.2. Body fat

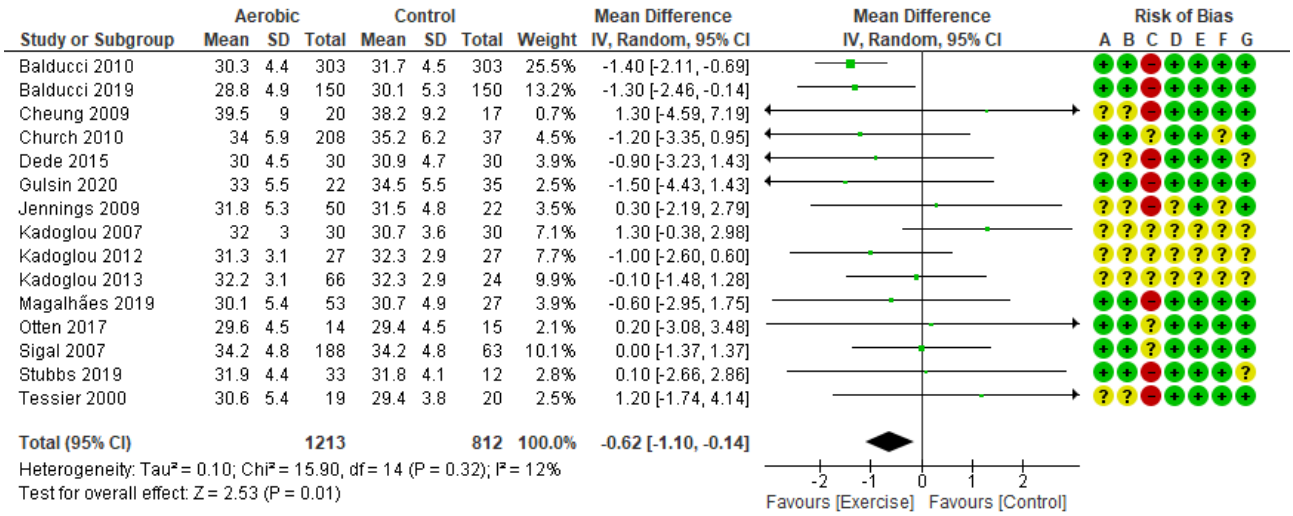
Forest plot for trials comparing the effects of regular physical exercise and no intervention on body fat (%) at endpoint.



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.



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. GRADE evidence table

Certainty assessment							Summary of findings		
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Relative effect (95%, CI)	Anticipated absolute effects	
								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 %	**MD 0.27 % lower** (da 0.13 lower a 0.42 lower)
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)
BMI (Kg/m^2)									
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/m^2 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).

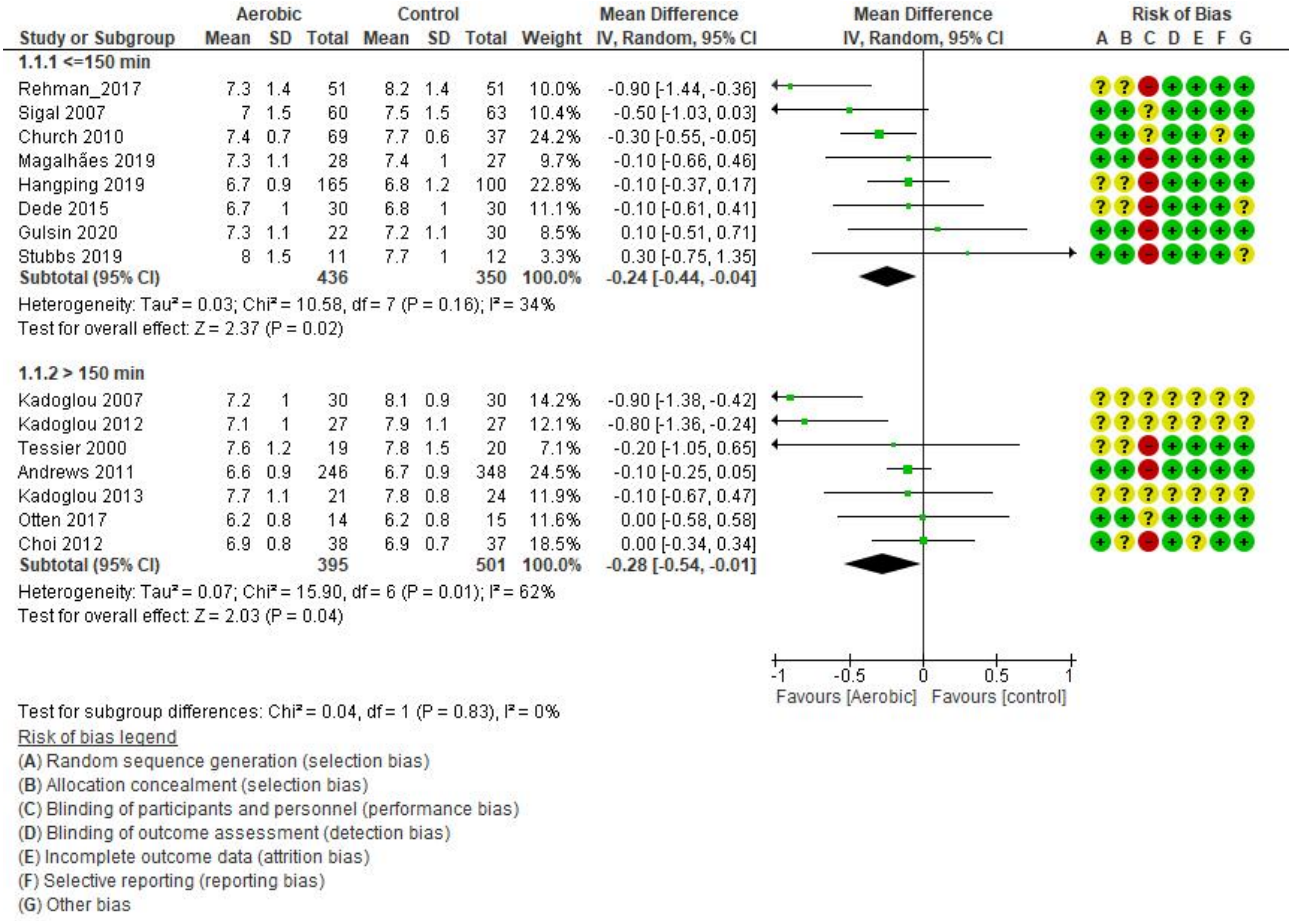
Author	Country	Intervention	Type of analysis	Incremental cost	Incremental cost (QALY)	Incremental cost per QALY gained	Authors' conclusions
Coyle 2012[19]	Canada	1) aerobic 2) anaerobic 3) combined 4) none The patient population for the model was the same as the DARE[2] clinical trial	Cost-effectiveness 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 €60 in cost of medications treating for T2D (p=0.014), and a significant decrease of €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 publication[18].

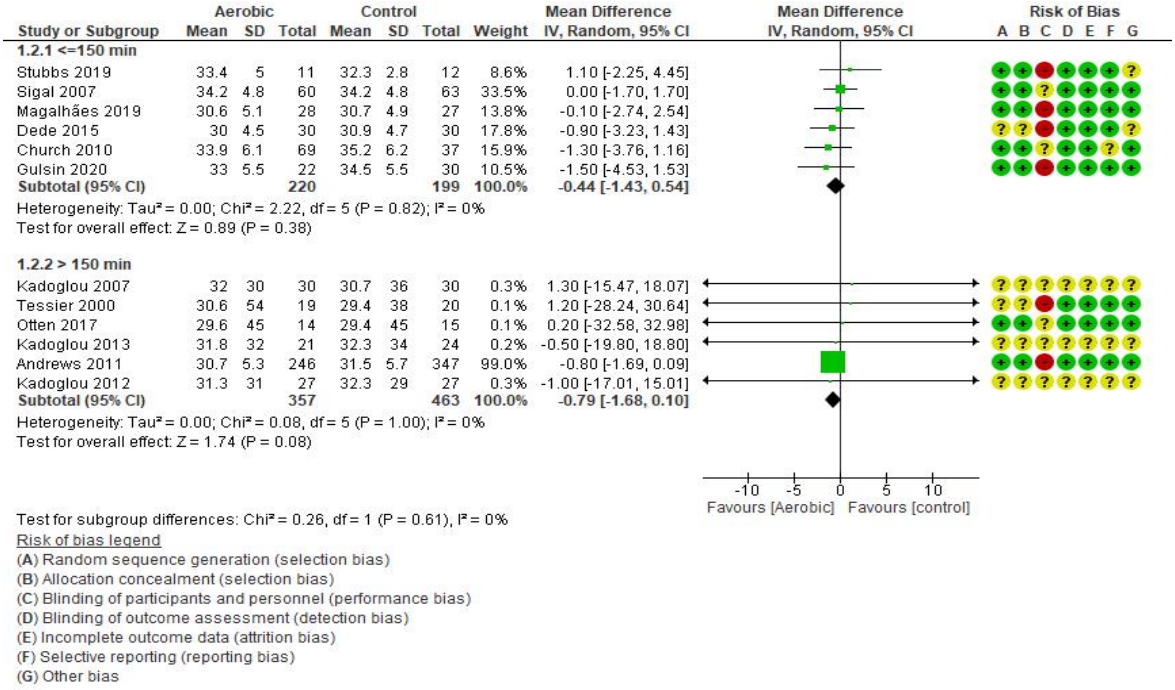
3.2.1. HbA1c

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



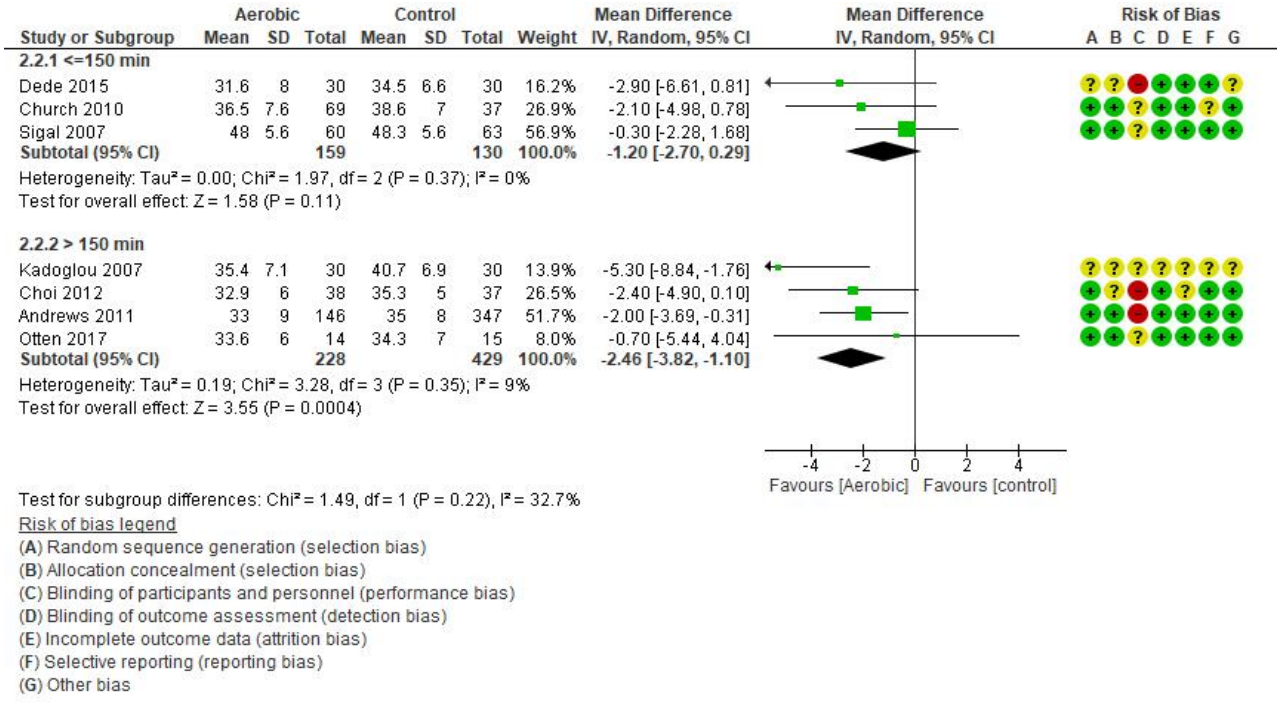
3.2.2. Body fat

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



3.2.3. BMI

Forest plot for trials comparing the effects of regular aerobic physical exercise (versus no intervention), with a duration> or ≤150 min/week on BMI (Kg/m^2) at endpoint.



3.2.4. GRADE evidence table

Certainty assessment							Summary of findings		
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Relative effect (95%, CI)	Anticipated absolute effects	
								Control	Intervention
HbA1c (%) for RCT with physical exercise ≤ 150 min/week									
786 (8 RCTs)	serious[a]	not serious	not serious	serious[b]	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 exercise >150 min/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 (%) for RCT with physical exercise ≤ 150 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 (%) per gli studi dii durata >150 min/ settimana									
657 (4RCTs)	serious[a]	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/m^2) 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 massa corporea (Kg/m^2) per gli studi dii durata >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 BMIat the end of the study: 31.2 Kg/m^2	MD 0.8 Kg/m^2 lower (from 1.7 lower to 0.10 more)

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.

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).

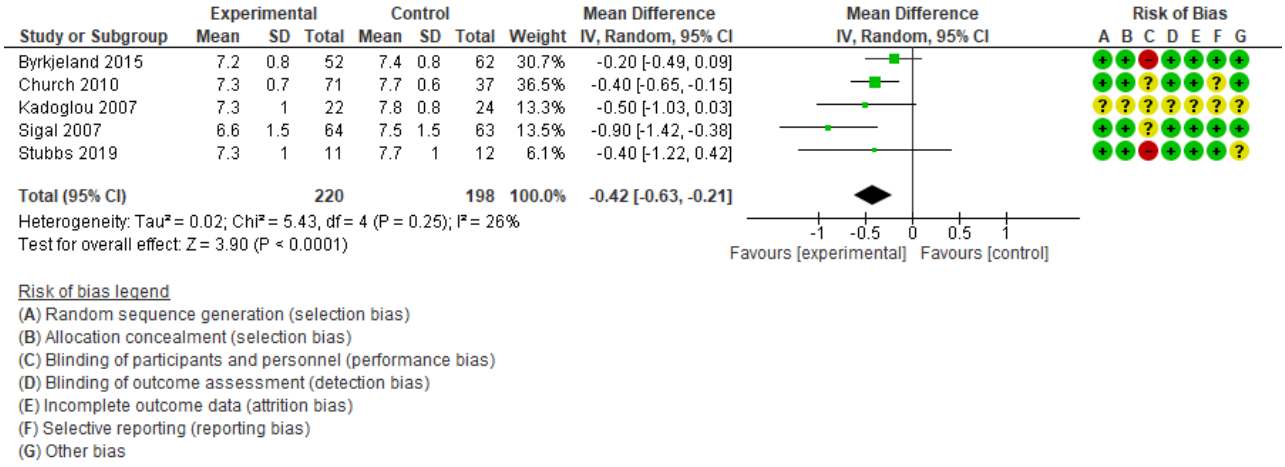
Author	Country	Intervention	Type of analysis	Incremental cost	Incremental cost (QALY)	Incremental cost per QALY gained	Authors' conclusions
No studies retrieved	-	-	-	-	-	-	-

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)
(G) Other bias

3.3.2. GRADE evidence table

Certainty assessment							Summary of findings		
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Relative effect** (95%, CI)	**Anticipated absolute effects**	
								Control	**Intervention**
HbA1c (%)									
418 (5 RCTs)	serious[a]	not serious	not serious	serious[b]	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)

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.

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 (QALY)	Incremental cost per QALY gained	Authors' conclusions
No studies retrieved	-	-	-	-	-	-	-

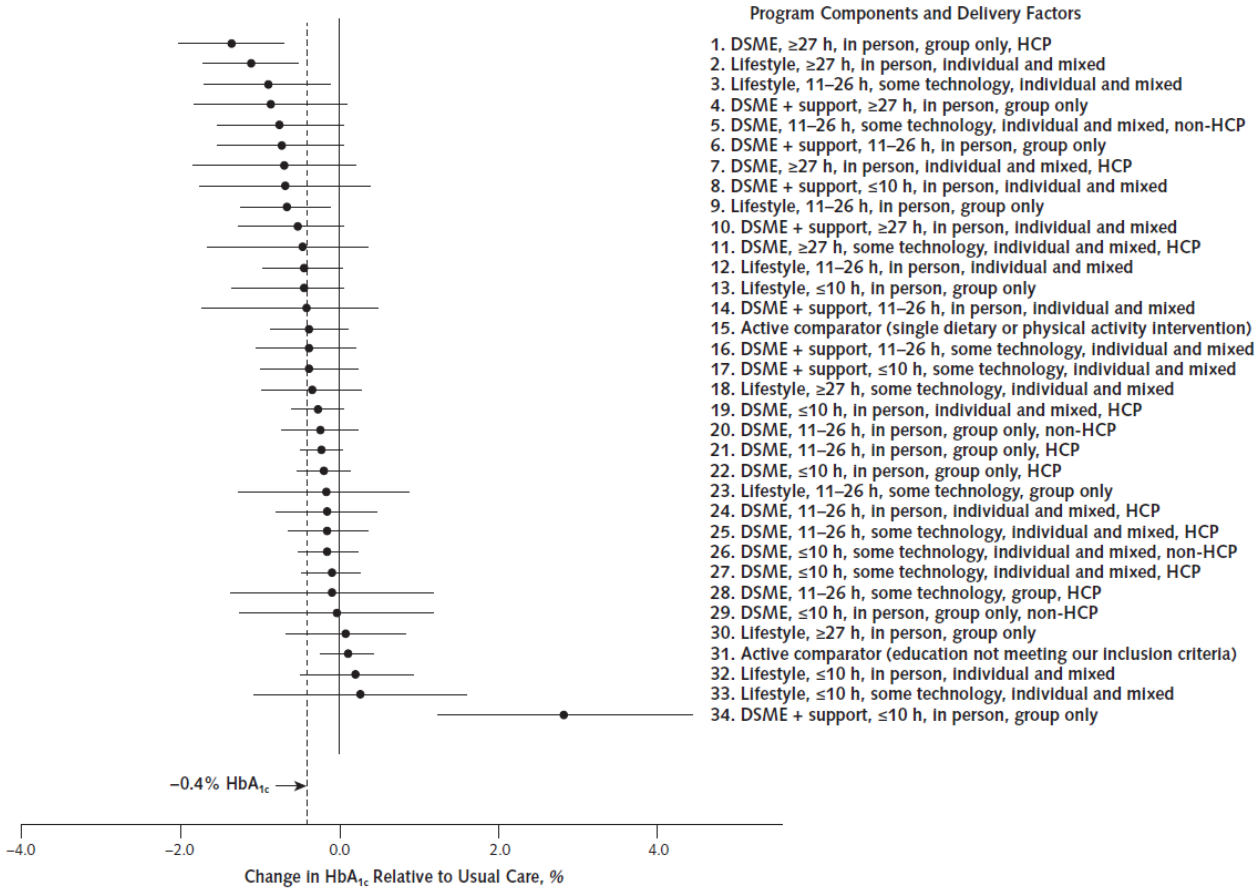
RECOMMENDATION # 4: EDUCATIONAL THERAPY.

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 publication[21].

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 assessment							Summary of findings		
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Relative effect (95%, CI)	Anticipated absolute effects	
								Control	Intervention
HbA1c (%)									
912 (5 RCTs)	serious[a]	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 (PAID scale)									
753 (5 RCTs)	serious[a]	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' adherence (RR)									
14,154 (81 RCTs)	serious[a]	serious[d]	not serious	not serious	none	⨁⨁◯◯ LOW	1.11 [0.82;1.49]	-	RR 11 higher (from 18 lower to 49 higher)
Hypoglycemia (RR)									
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

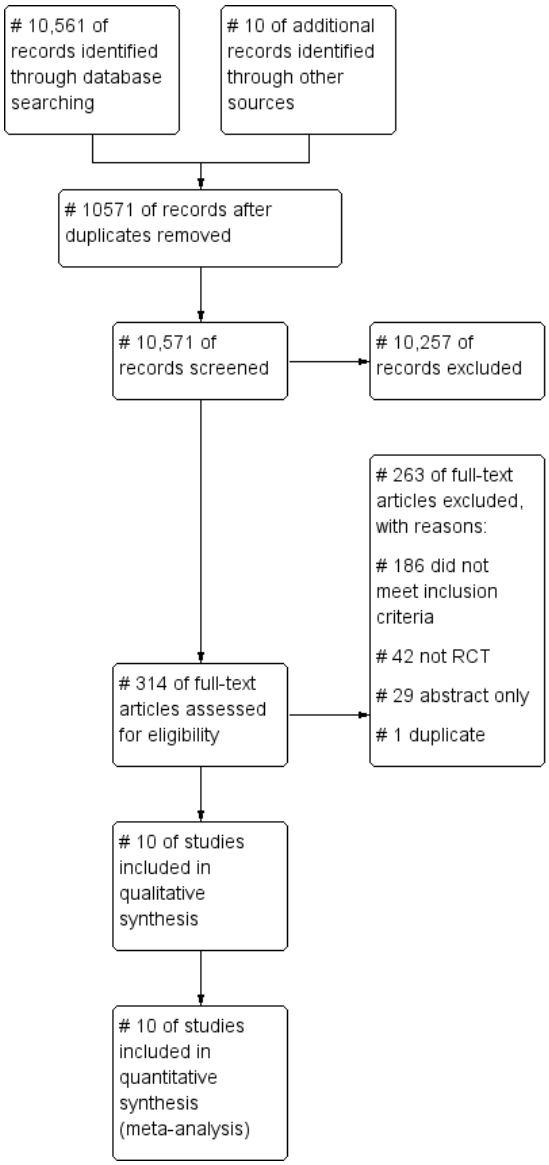
The search for pharmaeconomic studies has been performed including glycemic control as key-word; the study selection has been conducted considering the time horizon of the analysis, the target population, and excluding data deriving from drugs manufacturers.
Search string: (economic or cost or cost-effectiveness) 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 (QALY)	Incremental cost per QALY gained	Authors' conclusions
No studies retrieved	-	-	-	-	-	-	-

4.2. Group-based educational therapy

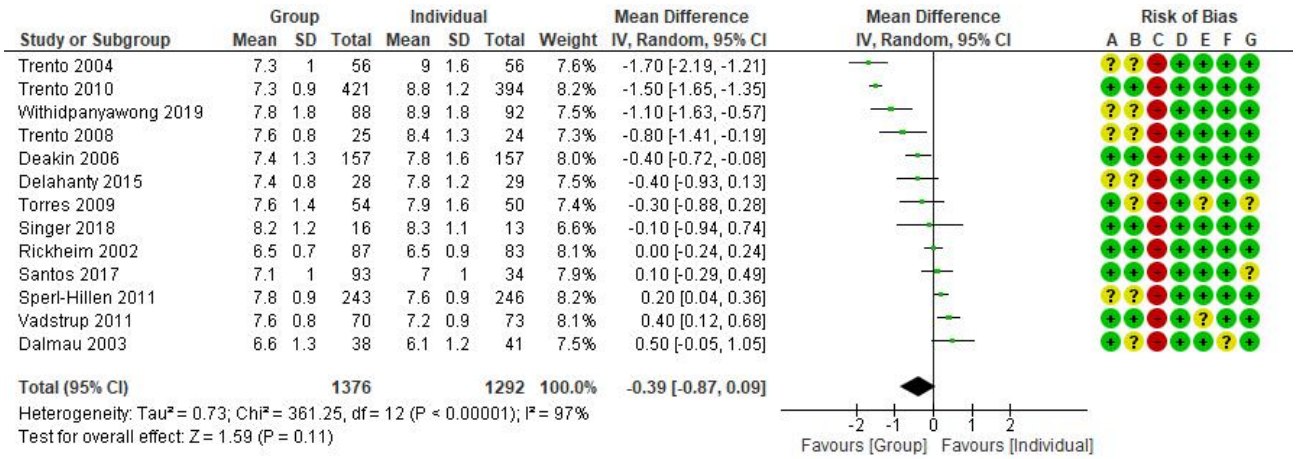
Considered evidence: A Medline and Embase search up to April 30st, 2021, was performed with the following key-words: "diabetes", "education", "group", "individual". RCT with at least a follow-up of 6 months, enrolling adult patients with type 2 diabetes and comparing individual with group settings for 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

