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contains detailed information only on PICO modified after updating the previous version of present guidelines and unpublished elsewhere. For unmodified PICO, please see the already published guidelines[1,2].

RECOMMENDATION # 1: THERAPEUTIC TARGETS.

1.2 HbA1c target in patients treated with drugs not inducing hypoglycemia

Figure 1 – Forest plot for trials comparing the effects of intensive glycemic control (using drugs associated with hypoglycemia) and standard care on MACE.

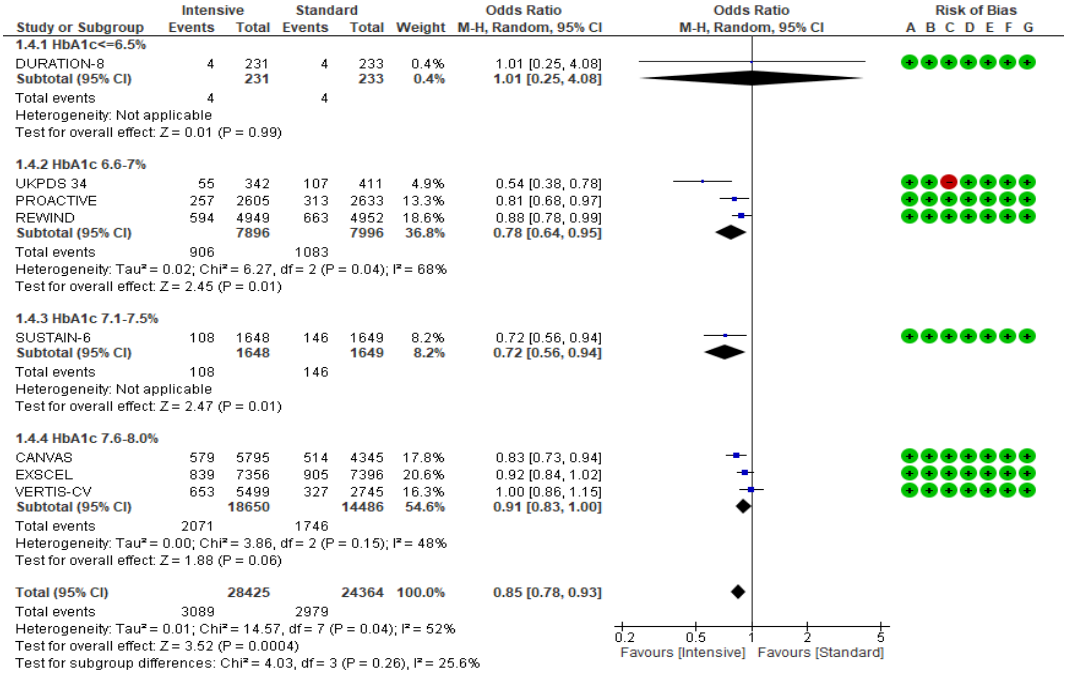