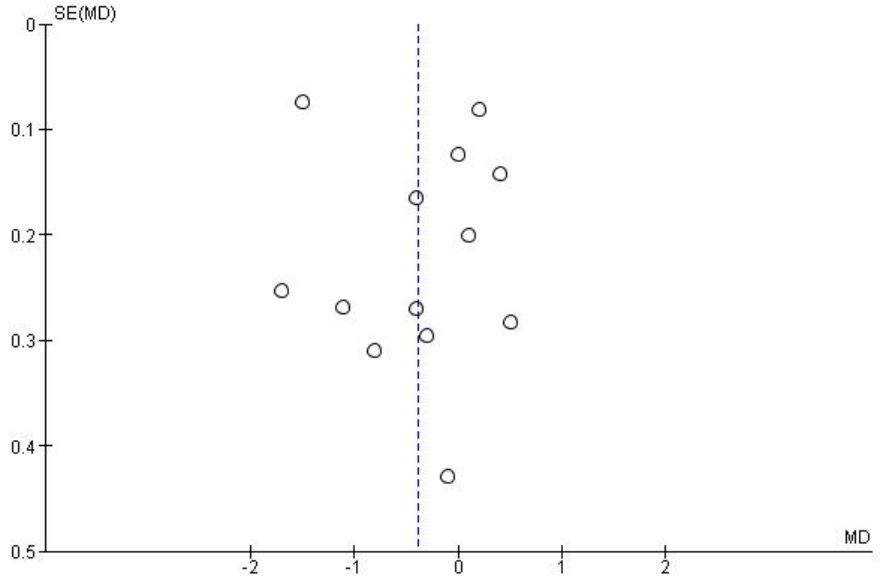


4.2.2. HbA1c

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

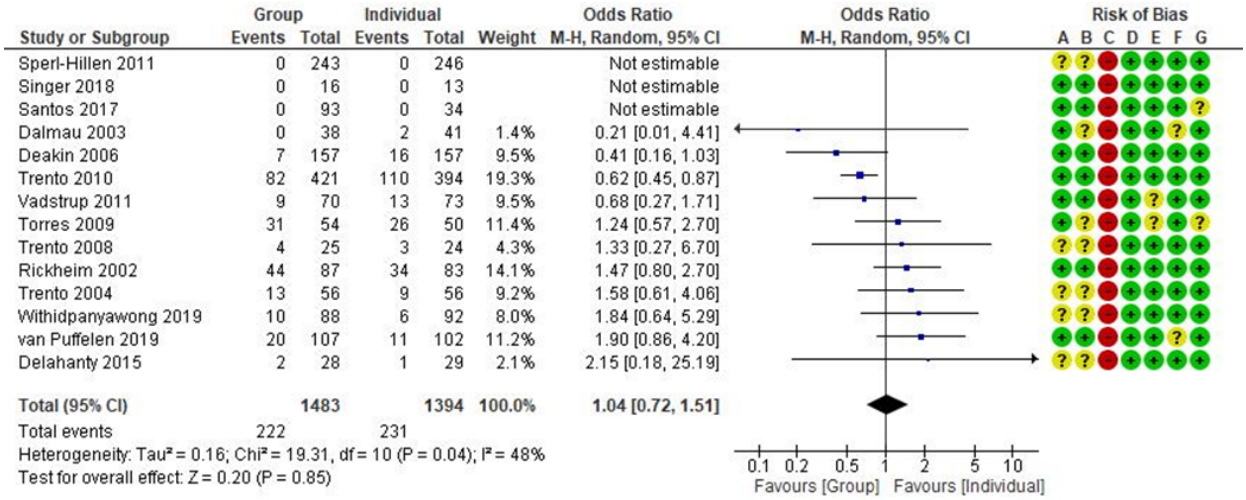


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

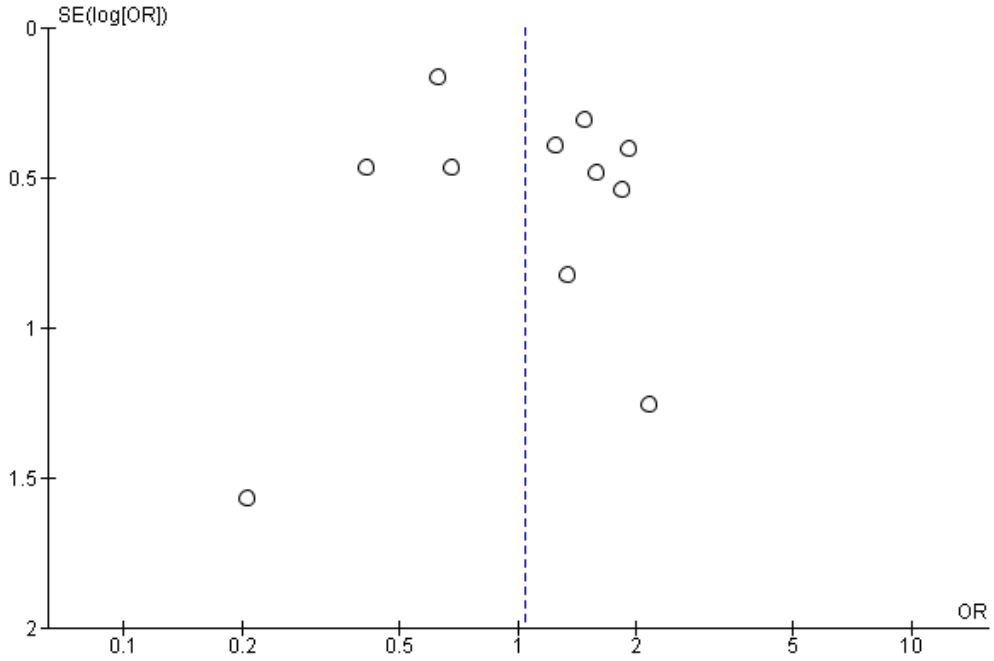


4.2.3. Patients' adherence

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

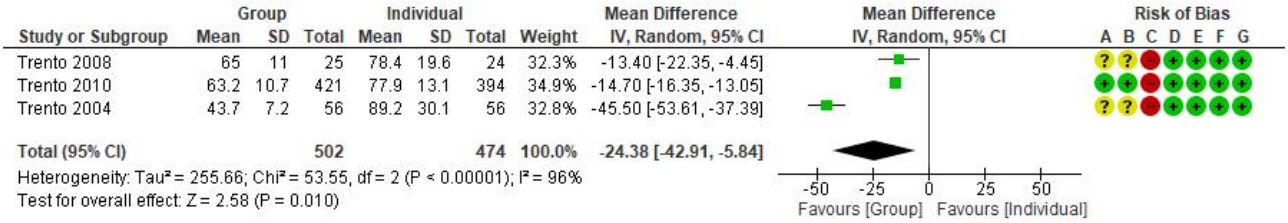


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias



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).



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

4.2.5. Trials' characteristics

Baseline characteristics of the trials included in the meta-analysis

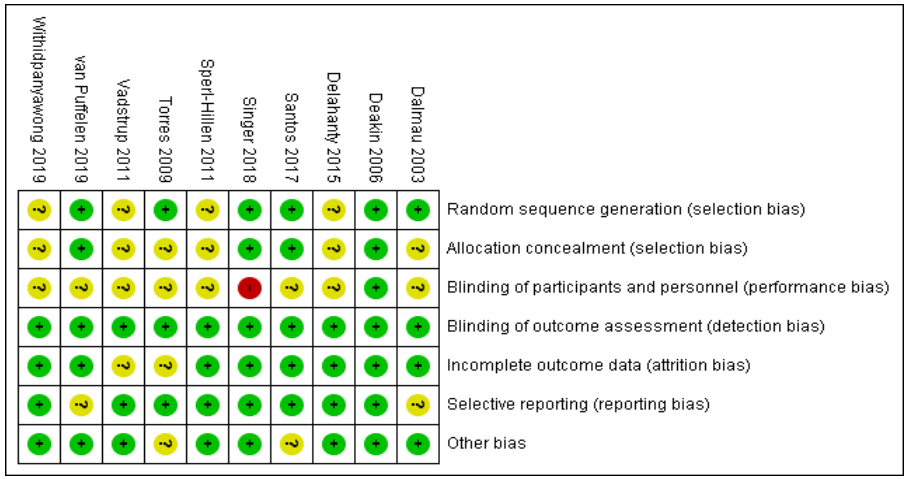
First author (ref)	**Group education** (#patients)	**Indivdual education** (#patients)	**Trial duration**(months)	**# sessions**	**Session lenght** (min.)	**Profess.**	**HbA1$_c$** (%)	**BMI** (Kg/m^2)	**Duration of diabetes** (years)	**Pts on insulin** (%)	**Lost at follow-up** (GE/IE)
Dalmau Llorca[22]	38	41	12	3	40	N, 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

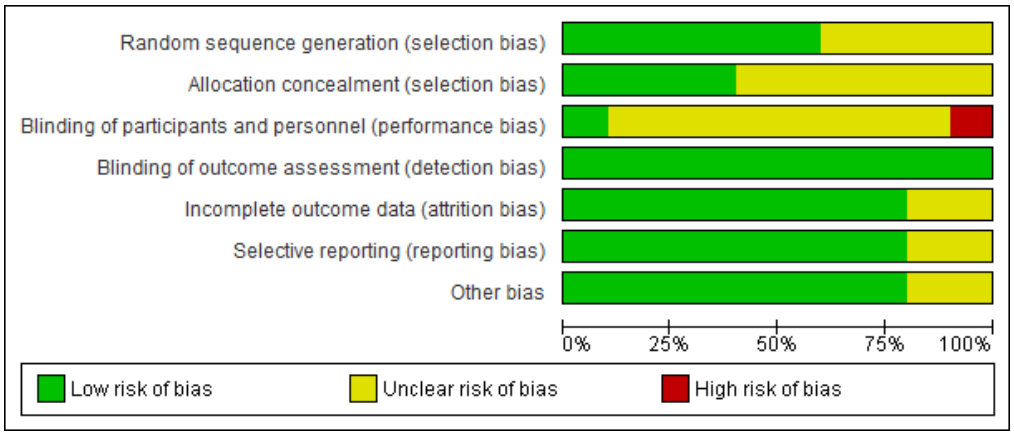
Van Puffelen[34]	107	102	6	4	120	N,P,PH	NR	NR	2	2.5	10/6
Withdpanywong[35]	98	98	9	4	45	N	9.1	27.6	6	0	10/6

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 assessment							Summary of findings		
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Relative effect (95%, CI)	Anticipated absolute effects	
								Control	Intervention
HbA1c (%)									
1,522 (9 RCTs)	serious[a]	serious[d]	not serious	not serious	none	⨁⨁◯◯ LOW	-0.10 [-0.39;0.20]	-	DM 0.10% lower (from 0.20 higher to 0.39 lower)
Aderenza al trattamento (persi al follow-up)									
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)	serious[a]	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.

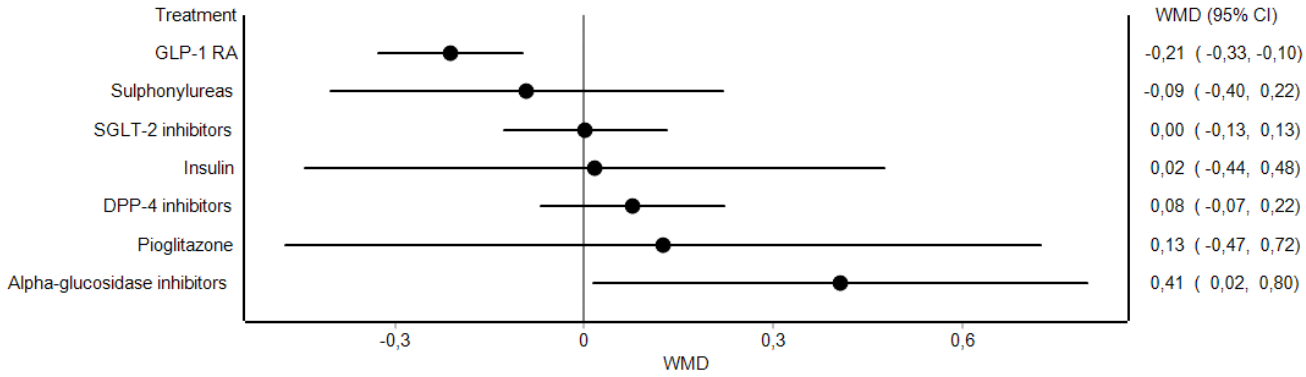
Considered evidence: Data on the effects of glucose-lowering agents on the medium- and long-term HbA1c and body weight are reported in an already published network metanalysis[9]. Data on the cardiovascular safety (MACE and hospitalization for heart failure) and mortality for each classes of drugs are reported in already published meta-analysis (i.e.: GLP-1[8], SGLT-2i[15], metformina[7], and insulin secretagogues[9]). 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 ≥ of 52 weeks[40].

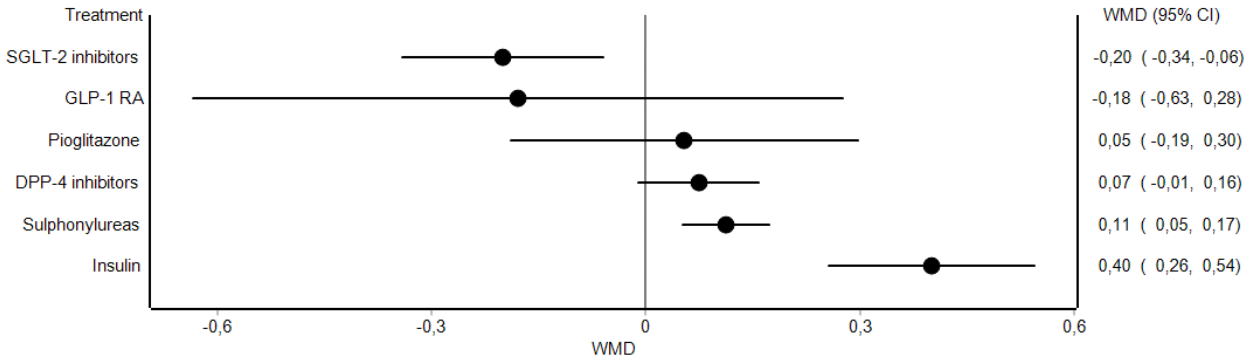
Network metanalysis of different glucose-lowering agents: forest plots of comparisons versus metformin. Panel A: 52 weeks; Panel B: ≥104 weeks. GLP-1 RA: Glucagon-Like Peptide-1 Receptor Agonists; SGLT-2: Sodium-Glucose Transporter-2; Sulfonylureas include also glinides.

A



Consistency H: 1.55

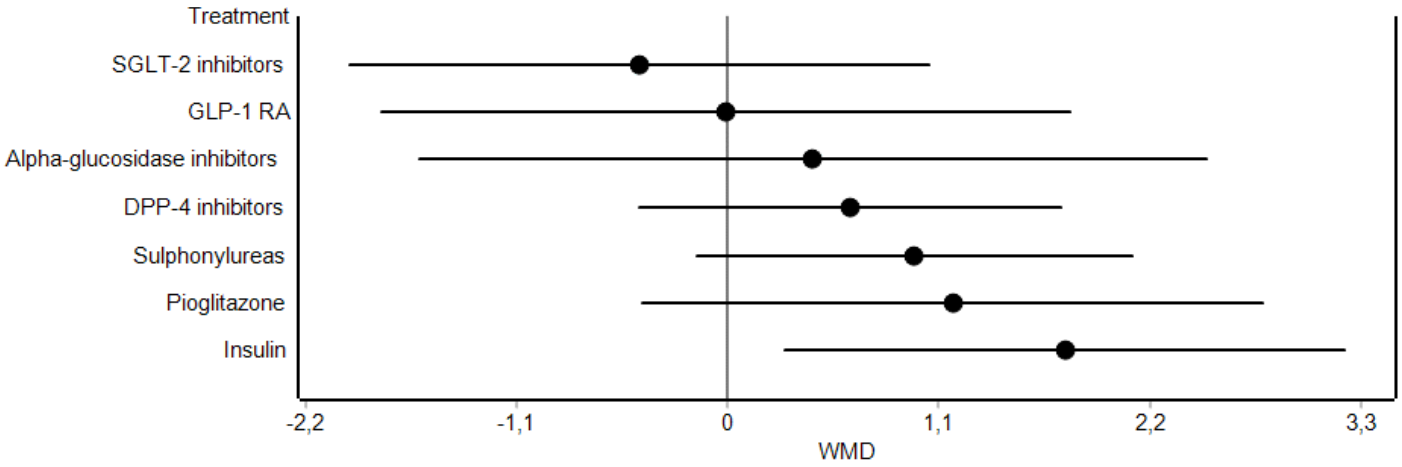
B



Consistency H:1.68

5.2. BMI

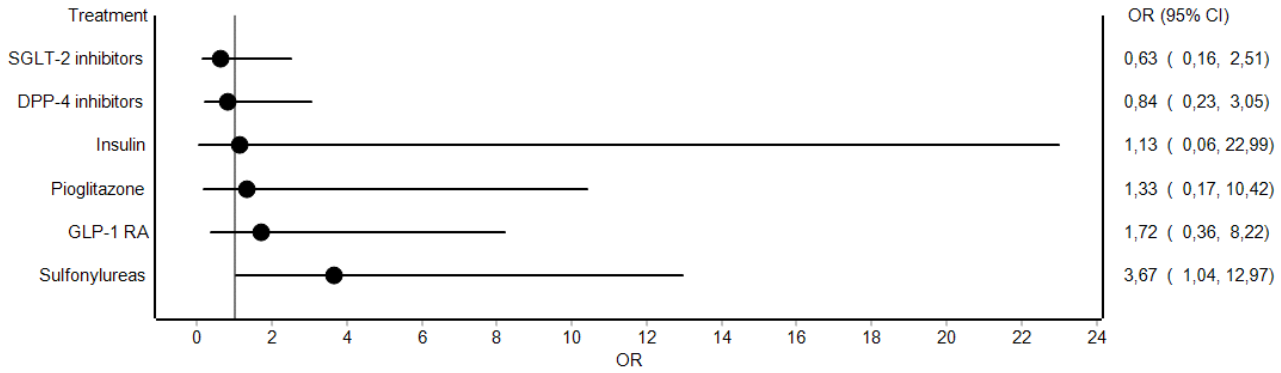
Network metanalysis of different glucose-lowering agents: forest plots of comparisons versus metformin for BMI at endpoint [40].



Consistency H: 2.056

5.3. Severe hypoglycemia

Network metanalysis of different glucose-lowering agents: forest plots of comparisons versus metformin for severe hypoglycemia[40].



Consistency H: 1.001

5.4. MACE, mortality, and heart failure hospitalization.

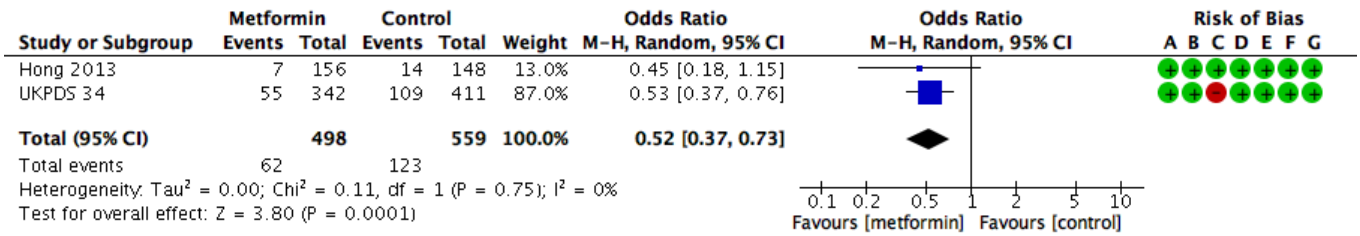
RCT with duration ≥52 weeks (published up to August 2020), in which metformin was compared with either placebo/no therapy or active comparators. MACEs (restricted for RCT reporting MACEs within their study endpoints) and all-cause mortality (irrespective of the inclusion of MACEs among the pre-specified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

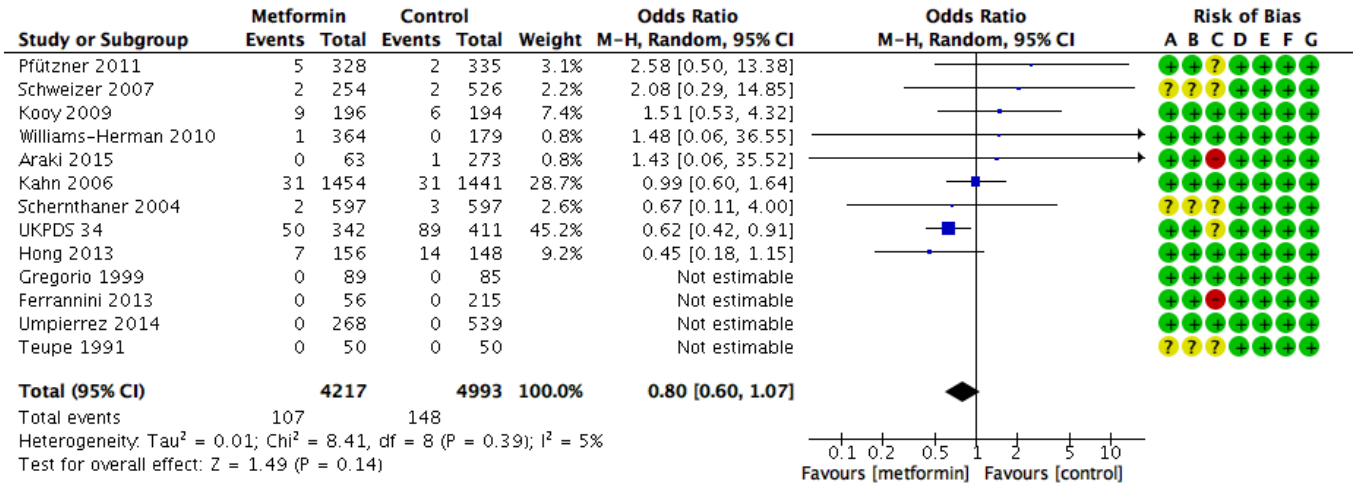
The systematic review has already been published; for complete search string, list and characteristics of included studies, and assessment of publication bias, please see the related publication [41].

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).

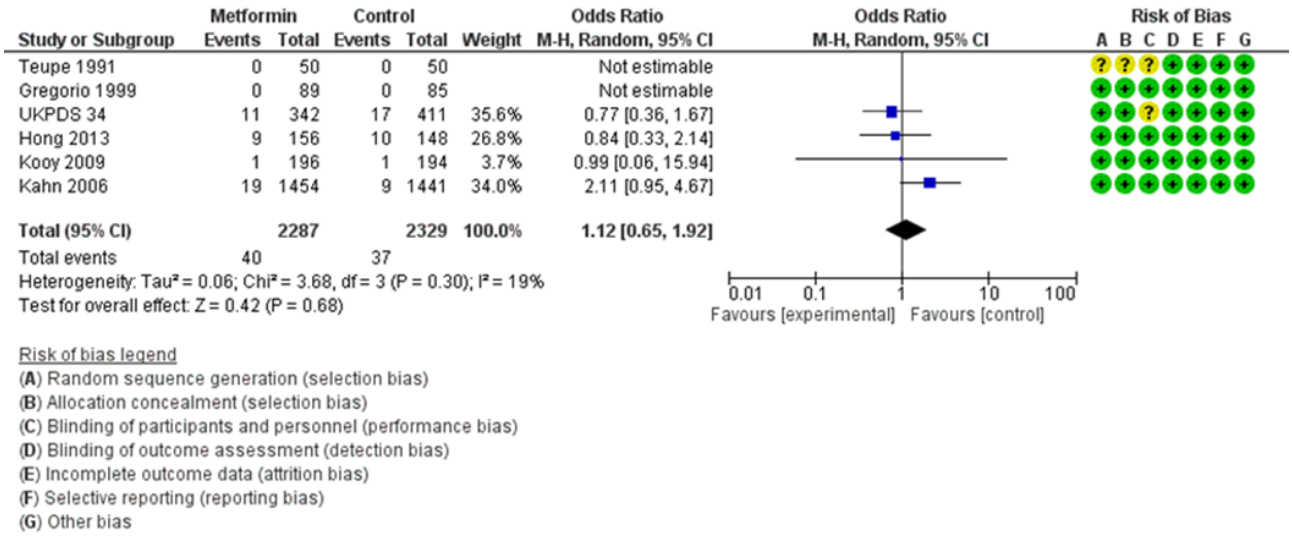
A



B



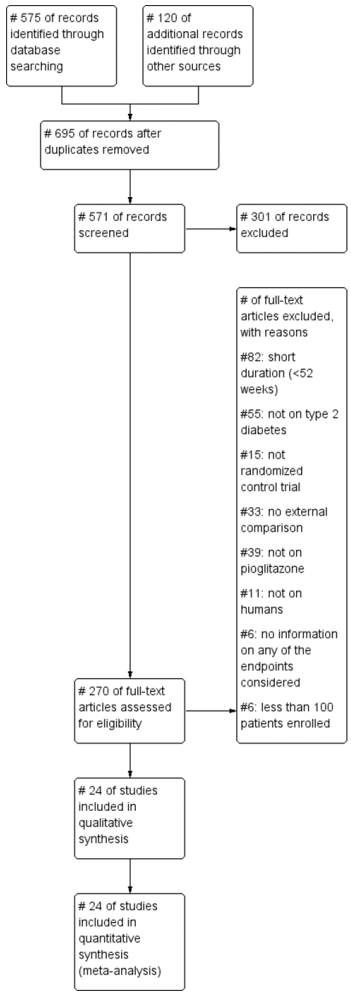
C



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.

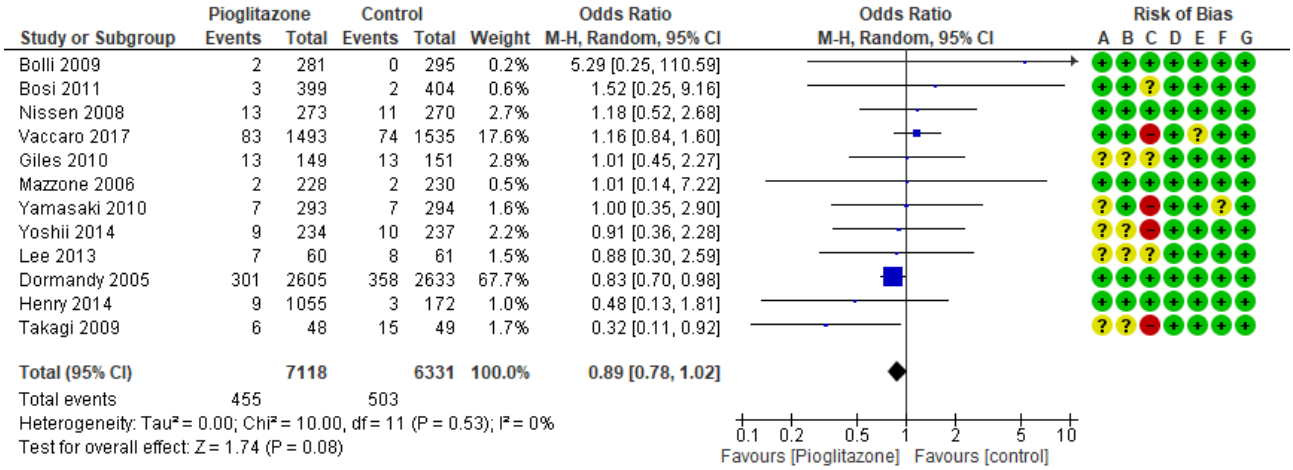
5.4.2.1. Trial flow summary



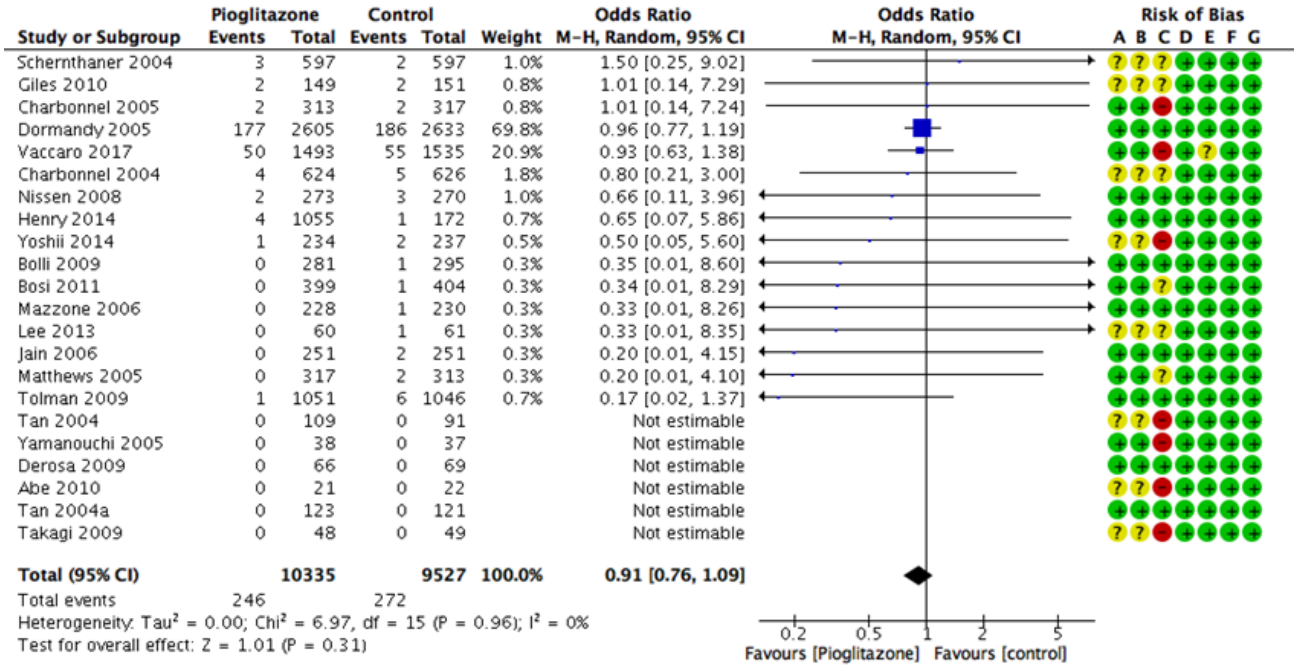
5.4.2.2. MACE, mortality, and hospitalization for heart failure

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).

A

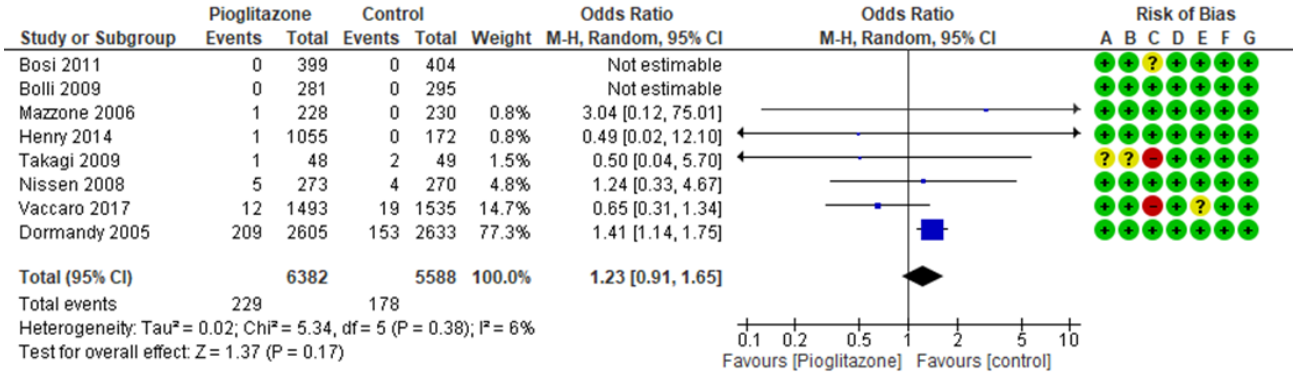


B



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

C



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

5.4.2.3. Trials' characteristics

Baseline characteristics of the trials included in the meta-analysis

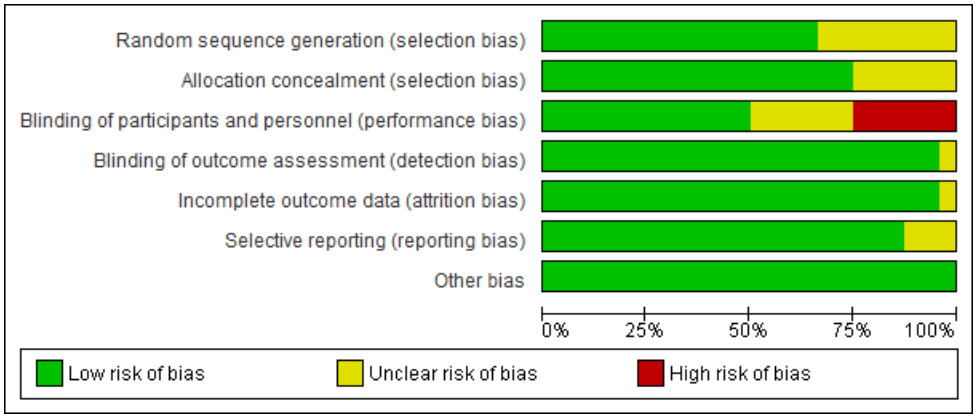
First author (reference)	**MACE within endpoints**	**Pioglit.** (n)	**Comparator** (molecule)	**Comparator** (n)	**Trial duration** (months)	**MACE***		**All-cause mortality**		**Heart failure***	
						Piogli.	*Comp.*	*Piogli.*	*Comp.*	*Piogli.*	*Comp.*
Bolli 2009[42]	NO	281	Vildagliptin	295	52	-	-	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 2005[47]	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

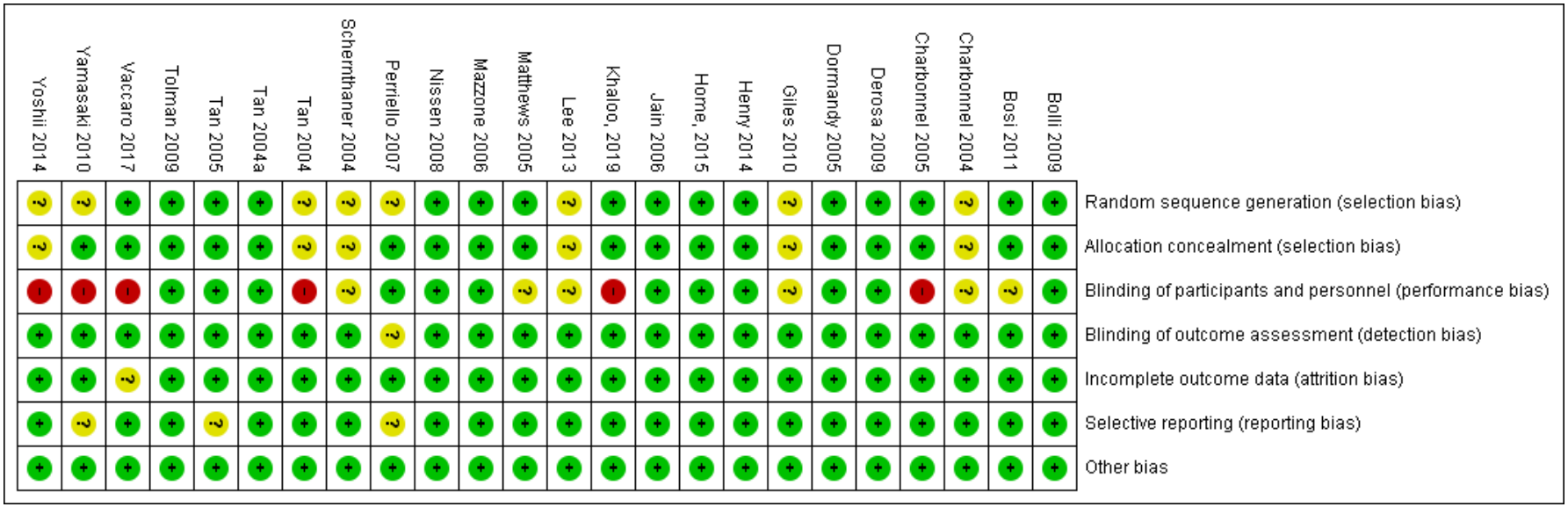
Nissen 2008[56]	YES	273	Glimepiride	270	78	13	11	3	3	5	4
Shernthaner 2004[57]	NO	597	Metformina	597	52	-	-	2	2	-	-
Tan 2004[58]	NO	109	Glyburide	91	52	-	-	0	0	-	-
Tan 2004[59]	NO	123	Glimepiride	121	52	-	-	0	0	-	-
Tolman 2009[60]	NO	1046	Glyburide	1051	144	-	-	1	1	-	-
Vaccaro 2017[61]	YES	1493	Sulfaniluree	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.



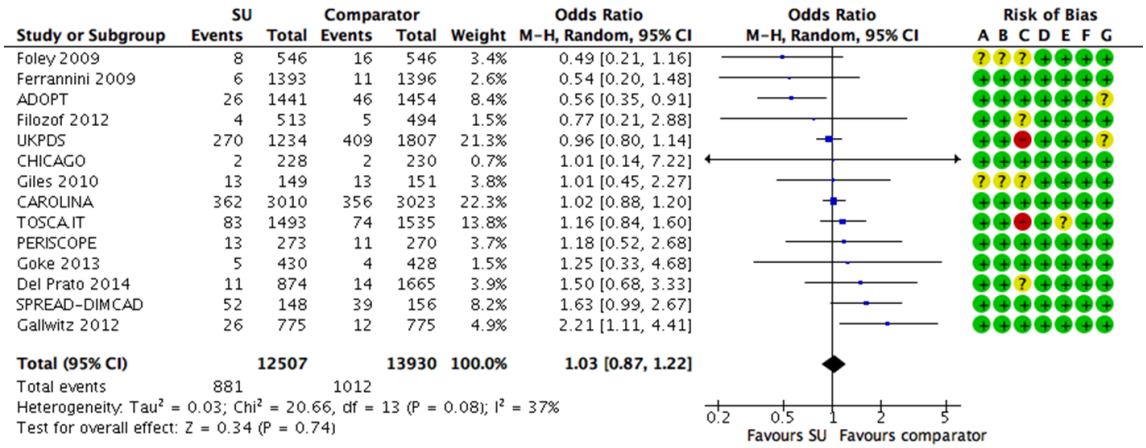


5.4.3. Insulin secretagogues

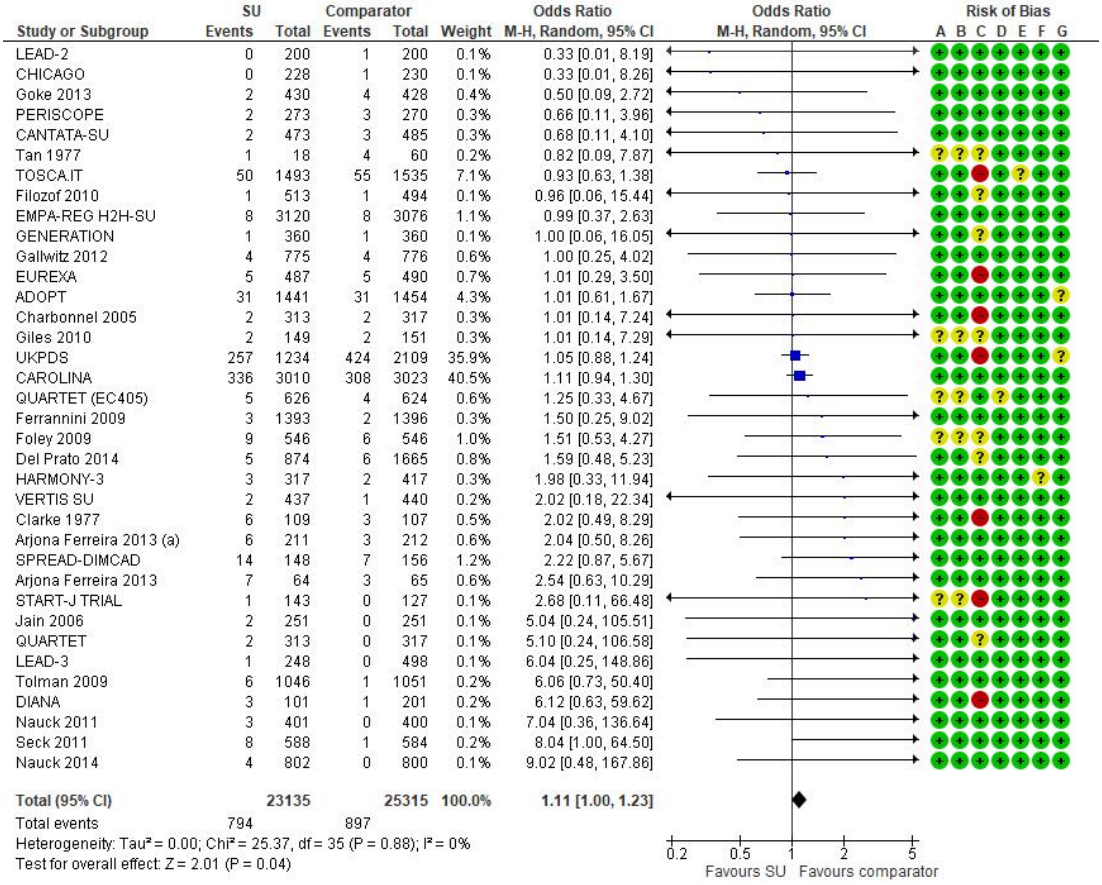
The systematic review has already been published; for complete search string, list and characteristics of included studies, and assessment of publication bias, please see the related publication [64]

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).

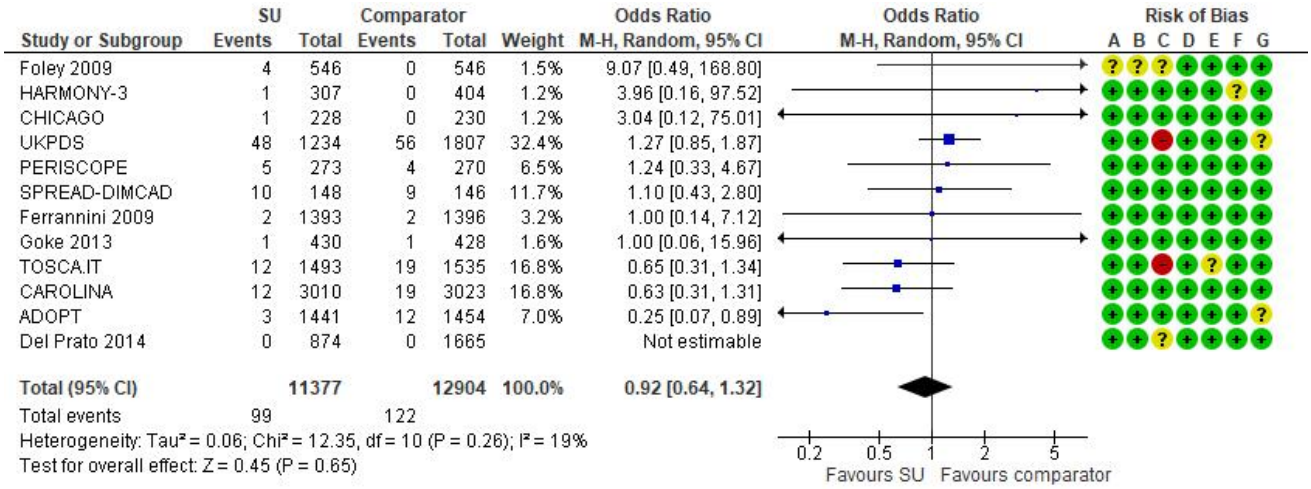
A



B



C



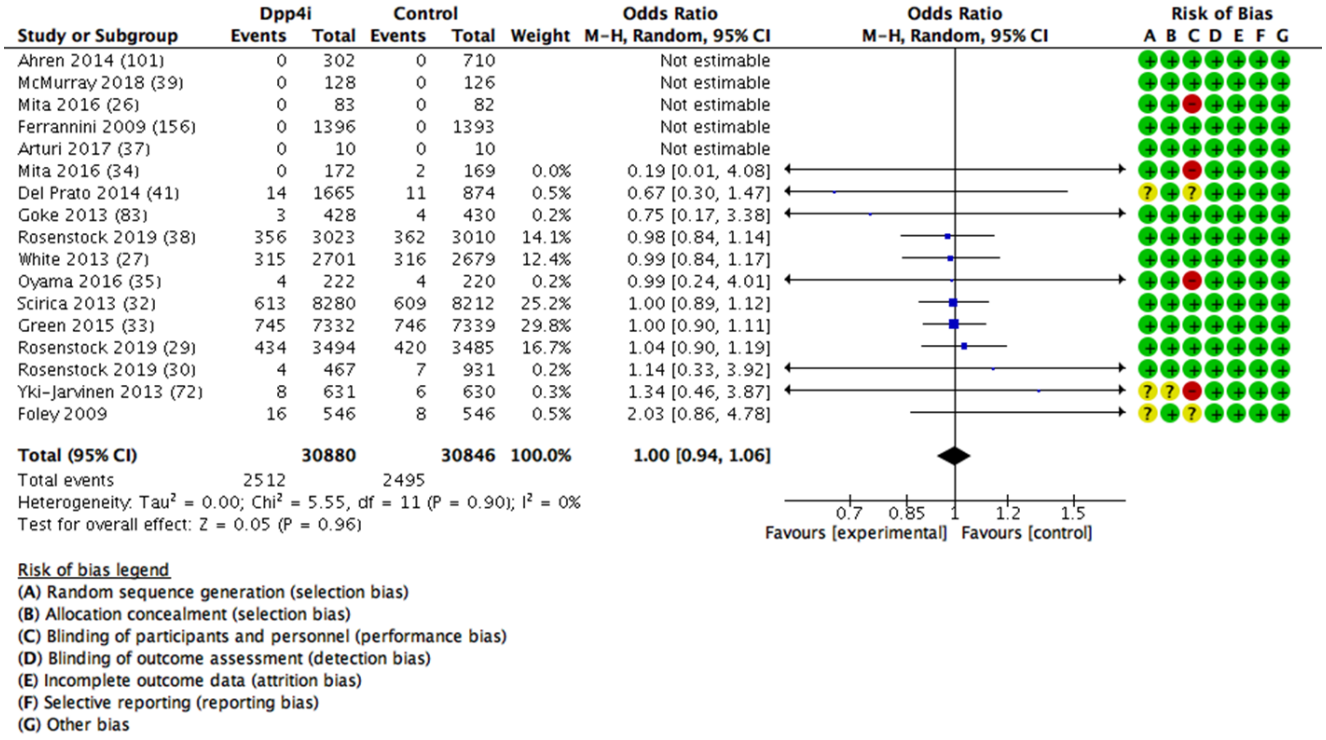
Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

5.4.4. *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 publication[65].

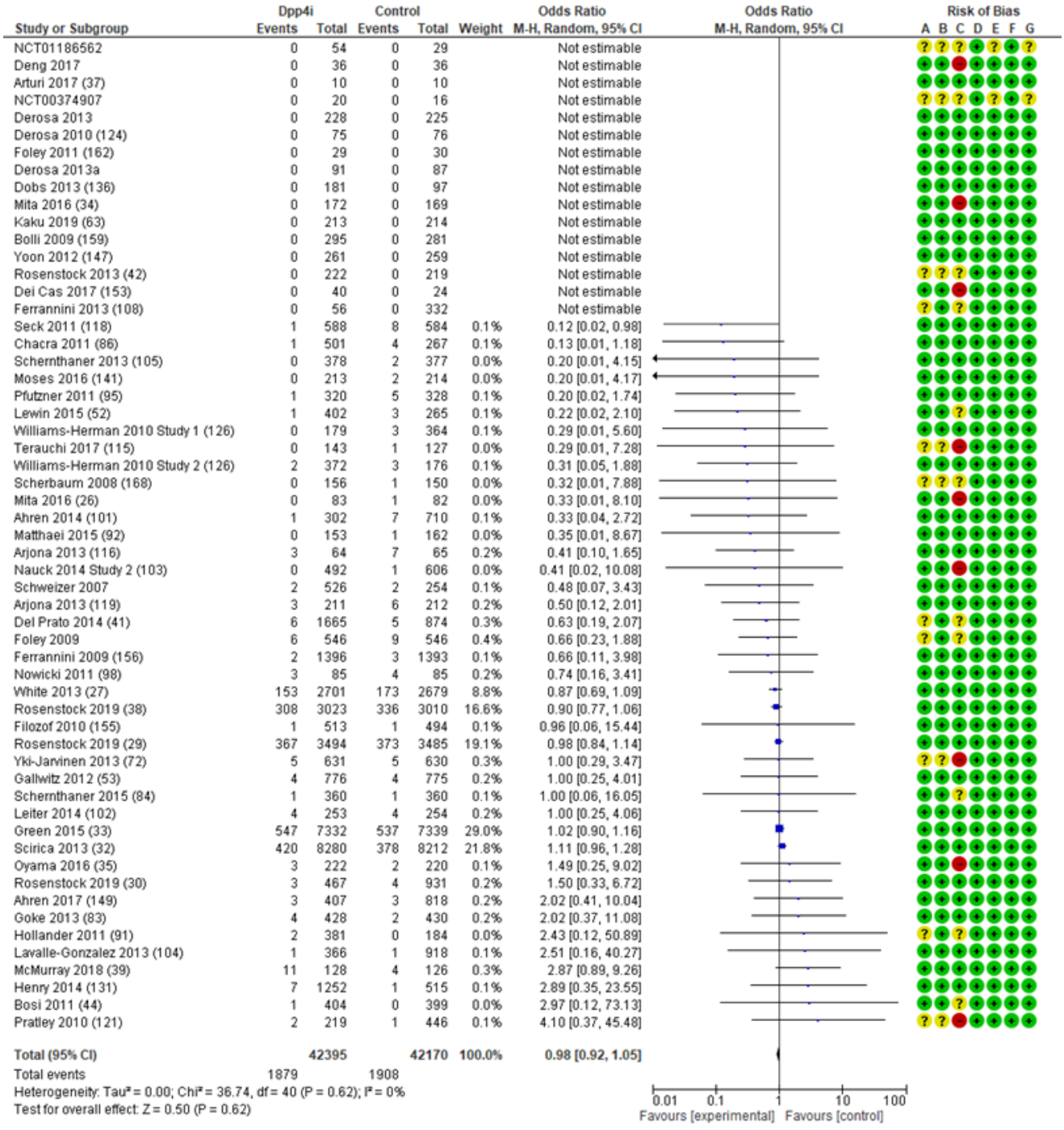
Forest plot for trials comparing the effects of DPP-4i and other glucose-lowering agents/placebo on MACE (Panel A), all-cause mortality (Panel B), and heart failure (Panel C).

A



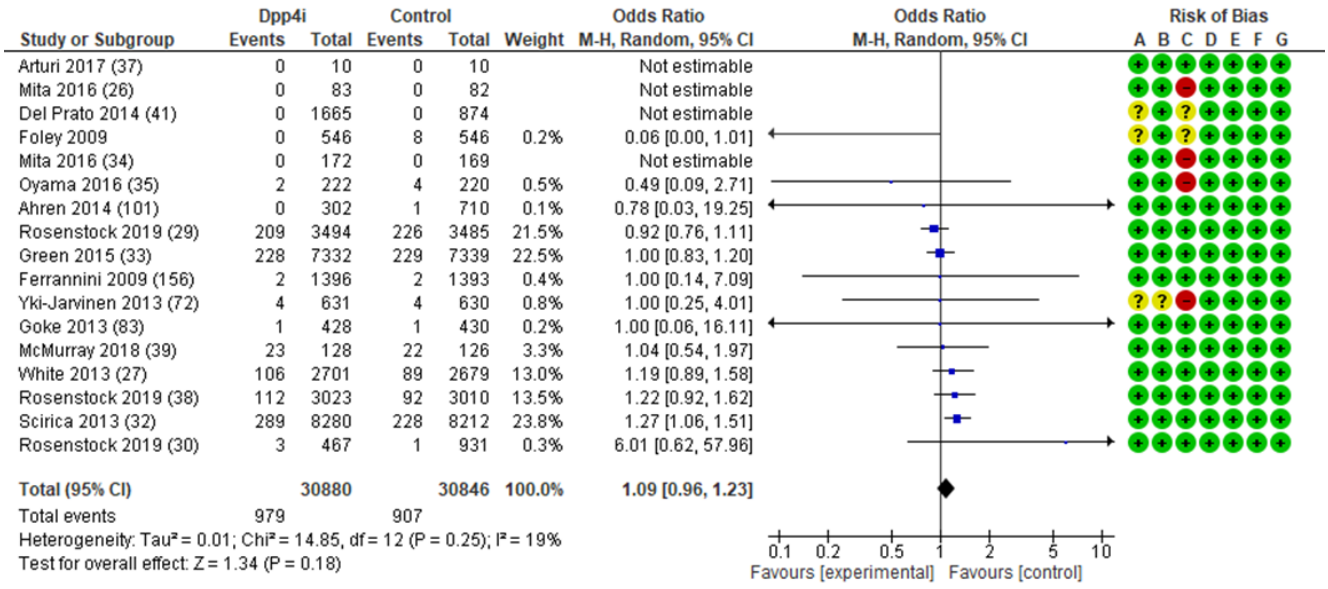
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

B



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

C



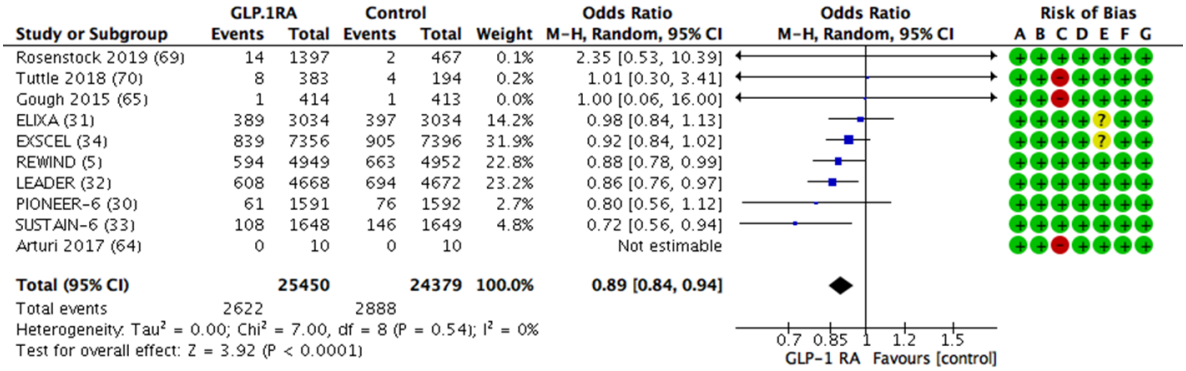
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

5.4.5. *Glucagon-Like Peptide-1 receptor agonists*

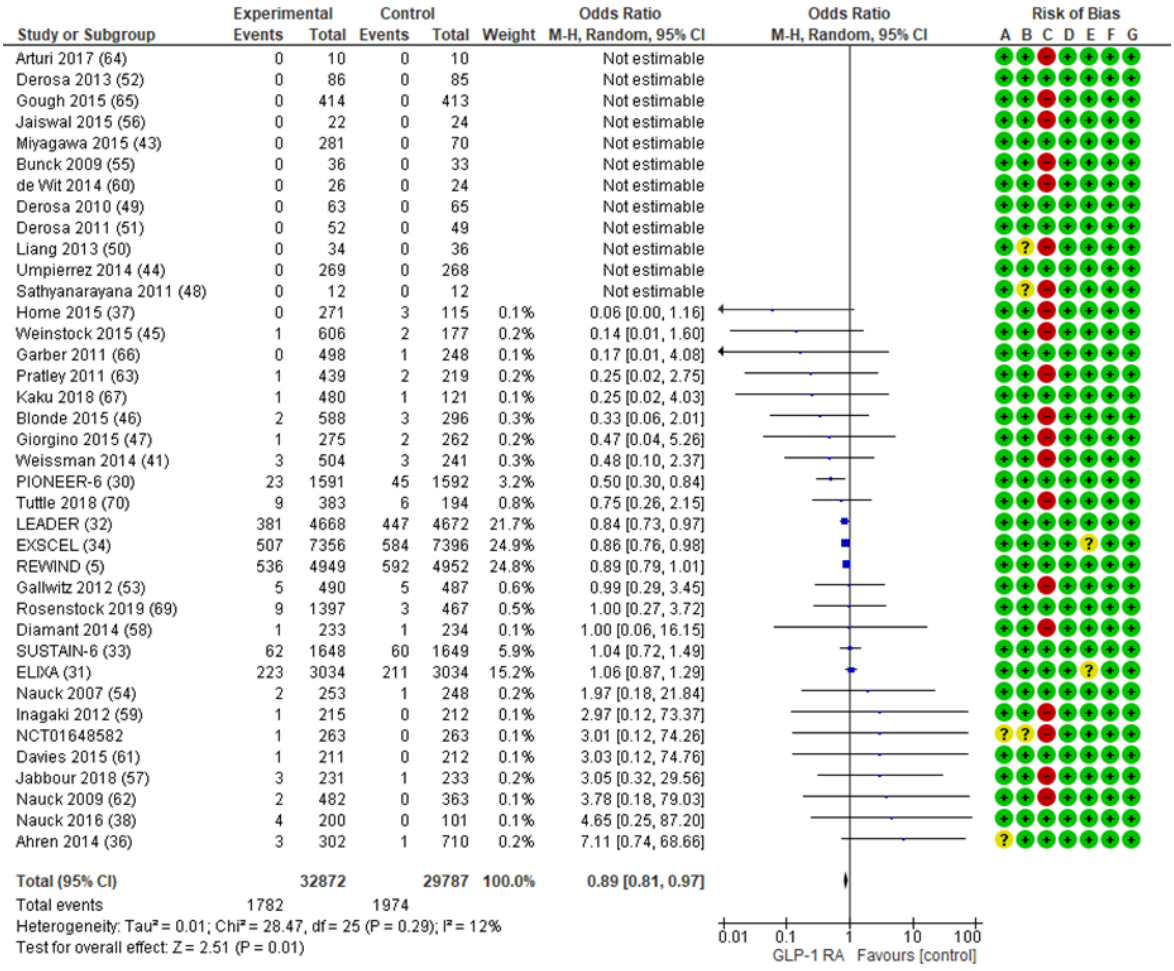
The systematic review has already been published; for complete search string, list and characteristics of included studies, and assessment of publication bias, please see the related publication[66].

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).

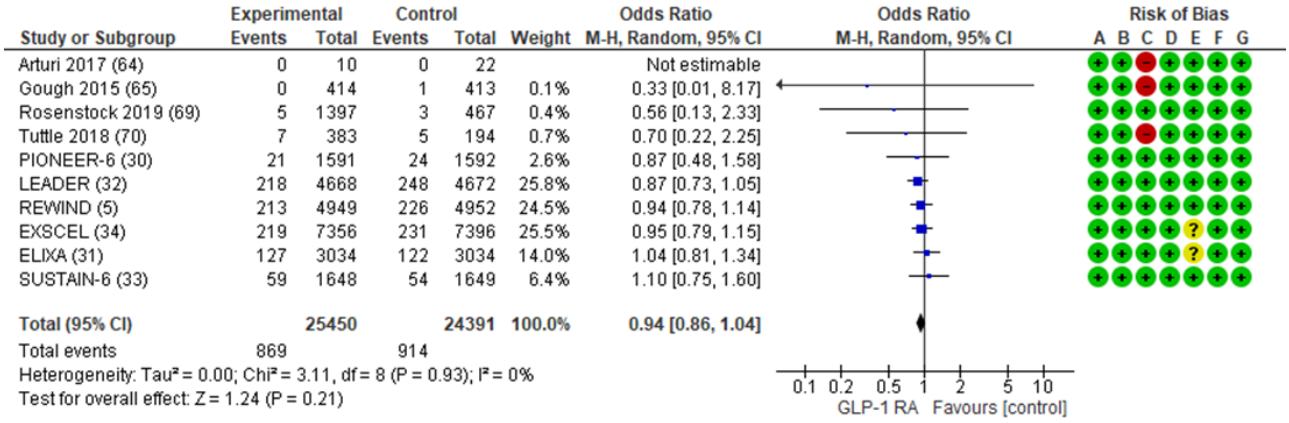
A



B



C



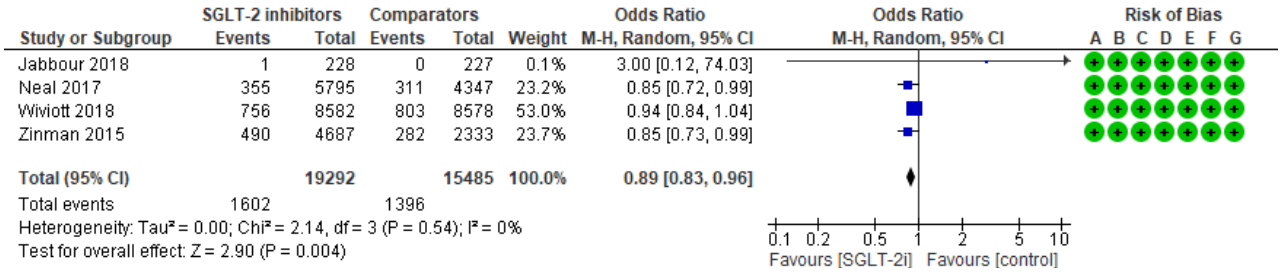
Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

5.4.6. *Sodium-Glucose Transporter-2 inhibitors*

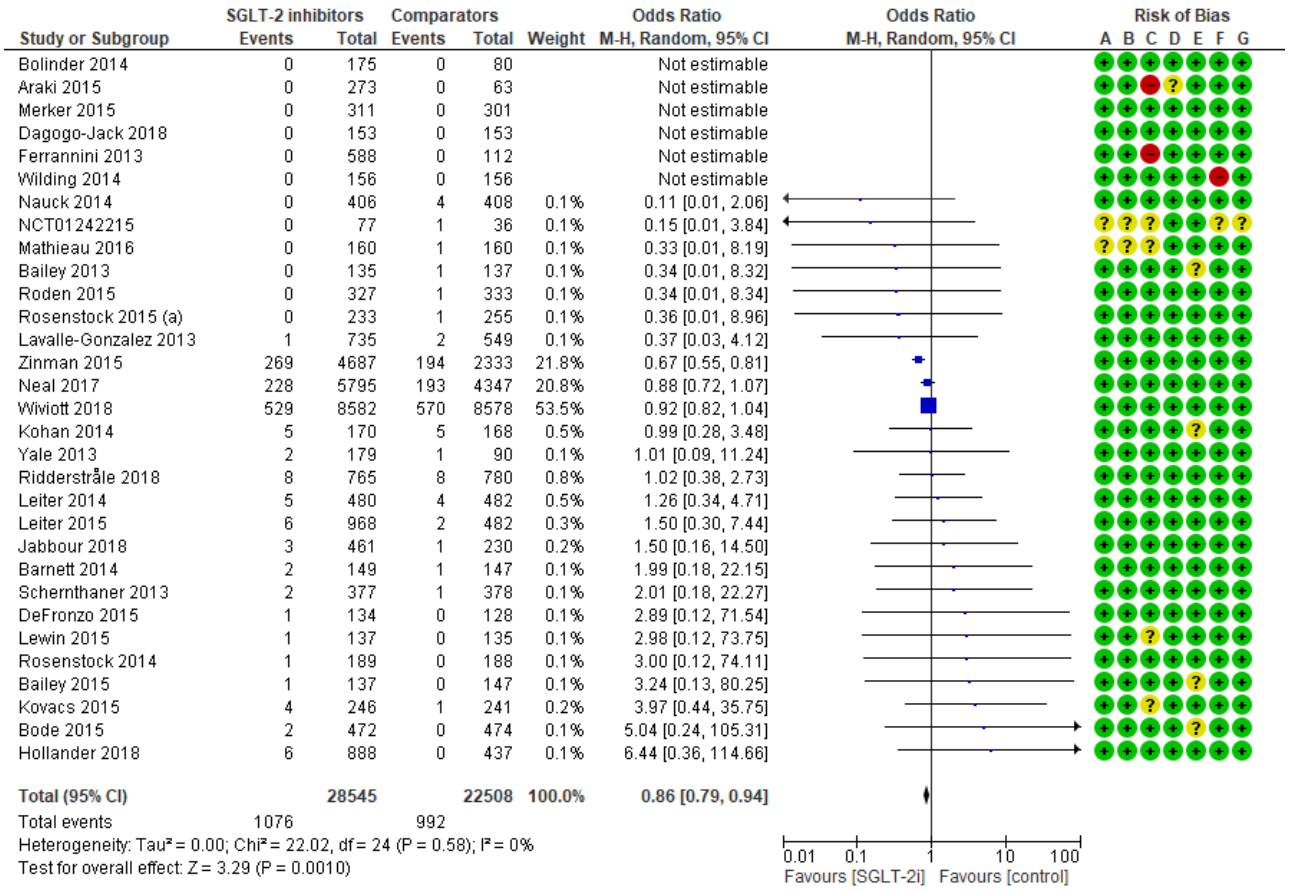
The systematic review has already been published; for complete search string, list and characteristics of included studies, and assessment of publication bias, please see the related publication[67].

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).

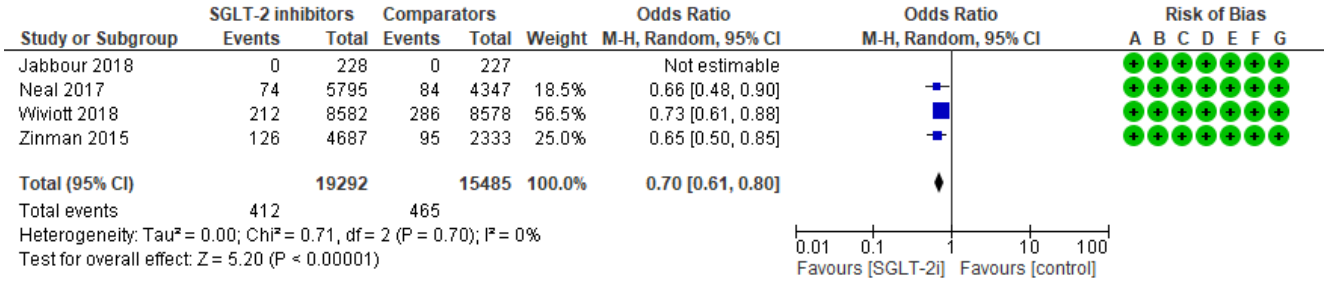
A



B



C

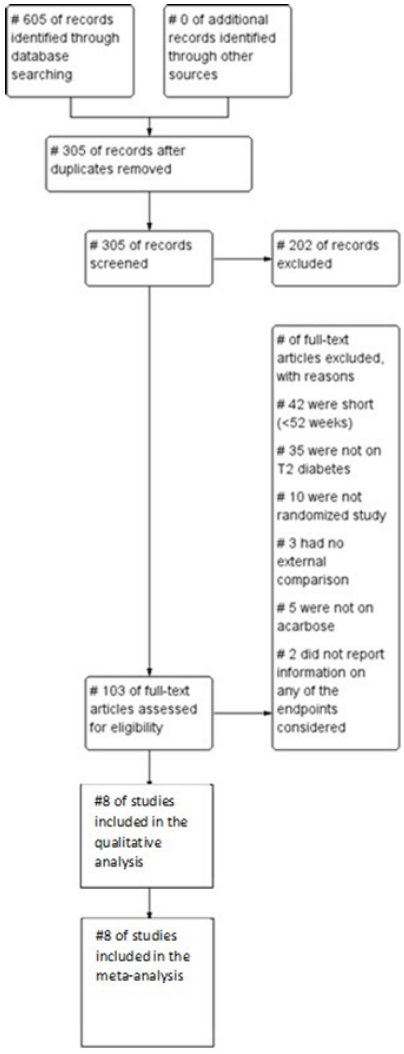


Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective 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.

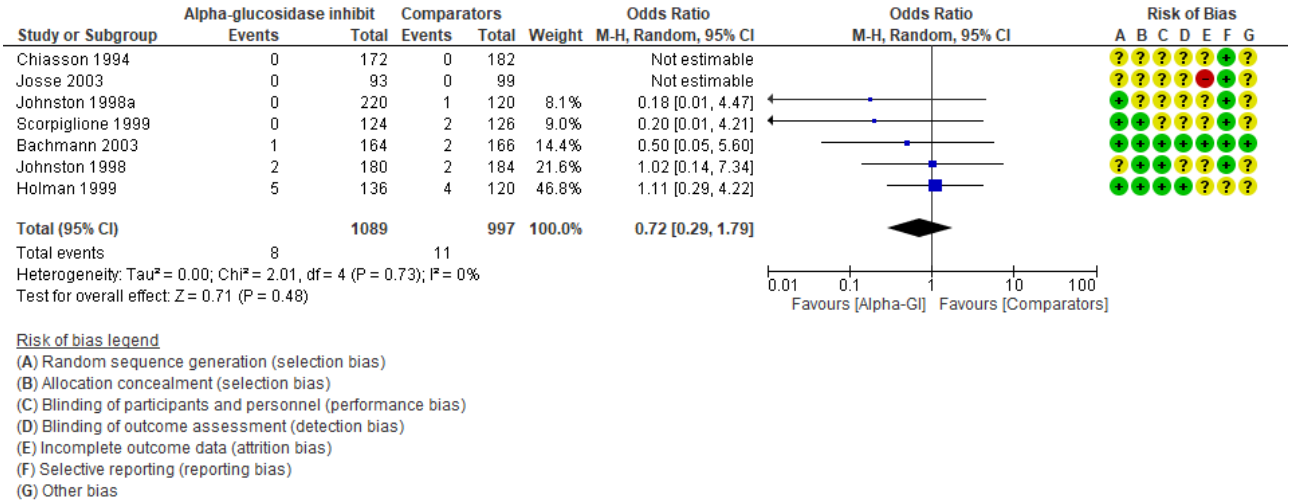
5.4.7.1. Trial flow summary



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).

A



B

No available data on this endpoint.

C

No available data on this endpoint.

5.4.7.3. Trials' characteristics

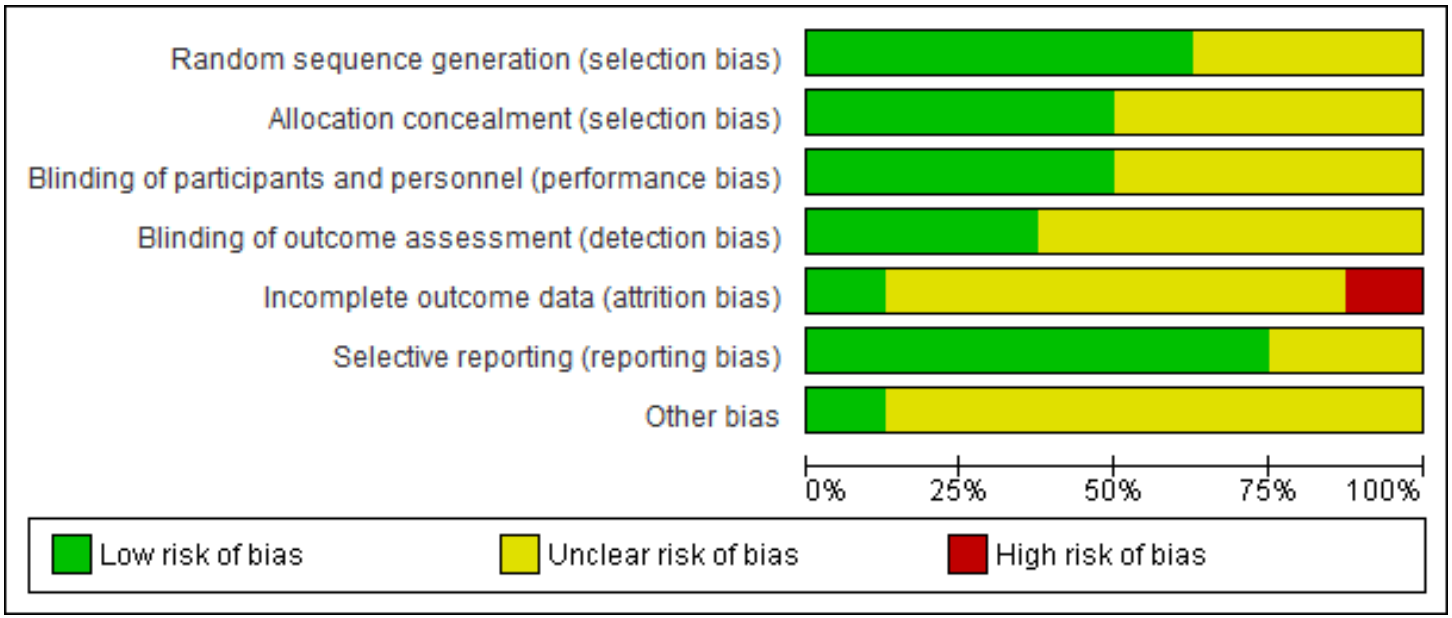
Baseline characteristics of the trials included in the meta-analysis

First author (ref.)	**Investigational drug** (ID)	**Comparator** (C)	**Trial duration** (weeks)	**# patients** (ID/C)	**Mean Age** (years)	**MACE**		**All-cause mortality**		**Heart failure**	
						ID	**C**	**ID**	**C**	**IC**	**C**
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

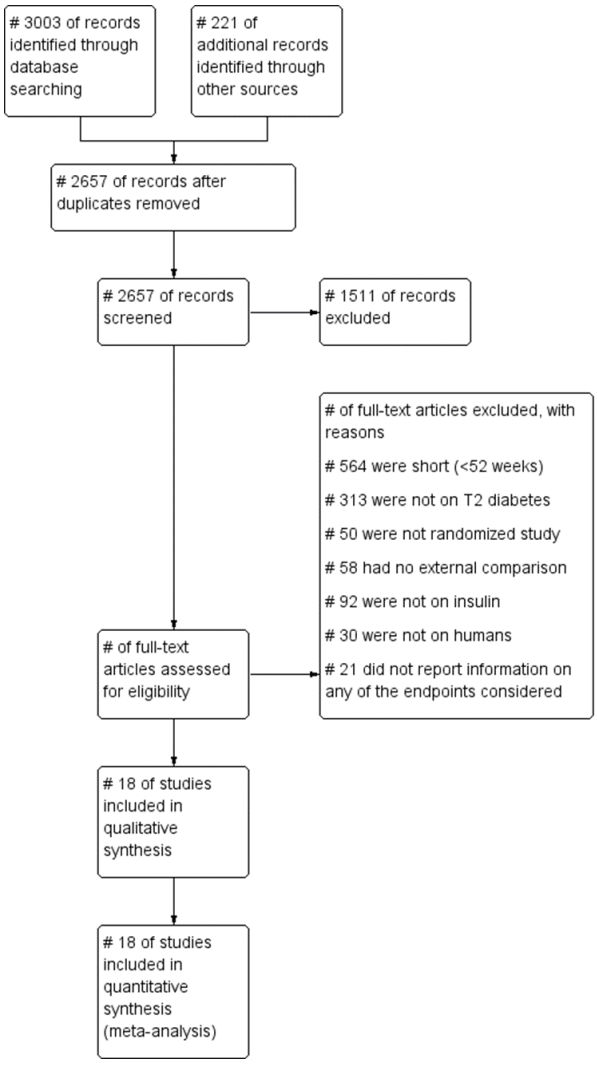
Graph and summary: review authors' judgements about each risk of bias item.



5.4.8. Insulin

The systematic review is in preparation.

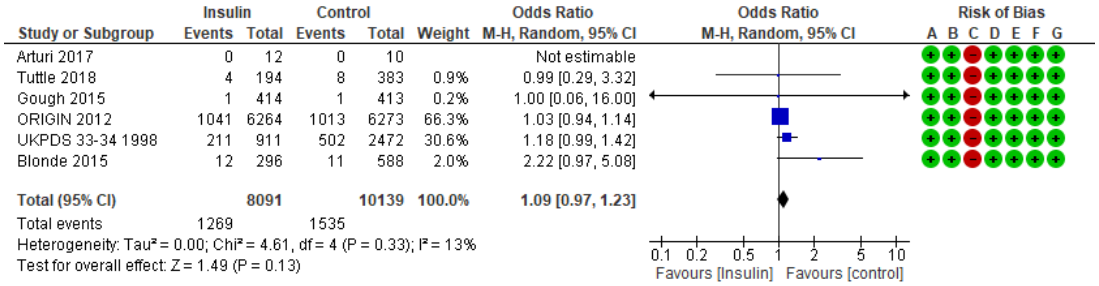
5.4.8.1. Trial flow summary



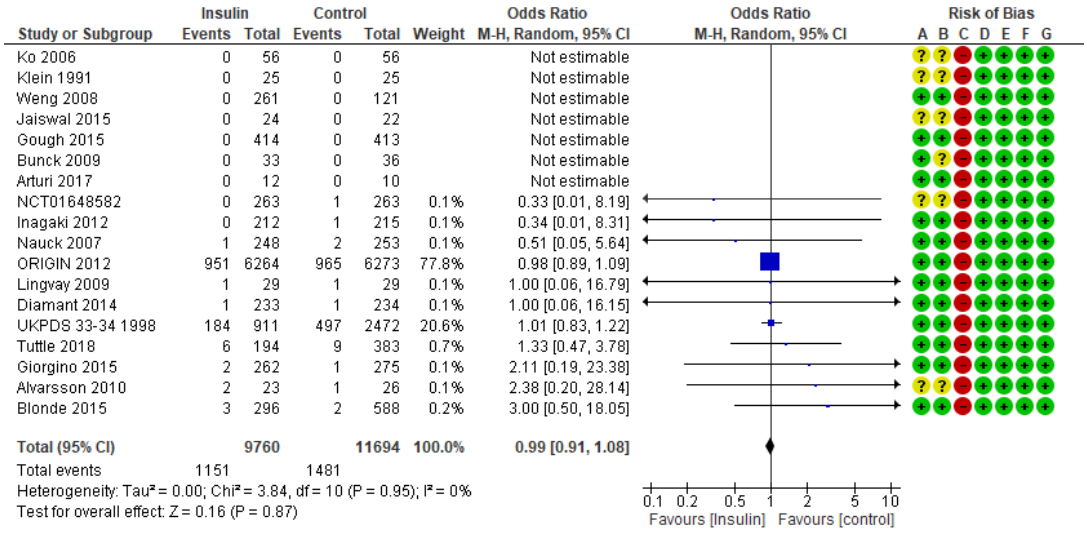
5.4.8.2. MACE, mortality, and hospitalization for heart failure

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).

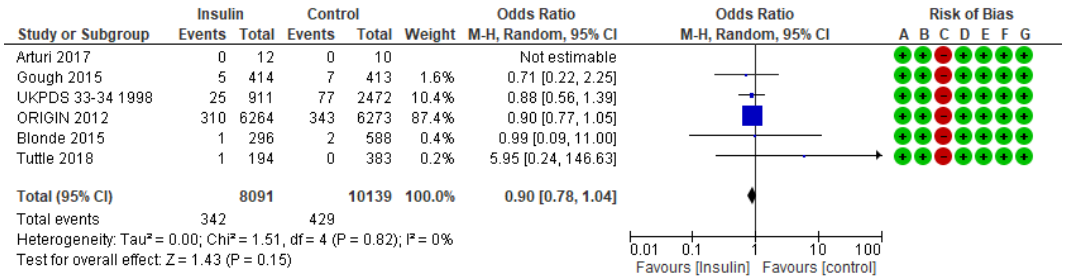
A



B



C



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

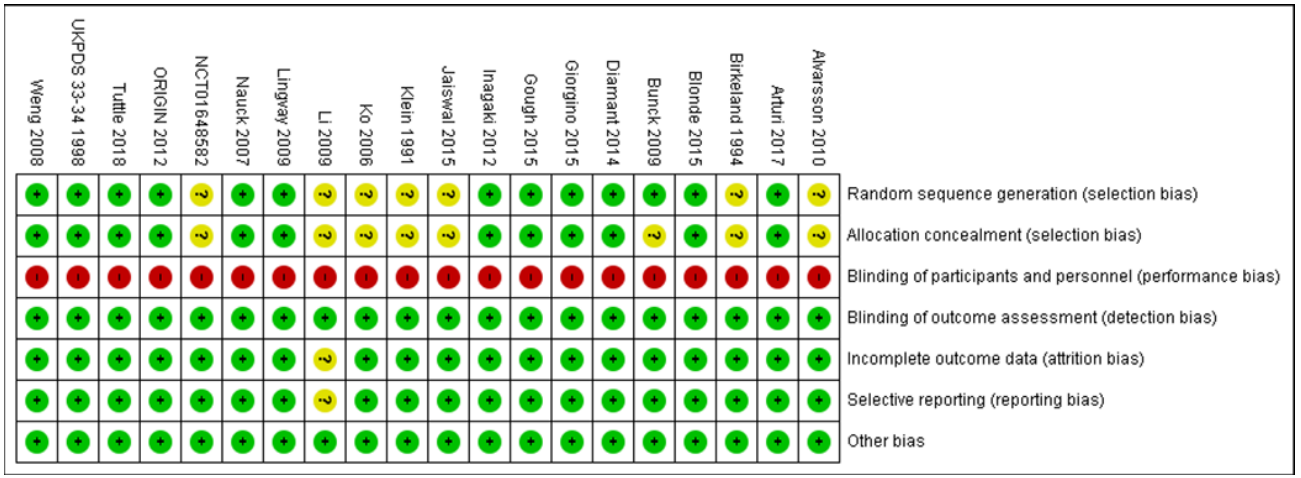
Baseline characteristics of the trials included in the meta-analysis

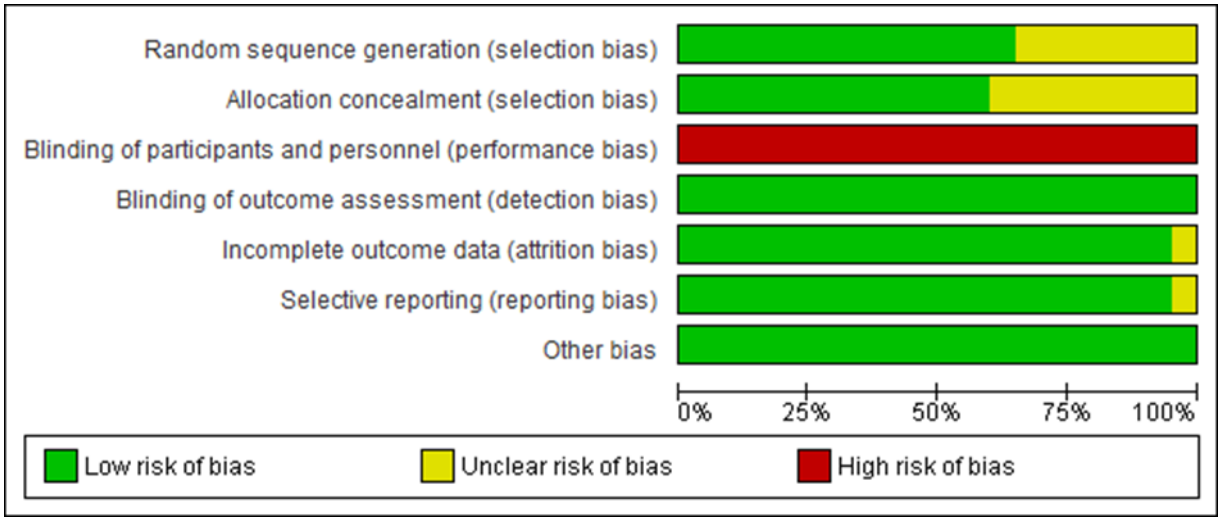
Study Name *(Reference)*	**Investigational drug**	**Comparator**	**Trial duration** (weeks)	**Patients** (ID/C)		**Age** (years)	**MACE**		**ALL-CAUSE MORTALITY**		**HEART FAILURE**	
				ID	**C**		**ID**	**C**	**ID**	**C**	**IC**	**C**
Alvarsson2008[76]	Human Insulin	Glibenclamide	330	23	26	53	NR	NR	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	343
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.





5.4.9 Grade of evidence

5.4.9.1 Grade of evidence common to all questions

Certainty assessment							Summary of findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Relative effect (95%, CI)	Anticipated absolute effects			
								Control		Intervention	
medium/lon-term HbA1c											
41,730 (68 RCTs)	not serious	serious [b]	not serious	not serious	none	⨁⨁⨁◯ MODERATE	-	-	-	-	-
Severe hypoglycemia											
41,730 (68 RCTs)	not serious	serious [b]	not serious	not serious	none	⨁⨁⨁◯ MODERATE	-	-	-	-	-
Quality of life											
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 assessment							Summary of findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							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											
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 secretagogues											
26,779 (14 RCTs)	not serious	not serious	serious[c]	not serious	none	⨁⨁⨁◯ MODERATE	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											
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

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 glucosidase inhibitors

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

Insulin

18,230 (6 RCTs)	serious[a]	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)

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 secretagogues

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)	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

21454 (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)

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											
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											
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-glucosidase inhibitors											
-	-	-	-	-	-	-	-	-	-	-	-
Insulin											
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)

CI: 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 assessment							Summary of findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							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	⨁⨁⨁◯ 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											
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 secretagogues											
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											
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

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 glucosidase inhibitors

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

Insulin

18,230 (6 RCTs)	serious[a]	not serious	not serious	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)

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 secretagogues

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	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)	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

21454 (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)

HOSPITALIZATION FOR HEART FAILURE

Metformin

4.616 (6 RCTs)	not serious	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 14 higher)

Pioglitazone

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											
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-glucosidase inhibitors											
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)

CI: 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 dapaglifozin had 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, empagliflozina 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

						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

						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 SU	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	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

							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) *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..
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) *Life expectancy (years)* 14.506 vs 14.369 *QALYs* 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 *liraglutide 1.2 mg* -higher treatment costs -lower complication costs -lower total costs Lower costs are associated with lower incidence of complications. *liraglutide 1.8 mg* -higher total costs -higher treatment costs -lower complication costs	Dual therapy: *liraglutide 1.2 mg* -higher QALYs -increase of life expenctancy *liraglutide 1.8 mg* -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 *Discounted life expectancy (years)* 13.54 vs 13.45 *QALYs* 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 *Discounted direct costs ($)* 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

				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)	Base case Liraglutide vs Sitagliptin *Discounted direct costs (€)* 43,031 vs 40,472 Liraglutide vs glimepiride *Discounted direct costs (€)* 41,481 vs 36,786 Increased costs are due to acquistion costs of Liraglutide in the first 5 years of the simulation. These costs are partially offset by the reduction of treatment of complications, in particular cardiovascular.	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.

		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 *Expected costs* 44,526 vs 43,256 *Discounting 0%* 64,850 vs 63,665 Discounting 6% 32,968 vs 31,678	Base case Exenatide vs Lispro *QALYs* 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 *Total costs ($)* 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 *LYs* 11.99 vs 11.76 (difference 0.23) *QALYs* 8.65 vs 8.35 (difference 0.31) CANA 100 mg vs SITA 100 mg *LYs* 12.04 vs 11.83 (difference 0.21) *QALYs* 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

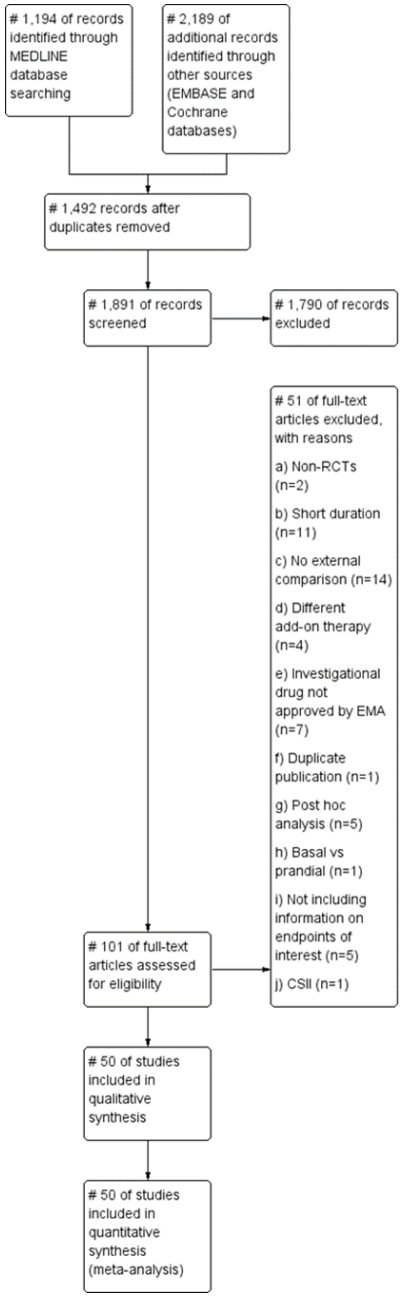
The systematic review has been already submitted to a medical journal. A Medline and EMBASE search was conducted up to January, 1st, 2020.

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 ≥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)

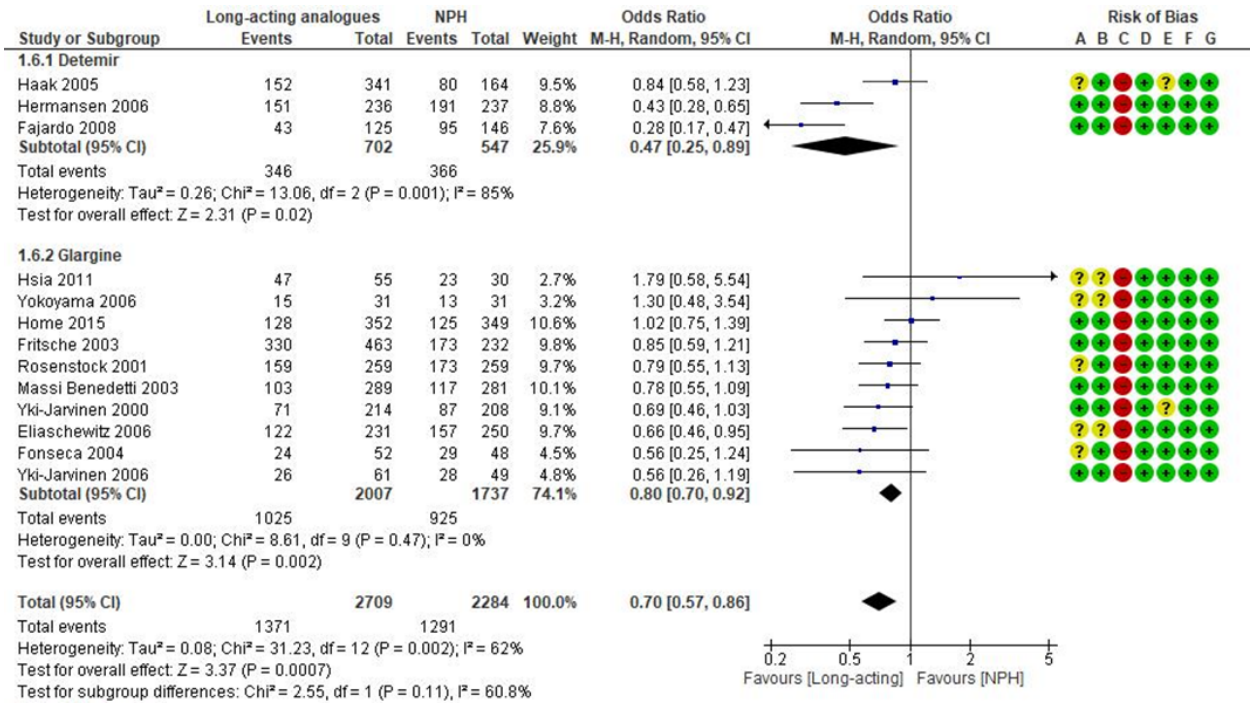
5.5.1. Trial flow summary



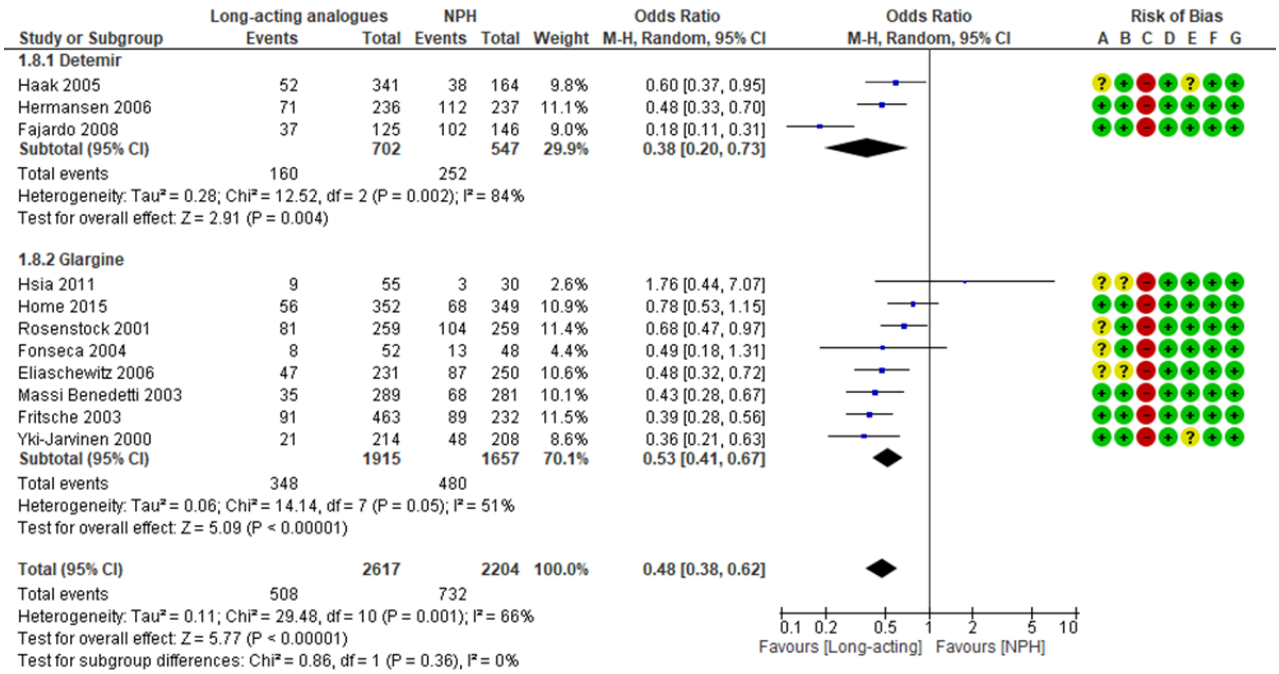
5.5.2. Hypoglycemia in trials with basal insulin therapy

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.

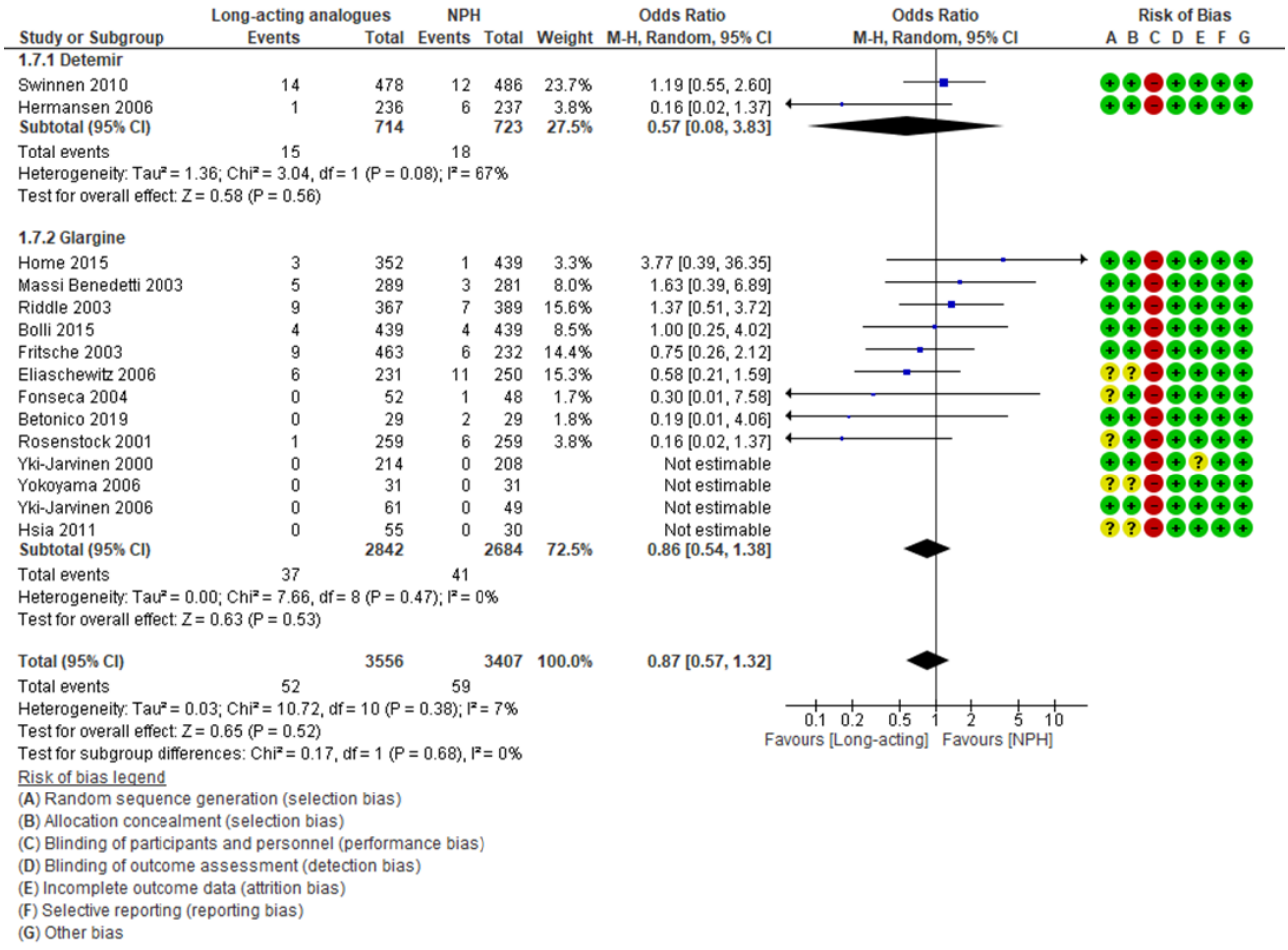
A



B



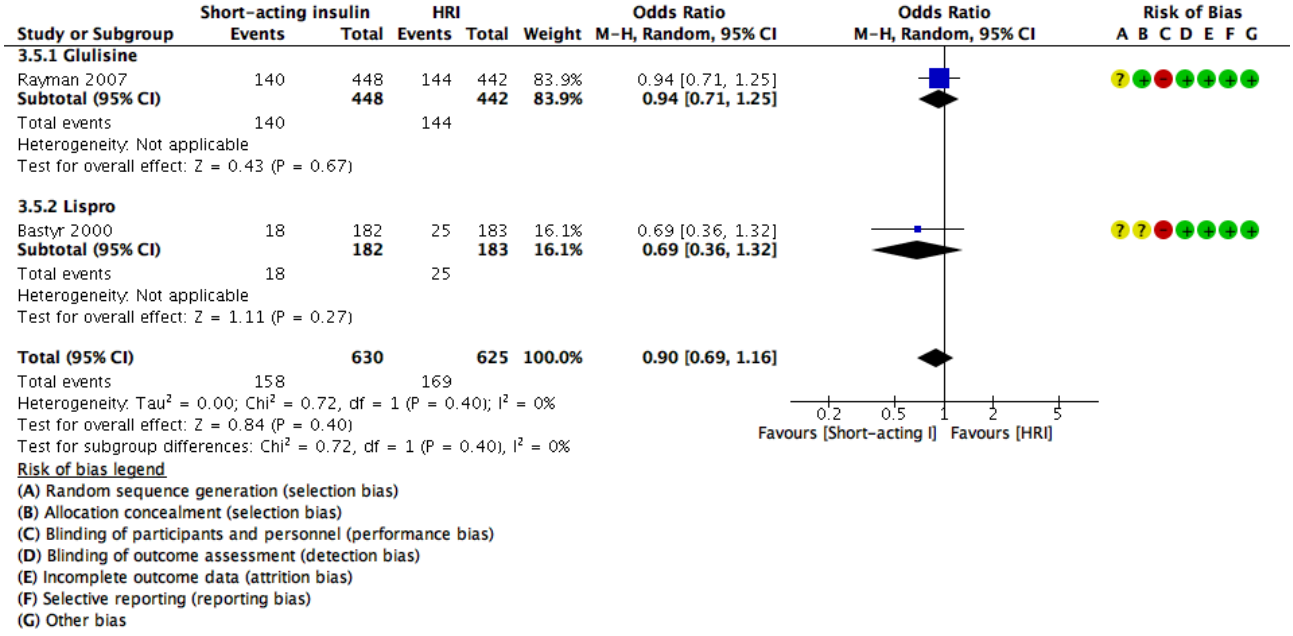
C


Long-acting analogues
NPH
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
A B C D E F G
1.7.1 Detemir
Swinnen 2010 14 478 12 486 23.7% 1.19 [0.55, 2.60]
Hermansen 2006 1 236 6 237 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: Tau² = 1.36; Chi² = 3.04, df = 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 30 Not estimable
Subtotal (95% CI) 2842 2684 72.5% 0.86 [0.54, 1.38]
Total events 37 41
Heterogeneity: Tau² = 0.00; Chi² = 7.66, df = 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: Tau² = 0.03; Chi² = 10.72, df = 10 (P = 0.38); I² = 7%
Test for overall effect: Z = 0.65 (P = 0.52)
Test for subgroup differences: Chi² = 0.17, df = 1 (P = 0.68), I² = 0%
0.1 0.2 0.5 1 2 5 10
Favours [Long-acting] Favours [NPH]
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

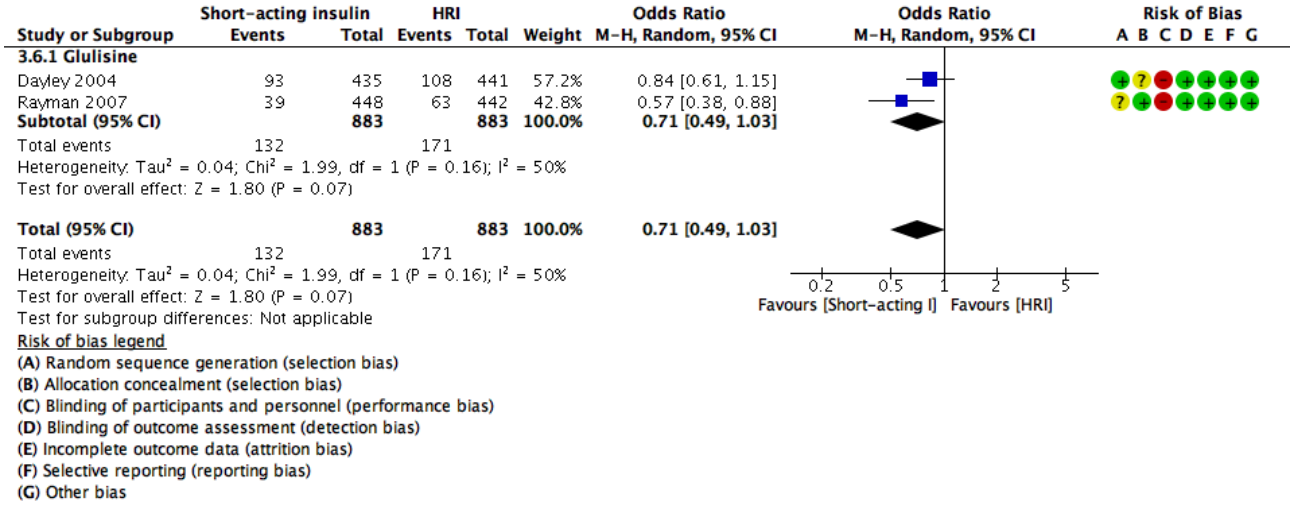
5.5.3. Hypoglycemia in trials with prandial insulin therapy

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.

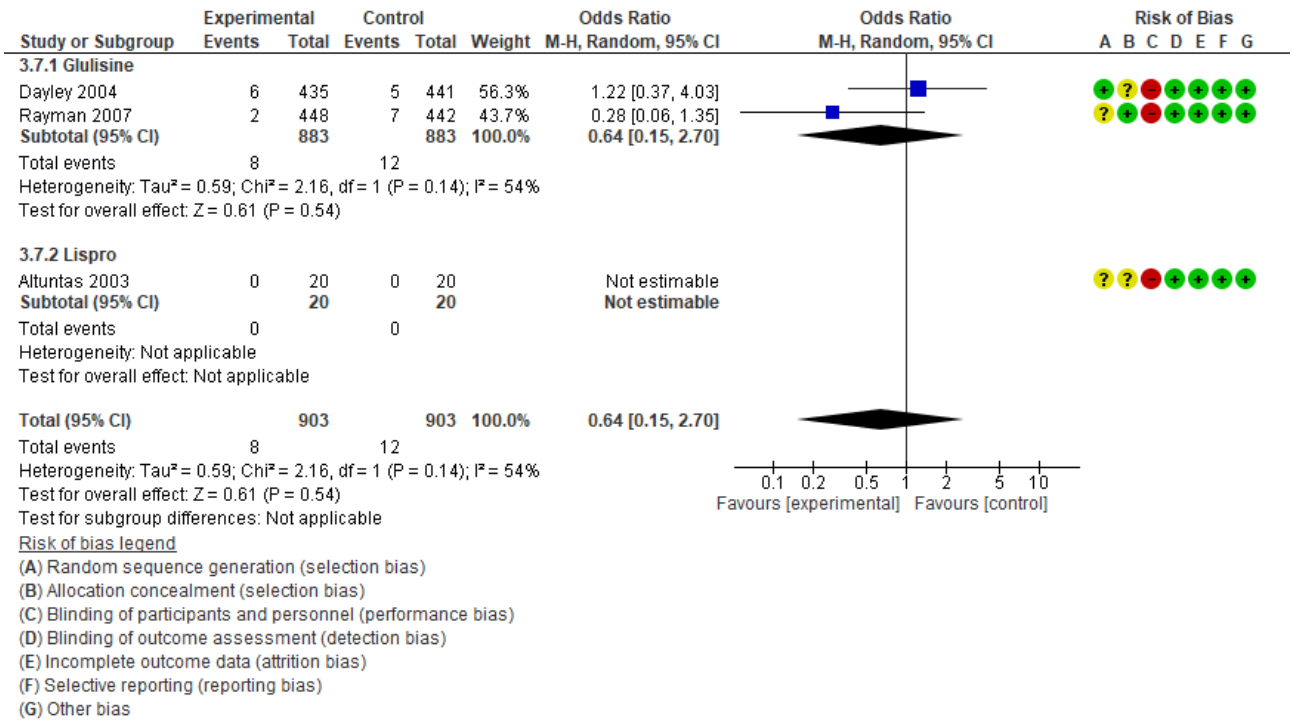
A



B

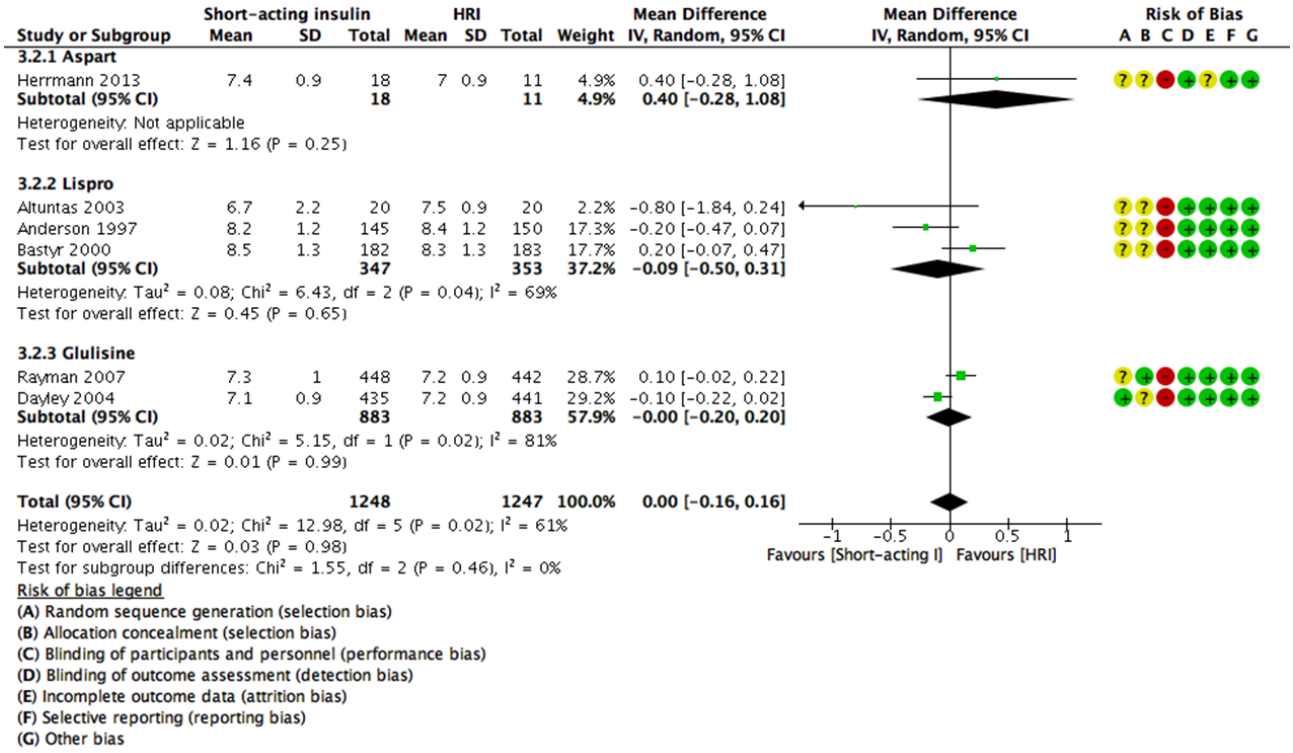


C


Experimental
Control
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
A B C D E F G
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: Tau² = 0.59; Chi² = 2.16, df = 1 (P = 0.14); I² = 54%
Test for overall effect: Z = 0.61 (P = 0.54)
3.7.2 Lispro
Altuntas 2003 0 20 0 20 Not estimable
Subtotal (95% CI) 20 20 Not estimable
Total events 0 0
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Total (95% CI) 903 903 100.0% 0.64 [0.15, 2.70]
Total events 8 12
Heterogeneity: Tau² = 0.59; Chi² = 2.16, df = 1 (P = 0.14); I² = 54%
Test for overall effect: Z = 0.61 (P = 0.54)
Test for subgroup differences: Not applicable
0.1 0.2 0.5 1 2 5 10
Favours [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

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.



5.5.5. Trials' characteristics

Baseline characteristics of the trials included in the meta-analysis

Study Name (Pub year)	Active Drug (AD)	Comparator	Trial Duration (weeks)	Patients AD	Patient Comp.	Mean age (years)	Mean HbA1c (%)	Mean BMI (Kg/m^2)	Dur. Diab. (years)	FPG (%)
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

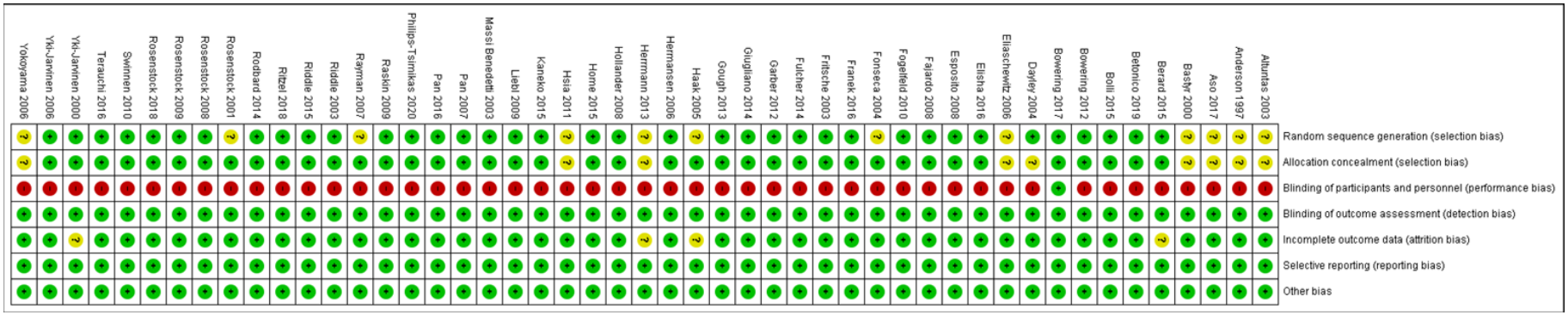
Gough 2013[131]	Degludec U200	Glargine U100	78	228	228	57.5	8.25	32.3	13.5	9.6
Haak 2005[132]	Detemir	NPH	48	341	164	60	7.9	30.4	NR	10.2
Hermansen 2006[133]	Detemir	NPH	26	236	237	61	8.55	29	8.2	11
Hollander 2008[134]	Detemir	Glargine U100	26	214	105	58.5	8.7	31.6	9.7	9.6
Home 2015[135]	Glargine U100	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

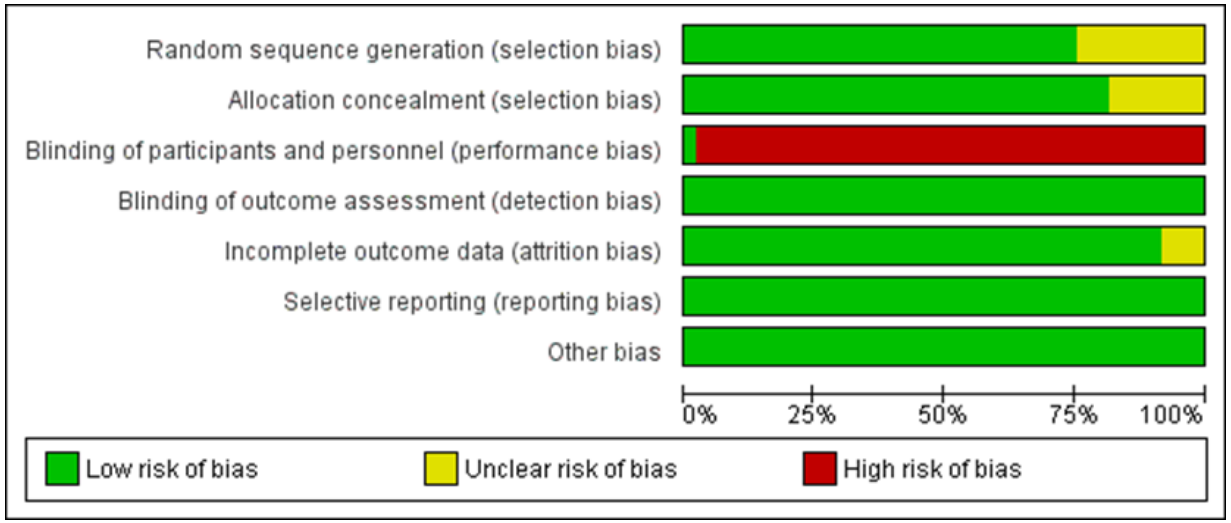
Terauchi 2016[154]	Glargine U300	Glargine U100	24	121	120	61	8	25.3	10.6	7.6
Yki-Jarvinen 2000[155]	Glargine U100	NPH	24	214	208	59	9	28.8	10	NR
Yki-Jarvinen 2006[156]	Glargine U100	NPH	24	61	49	56.5	9.55	31.7	14	13
Yki-Jarvinen 2014 -2015[157]	Glargine U300	Glargine U100	52	315	314	58.2	8.24	34.8	10	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 assessment							Summary of findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Standard care	With Intensive glycemic control		Risk with placebo	Risk difference with Intensive glycemic control
Total hypoglycemia											
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 hypoglycemia											
15892 (3 RCTs	serious[a]	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 hypoglycemia											
3297 (1 RCT)	serious[a]	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)

CI: 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 assessment							Summary of findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Standard care	With Intensive glycemic control		Risk with placebo	Risk difference with Intensive glycemic control
Total hypoglycemia											
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 hypoglycemia											
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 hypoglycemia											
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)

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

Certainty assessment							Summary of findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							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	Costeffectiveness 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 IGlar 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 *QALYs* 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 IGlar 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 *US Dollars*	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 IDegLIia (+£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.

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 *Euro*	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 lliraglutide added to basal insulin for T2DM unadequately controlled with basal insulin regimen when considering the US healthcare payer perspective.
Insulina prandiale							
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 ± 1.28 % in BIAsp 30 and 2.34 ±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

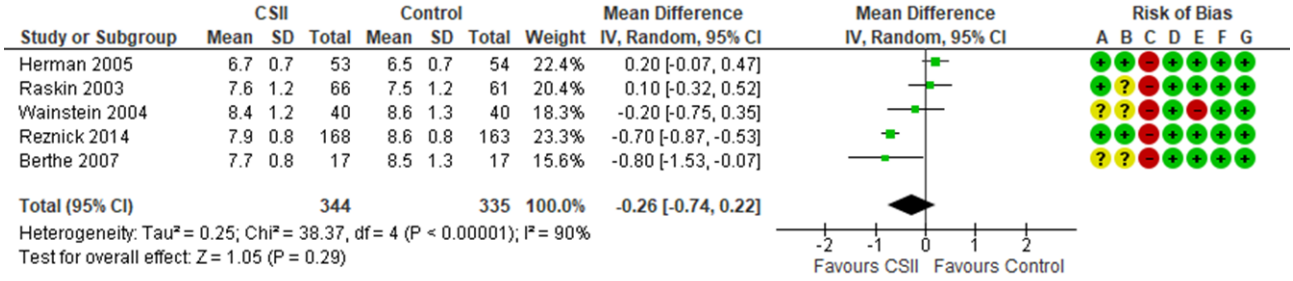
Author	Country	Intervention	Type of analysis	Incremental cost	Incremental cost (QALY)	Incremental cost per QALY gained	Authors' conclusions
					Minor, major, and nocturnal hypoglycemic events were more frequent among patients in the NPH/Reg arm (P <0.05 in all cases). BIAsp 30 significantly increased 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 publication[173]. An update of this meta-analysis was performed, without retrieving any further RCT.

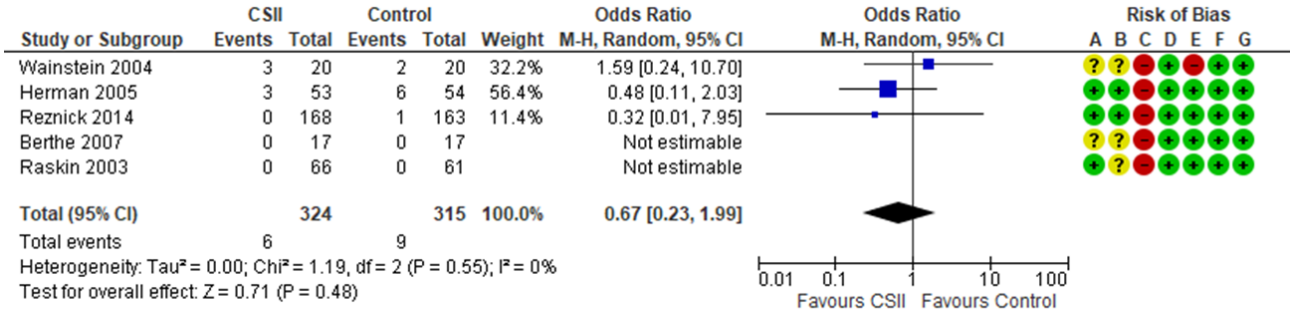
5.6.1. HbA1c

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



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.



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 assessment							Summary of findings			
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Relative effect (95%, CI)		Anticipated absolute effects	
									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 dei pazienti										
679 (5 RCTs)	serious[a]	serious[b]	not serious	serious[c]	none	⨁◯◯◯ VERY LOW	-	-	-	-
Qualità della vita										
679 (5 RCTs)	serious[a]	serious[b]	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 assessment							Summary of findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Stanfromrd care	With Intensive glycemic control		Risk with placebo	Risk difference with Intensive glycemic control
Ipoglicemia totale											
639 (5 RCTs)	serious[a]	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 studies retrieved							

.

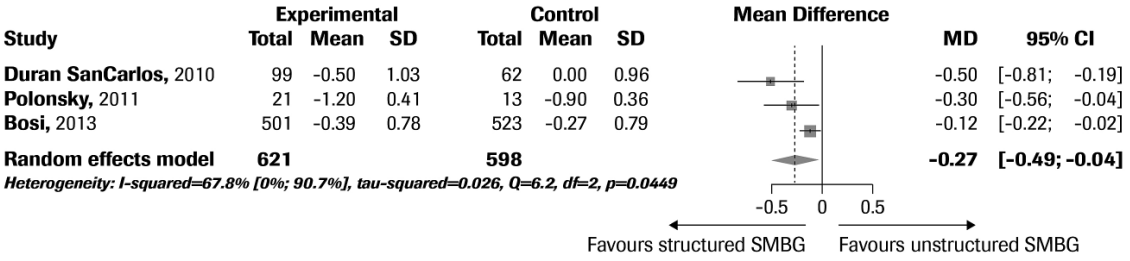
RECOMMENDATION # 6: GLUCOSE MONITORING.

6.1. Structured glucose monitoring

Considered evidence: RCT with a duration of at least 24 weeks, enrolling patients with non-insulin-treated 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 publication[180]. 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.



6.1.2. GRADE evidence table

Certainty assessment							Summary of findings		
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Relative effect** (95%, CI)	**Anticipated absolute effects**	
								Control	**Intervention**
HbA1c (%)									
1219 (3 RCTs)	serious[a]	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)

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 €0.93 to €1.07 in the meter and meter+app group respectively; In Germany cost-saving per patient/year ranged from €3.94 to €4.54; in Italy cost saving were €7.49 and €8.61 per year per patient; In Spain per patient/year savings were respectively e €0.80 in the meter and €0.91 in the meter + app groups; finally in UK savings per patient per year range from €0.88 to €1.01	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

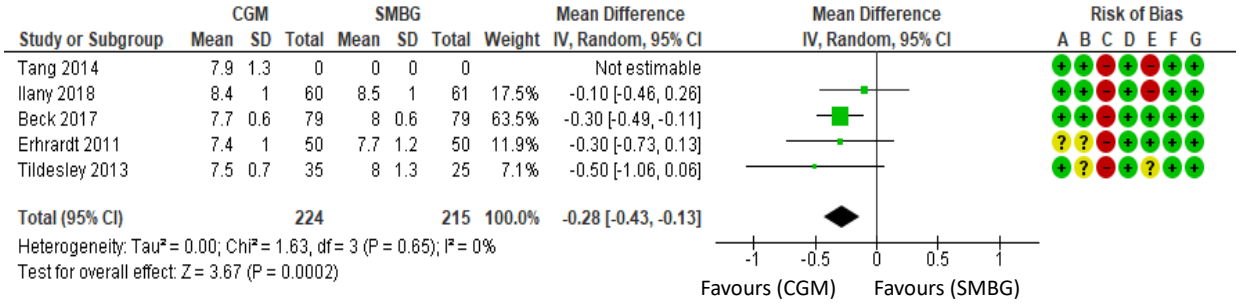
QALY: Quality Adjusted Life Years.

6.2. Structured glucose monitoring

Considered evidence: RCT with a duration of at least 12 weeks, enrolling patients with non-insulin-treated 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 publication[173]. 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 assessment							Summary of findings		
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Relative effect (95%, CI)	Anticipated absolute effects	
								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 vita									
436 (5 RCTs)	serious[a]	serious[b]	not serious	serious[c]	none	⨁◯◯◯ VERY LOW	-	-	**-**
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.

REFERENCES

1. Monami M, Candido R, Pintaudi B, Targher G, Mannucci E. Improvement of glycemic control in type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Nutrition, metabolism, and cardiovascular diseases : NMCD.* 2021;In press.
2. Chevalier P, Vandebrouck T, De Keyzer D, Mertens A, Lamotte M. Cost and co-morbidities associated with hypoglycemic inpatients in Belgium. *Journal of medical economics.* 2016;19(1):44-52.
3. Dalal MR, Kazemi M, Ye F, Xie L. Hypoglycemia After Initiation of Basal Insulin in Patients with Type 2 Diabetes in the United States: Implications for Treatment Discontinuation and Healthcare Costs and Utilization. *Advances in therapy.* 2017;34(9):2083-2092.
4. Tao L, Wilson EC, Wareham NJ, et al. Cost-effectiveness of intensive multifactorial treatment compared with routine care for individuals with screen-detected Type 2 diabetes: analysis of the ADDITION-UK cluster-randomized controlled trial. *Diabetic medicine : a journal of the British Diabetic Association.* 2015;32(7):907-919.
5. Díaz-Cerezo S, Romera I, Sicras-Mainar A, et al. Resource use and costs in patients with poorly controlled type 2 diabetes mellitus and obesity in routine clinical practice in Spain. *Current medical research and opinion.* 2020;36(9):1449-1456.
6. Elgart JF, Silvestrini C, Prestes M, Gonzalez L, Rucci E, Gagliardino JJ. Drug treatment of type 2 diabetes: Its cost is significantly associated with HbA1c levels. *International journal of clinical practice.* 2019;73(4):e13336.
7. Degli Esposti L, Saragoni S, Buda S, Sturani A, Degli Esposti E. Glycemic control and diabetes-related health care costs in type 2 diabetes; retrospective analysis based on clinical and administrative databases. *ClinicoEconomics and outcomes research : CEOR.* 2013;5:193-201.
8. Bruhn D, Martin AA, Tavares R, Hunt B, Pollock RF. Cost-utility of albiglutide versus insulin lispro, insulin glargine, and sitagliptin for the treatment of type 2 diabetes in the US. *Journal of medical economics.* 2016;19(7):672-683.
9. Tzanetakos C, Bargiota A, Kourlaba G, Gourzoulidis G, Maniadakis N. Cost Effectiveness of Exenatide Once Weekly Versus Insulin Glargine and Liraglutide for the Treatment of Type 2 Diabetes Mellitus in Greece. *Clinical drug investigation.* 2018;38(1):67-77.
10. Hunt B, Kragh N, McConnachie CC, Valentine WJ, Rossi MC, Montagnoli R. Long-term Cost-effectiveness of Two GLP-1 Receptor Agonists for the Treatment of Type 2 Diabetes Mellitus in the Italian Setting: Liraglutide Versus Lixisenatide. *Clinical therapeutics.* 2017;39(7):1347-1359.
11. Hunt B, Mocarski M, Valentine WJ, Langer J. Evaluation of the Short-Term Cost-Effectiveness of IDegLira Versus Continued Up-Titration of Insulin Glargine U100 in Patients with Type 2 Diabetes in the USA. *Advances in therapy.* 2017;34(4):954-965.
12. Gu S, Wang X, Qiao Q, Gao W, Wang J, Dong H. Cost-effectiveness of exenatide twice daily vs insulin glargine as add-on therapy to oral antidiabetic agents in patients with type 2 diabetes in China. *Diabetes Obes Metab.* 2017;19(12):1688-1697.
13. Møller G, Andersen HK, Snorgaard O. A systematic review and meta-analysis of nutrition therapy compared with dietary advice in patients with type 2 diabetes. *The American journal of clinical nutrition.* 2017;106(6):1394-1400.
14. Scrafford CG, Bi X, Multani JK, Murphy MM, Schmier JK, Barraj LM. Health Economic Evaluation Modeling Shows Potential Health Care Cost Savings with Increased Conformance with Healthy Dietary Patterns among Adults in the United States. *Journal of the Academy of Nutrition and Dietetics.* 2019;119(4):599-616.
15. Xin Y, Davies A, McCombie L, et al. Type 2 diabetes remission: economic evaluation of the DiRECT/Counterweight-Plus weight management programme within a primary care randomized controlled trial. *Diabetic medicine : a journal of the British Diabetic Association.* 2019;36(8):1003-1012.

16. Lanhers C, Walther G, Chapier R, et al. Long-term cost reduction of routine medications following a residential programme combining physical activity and nutrition in the treatment of type 2 diabetes: a prospective cohort study. *BMJ open.* 2017;7(4):e013763.
17. Silverii GA, Botarelli L, Dicembrini I, et al. Low-carbohydrate diets and type 2 diabetes treatment: a meta-analysis of randomized controlled trials. *Acta diabetologica.* 2020;57(11):1375-1382.
18. Mannucci E, Bonifazi A, Monami M. Comparison between different types of exercise training in patients with type 2 diabetes mellitus: A systematic review and network metanalysis of randomized controlled trials. *Nutrition, metabolism, and cardiovascular diseases : NMCD.* 2021;31(7):1985-1992.
19. Coyle D, Coyle K, Kenny GP, et al. Cost-effectiveness of exercise programs in type 2 diabetes. *Int J Technol Assess Health Care.* 2012;28(3):228-234.
20. Gavin C, Sigal RJ, Cousins M, et al. Resistance exercise but not aerobic exercise lowers remnant-like lipoprotein particle cholesterol in type 2 diabetes: a randomized controlled trial. *Atherosclerosis.* 2010;213(2):552-557.
21. Pillay J, Armstrong MJ, Butalia S, et al. Behavioral Programs for Type 2 Diabetes Mellitus: A Systematic Review and Network Meta-analysis. *Annals of internal medicine.* 2015;163(11):848-860.
22. Dalmau Llorca MR, García Bernal G, Aguilar Martín C, Palau Galindo A. [Group versus individual education for type-2 diabetes patients]. *Atencion primaria.* 2003;32(1):36-41.
23. Deakin TA, Cade JE, Williams R, Greenwood DC. Structured patient education: the diabetes X-PERT Programme makes a difference. *Diabetic medicine : a journal of the British Diabetic Association.* 2006;23(9):944-954.
24. Delahanty LM, Dalton KM, Porneala B, et al. Improving diabetes outcomes through lifestyle change--A randomized controlled trial. *Obesity (Silver Spring, Md).* 2015;23(9):1792-1799.
25. Santos JCD, Cortez DN, Macedo MML, Reis EA, Reis IA, Torres HC. Comparison of education group strategies and home visits in type 2 diabetes mellitus: clinical trial. *Revista latino-americana de enfermagem.* 2017;25:e2979.
26. Singer J, Levy S, Shimon I. Group versus Individual Care in Patients with Long-Standing Type 1 and Type 2 Diabetes: A One-Year Prospective Noninferiority Study in a Tertiary Diabetes Clinic. *Journal of diabetes research.* 2018;2018:1807246.
27. Sperl-Hillen J, Beaton S, Fernandes O, et al. Comparative effectiveness of patient education methods for type 2 diabetes: a randomized controlled trial. *Archives of internal medicine.* 2011;171(22):2001-2010.
28. Torres Hde C, Franco LJ, Stradioto MA, Hortale VA, Schall VT. [Evaluation of group and individual strategies in a diabetes education program]. *Revista de saude publica.* 2009;43(2):291-298.
29. Trento M, Passera P, Borgo E, et al. A 5-year randomized controlled study of learning, problem solving ability, and quality of life modifications in people with type 2 diabetes managed by group care. *Diabetes Care.* 2004;27(3):670-675.
30. Trento M, Basile M, Borgo E, et al. A randomised controlled clinical trial of nurse-, dietitian- and pedagogist-led Group Care for the management of Type 2 diabetes. *Journal of endocrinological investigation.* 2008;31(11):1038-1042.
31. Trento M, Gamba S, Gentile L, et al. Rethink Organization to iMprove Education and Outcomes (ROMEO): a multicenter randomized trial of lifestyle intervention by group care to manage type 2 diabetes. *Diabetes Care.* 2010;33(4):745-747.
32. Rickheim PL, Weaver TW, Flader JL, Kendall DM. Assessment of group versus individual diabetes education: a randomized study. *Diabetes Care.* 2002;25(2):269-274.
33. Vadstrup ES, Frølich A, Perrild H, Borg E, Røder M. Effect of a group-based rehabilitation programme on glycaemic control and cardiovascular risk factors in type 2 diabetes patients: the Copenhagen Type 2 Diabetes Rehabilitation Project. *Patient Educ Couns.* 2011;84(2):185-190.
34. van Puffelen AL, Rijken M, Heijmans M, Nijpels G, Schellevis FG. Effectiveness of a self-management support program for type 2 diabetes patients in the first years of illness: Results from a randomized controlled trial. *PloS one.* 2019;14(6):e0218242.

35. Withidpanyawong U, Lerkiatbundit S, Saengcharoen W. Family-based intervention by pharmacists for type 2 diabetes: A randomised controlled trial. *Patient Educ Couns.* 2019;102(1):85-92.
36. Gillett M, Dallosso HM, Dixon S, et al. Delivering the diabetes education and self management for ongoing and newly diagnosed (DESMOND) programme for people with newly diagnosed type 2 diabetes: cost effectiveness analysis. *BMJ (Clinical research ed).* 2010;341:c4093.
37. Prezio EA, Pagan JA, Shuval K, Culica D. The Community Diabetes Education (CoDE) program: cost-effectiveness and health outcomes. *Am J Prev Med.* 2014;47(6):771-779.
38. Mash R, Kroukamp R, Gaziano T, Levitt N. Cost-effectiveness of a diabetes group education program delivered by health promoters with a guiding style in underserved communities in Cape Town, South Africa. *Patient Educ Couns.* 2015;98(5):622-626.
39. Molsted S, Tribler J, Poulsen PB, Snorgaard O. The effects and costs of a group-based education programme for self-management of patients with Type 2 diabetes. A community-based study. *Health Educ Res.* 2012;27(5):804-813.
40. Mannucci E, Naletto L, Vaccaro G, et al. Efficacy and safety of glucose-lowering agents in patients with type 2 diabetes: A network meta-analysis of randomized, active comparator-controlled trials. *Nutrition, metabolism, and cardiovascular diseases : NMCD.* 2021;31(4):1027-1034.
41. Monami M, Candido R, Pintaudi B, Targher G, Mannucci E. Effect of metformin on all-cause mortality and major adverse cardiovascular events: An updated meta-analysis of randomized controlled trials. *Nutrition, metabolism, and cardiovascular diseases : NMCD.* 2020.
42. Bolli G, Dotta F, Colin L, Minic B, Goodman M. Comparison of vildagliptin and pioglitazone in patients with type 2 diabetes inadequately controlled with metformin. *Diabetes Obes Metab.* 2009;11(6):589-595.
43. Bosi E, Ellis GC, Wilson CA, Fleck PR. Alogliptin as a third oral antidiabetic drug in patients with type 2 diabetes and inadequate glycaemic control on metformin and pioglitazone: a 52-week, randomized, double-blind, active-controlled, parallel-group study. *Diabetes, obesity & metabolism.* 2011;13(12):1088-1096.
44. Charbonnel B, Dormandy J, Erdmann E, Massi-Benedetti M, Skene A. The prospective pioglitazone clinical trial in macrovascular events (PROactive): can pioglitazone reduce cardiovascular events in diabetes? Study design and baseline characteristics of 5238 patients. *Diabetes care.* 2004;27(7):1647-1653.
45. Charbonnel B, Schernthaner G, Brunetti P, et al. Long-term efficacy and tolerability of add-on pioglitazone therapy to failing monotherapy compared with addition of gliclazide or metformin in patients with type 2 diabetes. *Diabetologia.* 2005;48(6):1093-1104.
46. Derosa G, Mereu R, Salvadeo SA, et al. Pioglitazone metabolic effect in metformin-intolerant obese patients treated with sibutramine. *Internal medicine (Tokyo, Japan).* 2009;48(5):265-271.
47. Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet (London, England).* 2005;366(9493):1279-1289.
48. Giles TD, Elkayam U, Bhattacharya M, Perez A, Miller AB. Comparison of pioglitazone vs glyburide in early heart failure: insights from a randomized controlled study of patients with type 2 diabetes and mild cardiac disease. *Congestive heart failure (Greenwich, Conn).* 2010;16(3):111-117.
49. Henry RR, Staels B, Fonseca VA, et al. Efficacy and safety of initial combination treatment with sitagliptin and pioglitazone--a factorial study. *Diabetes, obesity & metabolism.* 2014;16(3):223-230.
50. Home PD, Shamanna P, Stewart M, et al. Efficacy and tolerability of albiglutide versus placebo or pioglitazone over 1 year in people with type 2 diabetes currently taking metformin and glimepiride: HARMONY 5. *Diabetes, obesity & metabolism.* 2015;17(2):179-187.
51. Khaloo P, Asadi Komeleh S, Alemi H, et al. Sitagliptin vs. pioglitazone as add-on treatments in patients with uncontrolled type 2 diabetes on the maximal dose of metformin plus sulfonylurea. *Journal of endocrinological investigation.* 2019;42(7):851-857.

52. Jain R, Osei K, Kupfer S, Perez AT, Zhang J. Long-term safety of pioglitazone versus glyburide in patients with recently diagnosed type 2 diabetes mellitus. *Pharmacotherapy.* 2006;26(10):1388-1395.
53. Lee HW, Lee HC, Kim BW, et al. Effects of low dose pioglitazone on restenosis and coronary atherosclerosis in diabetic patients undergoing drug eluting stent implantation. *Yonsei medical journal.* 2013;54(6):1313-1320.
54. Matthews DR, Charbonnel BH, Hanefeld M, Brunetti P, Schernthaner G. Long-term therapy with addition of pioglitazone to metformin compared with the addition of gliclazide to metformin in patients with type 2 diabetes: a randomized, comparative study. *Diabetes/metabolism research and reviews.* 2005;21(2):167-174.
55. Mazzone T, Meyer PM, Feinstein SB, et al. Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: a randomized trial. *Jama.* 2006;296(21):2572-2581.
56. Nissen SE, Nicholls SJ, Wolski K, et al. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. *Jama.* 2008;299(13):1561-1573.
57. Schernthaner G, Matthews DR, Charbonnel B, Hanefeld M, Brunetti P. Efficacy and safety of pioglitazone versus metformin in patients with type 2 diabetes mellitus: a double-blind, randomized trial. *The Journal of clinical endocrinology and metabolism.* 2004;89(12):6068-6076.
58. Tan MH, Glazer NB, Johns D, Widel M, Gilmore KJ. Pioglitazone as monotherapy or in combination with sulfonylurea or metformin enhances insulin sensitivity (HOMA-S or QUICKI) in patients with type 2 diabetes. *Current medical research and opinion.* 2004;20(5):723-728.
59. Tan M, Johns D, González Gálvez G, et al. Effects of pioglitazone and glimepiride on glycemic control and insulin sensitivity in Mexican patients with type 2 diabetes mellitus: A multicenter, randomized, double-blind, parallel-group trial. *Clinical therapeutics.* 2004;26(5):680-693.
60. Tolman KG, Freston JW, Kupfer S, Perez A. Liver safety in patients with type 2 diabetes treated with pioglitazone: results from a 3-year, randomized, comparator-controlled study in the US. *Drug safety.* 2009;32(9):787-800.
61. Vaccaro O, Masulli M, Nicolucci A, et al. Effects on the incidence of cardiovascular events of the addition of pioglitazone versus sulfonylureas in patients with type 2 diabetes inadequately controlled with metformin (TOSCA.IT): a randomised, multicentre trial. *The lancet Diabetes & endocrinology.* 2017;5(11):887-897.
62. Yamasaki Y, Katakami N, Furukado S, et al. Long-term effects of pioglitazone on carotid atherosclerosis in Japanese patients with type 2 diabetes without a recent history of macrovascular morbidity. *Journal of atherosclerosis and thrombosis.* 2010;17(11):1132-1140.
63. Yoshii H, Onuma T, Yamazaki T, et al. Effects of pioglitazone on macrovascular events in patients with type 2 diabetes mellitus at high risk of stroke: the PROFIT-J study. *Journal of atherosclerosis and thrombosis.* 2014;21(6):563-573.
64. Mannucci E, Monami M, Candido R, Pintaudi B, Targher G. Effect of insulin secretagogues on major cardiovascular events and all-cause mortality: A meta-analysis of randomized controlled trials. *Nutrition, metabolism, and cardiovascular diseases : NMCD.* 2020;30(10):1601-1608.
65. Mannucci E, Nreu B, Montereggi C, et al. Cardiovascular events and all-cause mortality in patients with type 2 diabetes treated with dipeptidyl peptidase-4 inhibitors: An extensive meta-analysis of randomized controlled trials. *Nutrition, metabolism, and cardiovascular diseases : NMCD.* 2021.
66. Nreu B, Dicembrini I, Tinti F, Sesti G, Mannucci E, Monami M. Major cardiovascular events, heart failure, and atrial fibrillation in patients treated with glucagon-like peptide-1 receptor agonists: An updated meta-analysis of randomized controlled trials. *Nutrition, metabolism, and cardiovascular diseases : NMCD.* 2020;30(7):1106-1114.
67. Silverii GA, Monami M, Mannucci E. Sodium-glucose co-transporter-2 inhibitors and all-cause mortality: A meta-analysis of randomized controlled trials. *Diabetes Obes Metab.* 2020.

68. Hasche H, Mertes G, Bruns C, et al. Effects of acarbose treatment in Type 2 diabetic patients under dietary training: a multicentre, double-blind, placebo-controlled, 2-year study. *Diabetes, nutrition & metabolism.* 1999;12(4):277-285.
69. Chiasson JL, Josse RG, Hunt JA, et al. The efficacy of acarbose in the treatment of patients with non-insulin-dependent diabetes mellitus. A multicenter controlled clinical trial. *Annals of internal medicine.* 1994;121(12):928-935.
70. Josse RG, Chiasson JL, Ryan EA, et al. Acarbose in the treatment of elderly patients with type 2 diabetes. *Diabetes research and clinical practice.* 2003;59(1):37-42.
71. Johnston PS, Lebovitz HE, Coniff RF, Simonson DC, Raskin P, Munera CL. Advantages of alpha-glucosidase inhibition as monotherapy in elderly type 2 diabetic patients. *The Journal of clinical endocrinology and metabolism.* 1998;83(5):1515-1522.
72. Johnston PS, Feig PU, Coniff RF, Krol A, Kelley DE, Mooradian AD. Chronic treatment of African-American type 2 diabetic patients with alpha-glucosidase inhibition. *Diabetes care.* 1998;21(3):416-422.
73. Scorpiglione N, Belfiglio M, Carinci F, et al. The effectiveness, safety and epidemiology of the use of acarbose in the treatment of patients with type II diabetes mellitus. A model of medicine-based evidence. *European journal of clinical pharmacology.* 1999;55(4):239-249.
74. Holman RR, Cull CA, Turner RC. A randomized double-blind trial of acarbose in type 2 diabetes shows improved glycemic control over 3 years (U.K. Prospective Diabetes Study 44). *Diabetes care.* 1999;22(6):960-964.
75. Bachmann W, Petzinna D, Raptis SA, Wascher T, Westermeier T. Long-term improvement of metabolic control by acarbose in type 2 diabetes patients poorly controlled with maximum sulfonylurea therapy. *Clinical drug investigation.* 2003;23(10):679-686.
76. Alvarsson M, Sundkvist G, Lager I, et al. Effects of insulin vs. glibenclamide in recently diagnosed patients with type 2 diabetes: a 4-year follow-up. *Diabetes, obesity & metabolism.* 2008;10(5):421-429.
77. Arturi F, Succurro E, Miceli S, et al. Liraglutide improves cardiac function in patients with type 2 diabetes and chronic heart failure. *Endocrine.* 2017;57(3):464-473.
78. Blonde L, Jendle J, Gross J, et al. Once-weekly dulaglutide versus bedtime insulin glargine, both in combination with prandial insulin lispro, in patients with type 2 diabetes (AWARD-4): a randomised, open-label, phase 3, non-inferiority study. *Lancet (London, England).* 2015;385(9982):2057-2066.
79. Bunck MC, Diamant M, Corner A, et al. One-year treatment with exenatide improves beta-cell function, compared with insulin glargine, in metformin-treated type 2 diabetic patients: a randomized, controlled trial. *Diabetes care.* 2009;32(5):762-768.
80. Diamant M, Van Gaal L, Guerci B, et al. Exenatide once weekly versus insulin glargine for type 2 diabetes (DURATION-3): 3-year results of an open-label randomised trial. *The lancet Diabetes & endocrinology.* 2014;2(6):464-473.
81. Giorgino F, Benroubi M, Sun JH, Zimmermann AG, Pechtner V. Efficacy and Safety of Once-Weekly Dulaglutide Versus Insulin Glargine in Patients With Type 2 Diabetes on Metformin and Glimepiride (AWARD-2). *Diabetes care.* 2015;38(12):2241-2249.
82. Gough SC, Bode BW, Woo VC, et al. One-year efficacy and safety of a fixed combination of insulin degludec and liraglutide in patients with type 2 diabetes: results of a 26-week extension to a 26-week main trial. *Diabetes, obesity & metabolism.* 2015;17(10):965-973.
83. Inagaki N, Atsumi Y, Oura T, Saito H, Imaoka T. Efficacy and safety profile of exenatide once weekly compared with insulin once daily in Japanese patients with type 2 diabetes treated with oral antidiabetes drug(s): results from a 26-week, randomized, open-label, parallel-group, multicenter, noninferiority study. *Clinical therapeutics.* 2012;34(9):1892-1908.e1891.
84. Jaiswal M, Martin CL, Brown MB, et al. Effects of exenatide on measures of diabetic neuropathy in subjects with type 2 diabetes: results from an 18-month proof-of-concept open-label randomized study. *Journal of diabetes and its complications.* 2015;29(8):1287-1294.

85. Klein W. Sulfonylurea-metformin-combination versus sulfonylurea-insulin-combination in secondary failures of sulfonylurea monotherapy. Results of a prospective randomized study in 50 patients. *Diabete Metab.* 1991;17(1 Pt 2):235-240.
86. Ko GT, Tsang PC, Wai HP, Kan EC, Chan HC. Rosiglitazone versus bedtime insulin in the treatment of patients with conventional oral antidiabetic drug failure: a 1-year randomized clinical trial. *Advances in therapy.* 2006;23(5):799-808.
87. Lingvay I, Legendre JL, Kaloyanova PF, Zhang S, Adams-Huet B, Raskin P. Insulin-based versus triple oral therapy for newly diagnosed type 2 diabetes: which is better? *Diabetes care.* 2009;32(10):1789-1795.
88. Gerstein HC, Bosch J, Dagenais GR, et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. *The New England journal of medicine.* 2012;367(4):319-328.
89. Tuttle KR, Lakshmanan MC, Gross JL, et al. Comparable glycemic control, greater weight loss, and lower hypoglycemia with once weekly dulaglutide versus insulin glargine, both combined with lispro, in type 2 diabetes and moderate to severe chronic kidney disease (AWARD-7). *Diabetology and Metabolic Syndrome.* 2018;10.
90. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet (London, England).* 1998;352(9131):837-853.
91. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet (London, England).* 1998;352(9131):854-865.
92. Weng J, Li Y, Xu W, et al. Effect of intensive insulin therapy on beta-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial. *Lancet (London, England).* 2008;371(9626):1753-1760.
93. Johnston R, Uthman O, Cummins E, et al. Canagliflozin, dapagliflozin and empagliflozin monotherapy for treating type 2 diabetes: systematic review and economic evaluation. *Health technology assessment (Winchester, England).* 2017;21(2):1-218.
94. Shyangdan D, Cummins E, Royle P, Waugh N. Liraglutide for the treatment of type 2 diabetes. *Health technology assessment (Winchester, England).* 2011;15 Suppl 1:77-86.
95. Geng J, Yu H, Mao Y, Zhang P, Chen Y. Cost effectiveness of dipeptidyl peptidase-4 inhibitors for type 2 diabetes. *PharmacoEconomics.* 2015;33(6):581-597.
96. Hong D, Si L, Jiang M, et al. Cost Effectiveness of Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors, Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists, and Dipeptidyl Peptidase-4 (DPP-4) Inhibitors: A Systematic Review. *PharmacoEconomics.* 2019;37(6):777-818.
97. Tzanetakos C, Tzioufas A, Goules A, et al. Cost-utility analysis of certolizumab pegol in combination with methotrexate in patients with moderate-to-severe active rheumatoid arthritis in Greece. *Rheumatology international.* 2017;37(9):1441-1452.
98. Hunt B, McConnachie CC, Gamble C, Dang-Tan T. Evaluating the short-term cost-effectiveness of liraglutide versus lixisenatide in patients with type 2 diabetes in the United States. *Journal of medical economics.* 2017;20(11):1117-1120.
99. Kvapil M, Prázný M, Holik P, Rychna K, Hunt B. Cost-Effectiveness of IDegLira Versus Insulin Intensification Regimens for the Treatment of Adults with Type 2 Diabetes in the Czech Republic. *Diabetes Ther.* 2017;8(6):1331-1347.
100. Davies MJ, Glah D, Chubb B, Konidaris G, McEwan P. Cost Effectiveness of IDegLira vs. Alternative Basal Insulin Intensification Therapies in Patients with Type 2 Diabetes Mellitus Uncontrolled on Basal Insulin in a UK Setting. *PharmacoEconomics.* 2016;34(9):953-966.
101. Kousoulakou H, Hatzikou M, Baroutsou V, Yfantopoulos J. Cost effectiveness of vildagliptin versus glimepiride as add-on treatment to metformin for the treatment of diabetes mellitus type 2 patients in Greece. *Cost effectiveness and resource allocation : C/E.* 2017;15:19.

102. Hunt B, Mocarski M, Valentine WJ, Langer J. Evaluation of the long-term cost-effectiveness of IDegLira versus liraglutide added to basal insulin for patients with type 2 diabetes failing to achieve glycemic control on basal insulin in the USA. *Journal of medical economics.* 2017;20(7):663-670.
103. Mezquita-Raya P, Ramírez de Arellano A, Kragh N, et al. Liraglutide Versus Lixisenatide: Long-Term Cost-Effectiveness of GLP-1 Receptor Agonist Therapy for the Treatment of Type 2 Diabetes in Spain. *Diabetes Ther.* 2017;8(2):401-415.
104. Ericsson Å, Lundqvist A. Cost Effectiveness of Insulin Degludec Plus Liraglutide (IDegLira) in a Fixed Combination for Uncontrolled Type 2 Diabetes Mellitus in Sweden. *Applied health economics and health policy.* 2017;15(2):237-248.
105. Zhang X, Liu S, Li Y, Wang Y, Tian M, Liu G. Long-Term Effectiveness and Cost-Effectiveness of Metformin Combined with Liraglutide or Exenatide for Type 2 Diabetes Mellitus Based on the CORE Diabetes Model Study. *PloS one.* 2016;11(6):e0156393.
106. Gu S, Mu Y, Zhai S, Zeng Y, Zhen X, Dong H. Cost-Effectiveness of Dapagliflozin versus Acarbose as a Monotherapy in Type 2 Diabetes in China. *PloS one.* 2016;11(11):e0165629.
107. Vega-Hernandez G, Wojcik R, Schlueter M. Cost-Effectiveness of Liraglutide Versus Dapagliflozin for the Treatment of Patients with Type 2 Diabetes Mellitus in the UK. *Diabetes Ther.* 2017;8(3):513-530.
108. Roussel R, Martinez L, Vandebrouck T, et al. Evaluation of the long-term cost-effectiveness of liraglutide therapy for patients with type 2 diabetes in France. *Journal of medical economics.* 2016;19(2):121-134.
109. Chuang LH, Verheggen BG, Charokopou M, Gibson D, Grandy S, Kartman B. Cost-effectiveness analysis of exenatide once-weekly versus dulaglutide, liraglutide, and lixisenatide for the treatment of type 2 diabetes mellitus: an analysis from the UK NHS perspective. *Journal of medical economics.* 2016;19(12):1127-1134.
110. Gordon J, McEwan P, Sabale U, Kartman B, Wolffenbuttel BH. The cost-effectiveness of exenatide twice daily (BID) vs insulin lispro three times daily (TID) as add-on therapy to titrated insulin glargine in patients with type 2 diabetes. *Journal of medical economics.* 2016;19(12):1167-1174.
111. Tzanetakos C, Tentolouris N, Kourlaba G, Maniadakis N. Cost-Effectiveness of Dapagliflozin as Add-On to Metformin for the Treatment of Type 2 Diabetes Mellitus in Greece. *Clinical drug investigation.* 2016;36(8):649-659.
112. Sabapathy S, Neslusan C, Yoong K, Teschemaker A, Johansen P, Willis M. Cost-effectiveness of Canagliflozin versus Sitagliptin When Added to Metformin and Sulfonylurea in Type 2 Diabetes in Canada. *Journal of population therapeutics and clinical pharmacology = Journal de la therapeutique des populations et de la pharamcologie clinique.* 2016;23(2):e151-168.
113. Permsuwan U, Dilokthornsakul P, Saokaew S, Thavorn K, Chaiyakunapruk N. Cost-effectiveness of dipeptidyl peptidase-4 inhibitor monotherapy in elderly type 2 diabetes patients in Thailand. *ClinicoEconomics and outcomes research : CEOR.* 2016;8:521-529.
114. Aso Y, Suzuki K, Chiba Y, et al. Effect of insulin degludec versus insulin glargine on glycemic control and daily fasting blood glucose variability in insulin-naive Japanese patients with type 2 diabetes: I'D GOT trial. *Diabetes research and clinical practice.* 2017;130:237-243.
115. Berard L, Cameron B, Woo V, Stewart J. Replacing Insulin Glargine with Neutral Protamine Hagedorn (NPH) Insulin in a Subpopulation of Study Subjects in the Action to Control Cardiovascular Risk in Diabetes (ACCORD): Effects on Blood Glucose Levels, Hypoglycemia and Patient Satisfaction. *Canadian journal of diabetes.* 2015;39(4):296-301.
116. Betônico CC, Titan SMO, Lira A, et al. Insulin Glargine U100 Improved Glycemic Control and Reduced Nocturnal Hypoglycemia in Patients with Type 2 Diabetes Mellitus and Chronic Kidney Disease Stages 3 and 4. *Clinical therapeutics.* 2019;41(10):2008-2020.e2003.
117. Bolli GB, Riddle MC, Bergenstal RM, et al. New insulin glargine 300 U/ml compared with glargine 100 U/ml in insulin-naive people with type 2 diabetes on oral glucose-lowering drugs: a randomized controlled trial (EDITION 3). *Diabetes Obes Metab.* 2015;17(4):386-394.
118. Bowering K, Reed VA, Felicio JS, Landry J, Ji L, Oliveira J. A study comparing insulin lispro mix 25 with glargine plus lispro therapy in patients with Type 2 diabetes who have inadequate glycaemic control

on oral anti-hyperglycaemic medication: results of the PARADIGM study. *Diabetic medicine : a journal of the British Diabetic Association.* 2012;29(9):e263-272.

119. Eliaschewitz FG, Calvo C, Valbuena H, et al. Therapy in type 2 diabetes: insulin glargine vs. NPH insulin both in combination with glimepiride. *Archives of medical research.* 2006;37(4):495-501.
120. Elisha B, Azar M, Taleb N, Bernard S, Iacobellis G, Rabasa-Lhoret R. Body Composition and Epicardial Fat in Type 2 Diabetes Patients Following Insulin Detemir Versus Insulin Glargine Initiation. *Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme.* 2016;48(1):42-47.
121. Esposito K, Ciotola M, Maiorino MI, et al. Addition of neutral protamine lispro insulin or insulin glargine to oral type 2 diabetes regimens for patients with suboptimal glycemic control: a randomized trial. *Annals of internal medicine.* 2008;149(8):531-539.
122. Fajardo Montanana C, Hernandez Herrero C, Rivas Fernandez M. Less weight gain and hypoglycaemia with once-daily insulin detemir than NPH insulin in intensification of insulin therapy in overweight Type 2 diabetes patients: the PREDICTIVE BMI clinical trial. *Diabetic medicine : a journal of the British Diabetic Association.* 2008;25(8):916-923.
123. Fogelfeld L, Dharmalingam M, Robling K, Jones C, Swanson D, Jacober S. A randomized, treat-to-target trial comparing insulin lispro protamine suspension and insulin detemir in insulin-naive patients with Type 2 diabetes. *Diabetic medicine : a journal of the British Diabetic Association.* 2010;27(2):181-188.
124. Fonseca V, Bell DS, Berger S, Thomson S, Mecca TE. A comparison of bedtime insulin glargine with bedtime neutral protamine hagedorn insulin in patients with type 2 diabetes: subgroup analysis of patients taking once-daily insulin in a multicenter, randomized, parallel group study. *The American journal of the medical sciences.* 2004;328(5):274-280.
125. Franek E, Haluzik M, Canecki Varzic S, et al. Twice-daily insulin degludec/insulin aspart provides superior fasting plasma glucose control and a reduced rate of hypoglycaemia compared with biphasic insulin aspart 30 in insulin-naive adults with Type 2 diabetes. *Diabetic medicine : a journal of the British Diabetic Association.* 2016;33(4):497-505.
126. Fritsche A, Schweitzer MA, Haring HU. Glimepiride combined with morning insulin glargine, bedtime neutral protamine hagedorn insulin, or bedtime insulin glargine in patients with type 2 diabetes. A randomized, controlled trial. *Annals of internal medicine.* 2003;138(12):952-959.
127. Fulcher GR, Christiansen JS, Bantwal G, et al. Comparison of insulin degludec/insulin aspart and biphasic insulin aspart 30 in uncontrolled, insulin-treated type 2 diabetes: a phase 3a, randomized, treat-to-target trial. *Diabetes Care.* 2014;37(8):2084-2090.
128. Garber AJ, King AB, Del Prato S, et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. *Lancet (London, England).* 2012;379(9825):1498-1507.
129. Hollander P, King AB, Del Prato S, et al. Insulin degludec improves long-term glycaemic control similarly to insulin glargine but with fewer hypoglycaemic episodes in patients with advanced type 2 diabetes on basal-bolus insulin therapy. *Diabetes, obesity & metabolism.* 2015;17(2):202-206.
130. Giugliano D, Tracz M, Shah S, et al. Initiation and gradual intensification of premixed insulin lispro therapy versus Basal {+/-} mealtime insulin in patients with type 2 diabetes eating light breakfasts. *Diabetes Care.* 2014;37(2):372-380.
131. Gough SC, Bhargava A, Jain R, Mersebach H, Rasmussen S, Bergenstal RM. Low-volume insulin degludec 200 units/ml once daily improves glycemic control similarly to insulin glargine with a low risk of hypoglycemia in insulin-naive patients with type 2 diabetes: a 26-week, randomized, controlled, multinational, treat-to-target trial: the BEGIN LOW VOLUME trial. *Diabetes care.* 2013;36(9):2536-2542.
132. Haak T, Tiengo A, Draeger E, Suntum M, Waldhausl W. Lower within-subject variability of fasting blood glucose and reduced weight gain with insulin detemir compared to NPH insulin in patients with type 2 diabetes. *Diabetes Obes Metab.* 2005;7(1):56-64.

133. Hermansen K, Davies M, Derezinski T, Martinez Ravn G, Clauson P, Home P. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetes Care.* 2006;29(6):1269-1274.
134. Hollander P, Cooper J, Bregnhoj J, Pedersen CB. A 52-week, multinational, open-label, parallel-group, noninferiority, treat-to-target trial comparing insulin detemir with insulin glargine in a basal-bolus regimen with mealtime insulin aspart in patients with type 2 diabetes. *Clinical therapeutics.* 2008;30(11):1976-1987.
135. Home PD, Bolli GB, Mathieu C, et al. Modulation of insulin dose titration using a hypoglycaemia-sensitive algorithm: insulin glargine versus neutral protamine Hagedorn insulin in insulin-naive people with type 2 diabetes. *Diabetes, obesity & metabolism.* 2015;17(1):15-22.
136. Hsia SH. Insulin glargine compared to NPH among insulin-naive, U.S. inner city, ethnic minority type 2 diabetic patients. *Diabetes research and clinical practice.* 2011;91(3):293-299.
137. Kaneko S, Chow F, Choi DS, et al. Insulin degludec/insulin aspart versus biphasic insulin aspart 30 in Asian patients with type 2 diabetes inadequately controlled on basal or pre-/self-mixed insulin: a 26-week, randomised, treat-to-target trial. *Diabetes research and clinical practice.* 2015;107(1):139-147.
138. Liebl A, Prager R, Binz K, Kaiser M, Bergenstal R, Gallwitz B. Comparison of insulin analogue regimens in people with type 2 diabetes mellitus in the PREFER Study: a randomized controlled trial. *Diabetes Obes Metab.* 2009;11(1):45-52.
139. Massi Benedetti M, Humburg E, Dressler A, Ziemen M. A one-year, randomised, multicentre trial comparing insulin glargine with NPH insulin in combination with oral agents in patients with type 2 diabetes. *Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme.* 2003;35(3):189-196.
140. Pan CY, Sinnassamy P, Chung KD, Kim KW. Insulin glargine versus NPH insulin therapy in Asian Type 2 diabetes patients. *Diabetes research and clinical practice.* 2007;76(1):111-118.
141. Pan C, Gross JL, Yang W, et al. A Multinational, Randomized, Open-label, Treat-to-Target Trial Comparing Insulin Degludec and Insulin Glargine in Insulin-Naive Patients with Type 2 Diabetes Mellitus. *Drugs in R&D.* 2016;16(2):239-249.
142. Philis-Tsimikas A, Klonoff DC, Khunti K, et al. Risk of hypoglycaemia with insulin degludec versus insulin glargine U300 in insulin-treated patients with type 2 diabetes: the randomised, head-to-head CONCLUDE trial. *Diabetologia.* 2020;63(4):698-710.
143. Raskin P, Gylvin T, Weng W, Chaykin L. Comparison of insulin detemir and insulin glargine using a basal-bolus regimen in a randomized, controlled clinical study in patients with type 2 diabetes. *Diabetes/metabolism research and reviews.* 2009;25(6):542-548.
144. Riddle MC, Rosenstock J, Gerich J. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care.* 2003;26(11):3080-3086.
145. Riddle MC, Yki-Jarvinen H, Bolli GB, et al. One-year sustained glycaemic control and less hypoglycaemia with new insulin glargine 300 U/ml compared with 100 U/ml in people with type 2 diabetes using basal plus meal-time insulin: the EDITION 1 12-month randomized trial, including 6-month extension. *Diabetes Obes Metab.* 2015;17(9):835-842.
146. Ritzel R, Harris SB, Baron H, et al. A Randomized Controlled Trial Comparing Efficacy and Safety of Insulin Glargine 300 Units/mL Versus 100 Units/mL in Older People With Type 2 Diabetes: Results From the SENIOR Study. *Diabetes Care.* 2018;41(8):1672-1680.
147. Rodbard HW, Cariou B, Zinman B, et al. Health status and hypoglycaemia with insulin degludec versus insulin glargine: a 2-year trial in insulin-naive patients with type 2 diabetes. *Diabetes Obes Metab.* 2014;16(9):869-872.
148. Zinman B, Philis-Tsimikas A, Cariou B, et al. Insulin degludec versus insulin glargine in insulin-naive patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN Once Long). *Diabetes care.* 2012;35(12):2464-2471.

149. Rosenstock J, Schwartz SL, Clark CM, Jr., Park GD, Donley DW, Edwards MB. Basal insulin therapy in type 2 diabetes: 28-week comparison of insulin glargine (HOE 901) and NPH insulin. *Diabetes Care.* 2001;24(4):631-636.
150. Rosenstock J, Davies M, Home PD, Larsen J, Koenen C, Schernthaner G. A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetologia.* 2008;51(3):408-416.
151. Rosenstock J, Fonseca V, McGill JB, et al. Similar progression of diabetic retinopathy with insulin glargine and neutral protamine Hagedorn (NPH) insulin in patients with type 2 diabetes: a long-term, randomised, open-label study. *Diabetologia.* 2009;52(9):1778-1788.
152. Del Prato S, Rosenstock J, Garcia-Sanchez R, et al. Safety and tolerability of dapagliflozin, saxagliptin and metformin in combination: Post-hoc analysis of concomitant add-on versus sequential add-on to metformin and of triple versus dual therapy with metformin. *Diabetes Obes Metab.* 2018;20(6):1542-1546.
153. Swinnen SG, Dain MP, Aronson R, et al. A 24-week, randomized, treat-to-target trial comparing initiation of insulin glargine once-daily with insulin detemir twice-daily in patients with type 2 diabetes inadequately controlled on oral glucose-lowering drugs. *Diabetes Care.* 2010;33(6):1176-1178.
154. Terauchi Y, Koyama M, Cheng X, et al. New insulin glargine 300 U/ml versus glargine 100 U/ml in Japanese people with type 2 diabetes using basal insulin and oral antihyperglycaemic drugs: glucose control and hypoglycaemia in a randomized controlled trial (EDITION JP 2). *Diabetes Obes Metab.* 2016;18(4):366-374.
155. Yki-Jarvinen H, Dressler A, Ziemen M. Less nocturnal hypoglycemia and better post-dinner glucose control with bedtime insulin glargine compared with bedtime NPH insulin during insulin combination therapy in type 2 diabetes. HOE 901/3002 Study Group. *Diabetes Care.* 2000;23(8):1130-1136.
156. Yki-Jarvinen H, Kauppinen-Makelin R, Tiikkainen M, et al. Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study. *Diabetologia.* 2006;49(3):442-451.
157. Yki-Jarvinen H, Bergenstal RM, Bolli GB, et al. Glycaemic control and hypoglycaemia with new insulin glargine 300 U/ml versus insulin glargine 100 U/ml in people with type 2 diabetes using basal insulin and oral antihyperglycaemic drugs: the EDITION 2 randomized 12-month trial including 6-month extension. *Diabetes Obes Metab.* 2015;17(12):1142-1149.
158. Yokoyama H, Tada J, Kamikawa F, Kanno S, Yokota Y, Kuramitsu M. Efficacy of conversion from bedtime NPH insulin to morning insulin glargine in type 2 diabetic patients on basal-prandial insulin therapy. *Diabetes research and clinical practice.* 2006;73(1):35-40.
159. Altuntas Y, Ozen B, Ozturk B, et al. Comparison of additional metformin or NPH insulin to mealtime insulin lispro therapy with mealtime human insulin therapy in secondary OAD failure. *Diabetes, obesity & metabolism.* 2003;5(6):371-378.
160. Anderson JH, Jr., Brunelle RL, Koivisto VA, Trautmann ME, Vignati L, DiMarchi R. Improved mealtime treatment of diabetes mellitus using an insulin analogue. Multicenter Insulin Lispro Study Group. *Clinical therapeutics.* 1997;19(1):62-72.
161. Bastyr EJ, 3rd, Huang Y, Brunelle RL, Vignati L, Cox DJ, Kotsanos JG. Factors associated with nocturnal hypoglycaemia among patients with type 2 diabetes new to insulin therapy: experience with insulin lispro. *Diabetes Obes Metab.* 2000;2(1):39-46.
162. Dailey G, Rosenstock J, Moses RG, Ways K. Insulin glulisine provides improved glycemic control in patients with type 2 diabetes. *Diabetes care.* 2004;27(10):2363-2368.
163. Herrmann BL, Kasser C, Keuthage W, Huptas M, Dette H, Klute A. Comparison of insulin aspart vs. regular human insulin with or without insulin detemir concerning adipozytokines and metabolic effects in patients with type 2 diabetes mellitus. *Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association.* 2013;121(4):210-213.

164. Bowering K, Case C, Harvey J, et al. Faster Aspart Versus Insulin Aspart as Part of a Basal-Bolus Regimen in Inadequately Controlled Type 2 Diabetes: The onset 2 Trial. *Diabetes care.* 2017;40(7):951-957.
165. Rayman G, Profozic V, Middle M. Insulin glulisine imparts effective glycaemic control in patients with Type 2 diabetes. *Diabetes research and clinical practice.* 2007;76(2):304-312.
166. Permsuwan U, Chaiyakunapruk N, Dilokthornsakul P, Thavorn K, Saokaew S. Long-Term Cost-Effectiveness of Insulin Glargine Versus Neutral Protamine Hagedorn Insulin for Type 2 Diabetes in Thailand. *Applied health economics and health policy.* 2016;14(3):281-292.
167. Permsuwan U, Thavorn K, Dilokthornsakul P, Saokaew S, Chaiyakunapruk N. Cost-effectiveness of insulin detemir versus insulin glargine for Thai type 2 diabetes from a payer's perspective. *Journal of medical economics.* 2017;20(9):991-999.
168. Brändle M, Azoulay M, Greiner RA. Cost-effectiveness of insulin glargine versus NPH insulin for the treatment of Type 2 diabetes mellitus, modeling the interaction between hypoglycemia and glycemic control in Switzerland. *International journal of clinical pharmacology and therapeutics.* 2011;49(3):217-230.
169. Cheng H, Wan X, Ma J, Wu B. Cost-effectiveness of Insulin Degludec Versus Insulin Glargine in Insulin-naive Chinese Patients With Type 2 Diabetes. *Clinical therapeutics.* 2019;41(3):445-455.e444.
170. Drummond R, Malkin S, Du Preez M, Lee XY, Hunt B. The management of type 2 diabetes with fixed-ratio combination insulin degludec/liraglutide (IDegLira) versus basal-bolus therapy (insulin glargine U100 plus insulin aspart): A short-term cost-effectiveness analysis in the UK setting. *Diabetes Obes Metab.* 2018;20(10):2371-2378.
171. Torre E, Bruno GM, Di Matteo S, et al. Cost-minimization analysis of degludec/liraglutide versus glargine/aspart: economic implications of the DUAL VII study outcomes. *ClinicoEconomics and outcomes research : CEOR.* 2018;10:413-421.
172. Farshchi A, Aghili R, Oskuee M, et al. Biphasic insulin Aspart 30 vs. NPH plus regular human insulin in type 2 diabetes patients; a cost-effectiveness study. *BMC endocrine disorders.* 2016;16(1):35.
173. Dicembrini I, Mannucci E, Monami M, Pala L. Impact of technology on glycaemic control in type 2 diabetes: A meta-analysis of randomized trials on continuous glucose monitoring and continuous subcutaneous insulin infusion. *Diabetes Obes Metab.* 2019;21(12):2619-2625.
174. Berthe E, Lireux B, Coffin C, et al. Effectiveness of intensive insulin therapy by multiple daily injections and continuous subcutaneous infusion: a comparison study in type 2 diabetes with conventional insulin regimen failure. *Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme.* 2007;39(3):224-229.
175. Herman WH, Ilag LL, Johnson SL, et al. A clinical trial of continuous subcutaneous insulin infusion versus multiple daily injections in older adults with type 2 diabetes. *Diabetes Care.* 2005;28(7):1568-1573.
176. Jennings AM, Lewis KS, Murdoch S, Talbot JF, Bradley C, Ward JD. Randomized trial comparing continuous subcutaneous insulin infusion and conventional insulin therapy in type II diabetic patients poorly controlled with sulfonylureas. *Diabetes Care.* 1991;14(8):738-744.
177. Raskin P, Allen E, Hollander P, et al. Initiating insulin therapy in type 2 Diabetes: a comparison of biphasic and basal insulin analogs. *Diabetes Care.* 2005;28(2):260-265.
178. Reznik Y, Habteab A, Castaneda J, Shin J, Joubert M. Contribution of basal and postprandial hyperglycaemia in type 2 diabetes patients treated by an intensified insulin regimen: Impact of pump therapy in the OPT2mise trial. *Diabetes Obes Metab.* 2018;20(10):2435-2441.
179. Wainstein J, Metzger M, Boaz M, et al. Insulin pump therapy vs. multiple daily injections in obese Type 2 diabetic patients. *Diabetic medicine : a journal of the British Diabetic Association.* 2005;22(8):1037-1046.
180. Mannucci E, Antenore A, Giorgino F, Scavini M. Effects of Structured Versus Unstructured Self-Monitoring of Blood Glucose on Glucose Control in Patients With Non-insulin-treated Type 2 Diabetes: A Meta-Analysis of Randomized Controlled Trials. *Journal of diabetes science and technology.* 2018;12(1):183-189.

181. Aghili R, Khamseh ME, Malek M, Yarahmadi S, Farshchi A. Structured self monitoring of blood glucose in Iranian people with type 2 diabetes; A cost consequence analysis. *Daru : journal of Faculty of Pharmacy, Tehran University of Medical Sciences.* 2012;20(1):32.
182. Fritzen K, Basinska K, Rubio-Almanza M, et al. Pan-European Economic Analysis to Identify Cost Savings for the Health Care Systems as a Result of Integrating Glucose Monitoring Based Telemedical Approaches Into Diabetes Management. *Journal of diabetes science and technology.* 2019;13(6):1112-1122.
183. Scotland HI. What is the clinical and cost effectiveness of Freestyle Libre flash glucose monitoring for patients with diabetes mellitus treated with intensive insulin therapy? . 2018.
184. Bilir SP, Hellmund R, Wehler E, Li H, Munakata J, Lamotte M. The Cost-effectiveness of a Flash Glucose Monitoring System for Management of Patients with Type 2 Diabetes Receiving Intensive Insulin Treatment in Sweden. *Eur Endocrinol.* 2018;14(2):80-85.
185. Fonda SJ, Graham C, Munakata J, Powers JM, Price D, Vigersky RA. The Cost-Effectiveness of Real-Time Continuous Glucose Monitoring (RT-CGM) in Type 2 Diabetes. *Journal of diabetes science and technology.* 2016;10(4):898-904.
186. García-Lorenzo B, Rivero-Santana A, Vallejo-Torres L, et al. Cost-effectiveness analysis of real-time continuous monitoring glucose compared to self-monitoring of blood glucose for diabetes mellitus in Spain. *Journal of evaluation in clinical practice.* 2018;24(4):772-781.
187. Hellmund R, Weitgasser R, Blissett D. Cost Calculation for a Flash Glucose Monitoring System for Adults with Type 2 Diabetes Mellitus Using Intensive Insulin - a UK Perspective. *Eur Endocrinol.* 2018;14(2):86-92.
188. Sierra JA, Shah M, Gill MS, et al. Clinical and economic benefits of professional CGM among people with type 2 diabetes in the United States: analysis of claims and lab data. *Journal of medical economics.* 2018;21(3):225-230.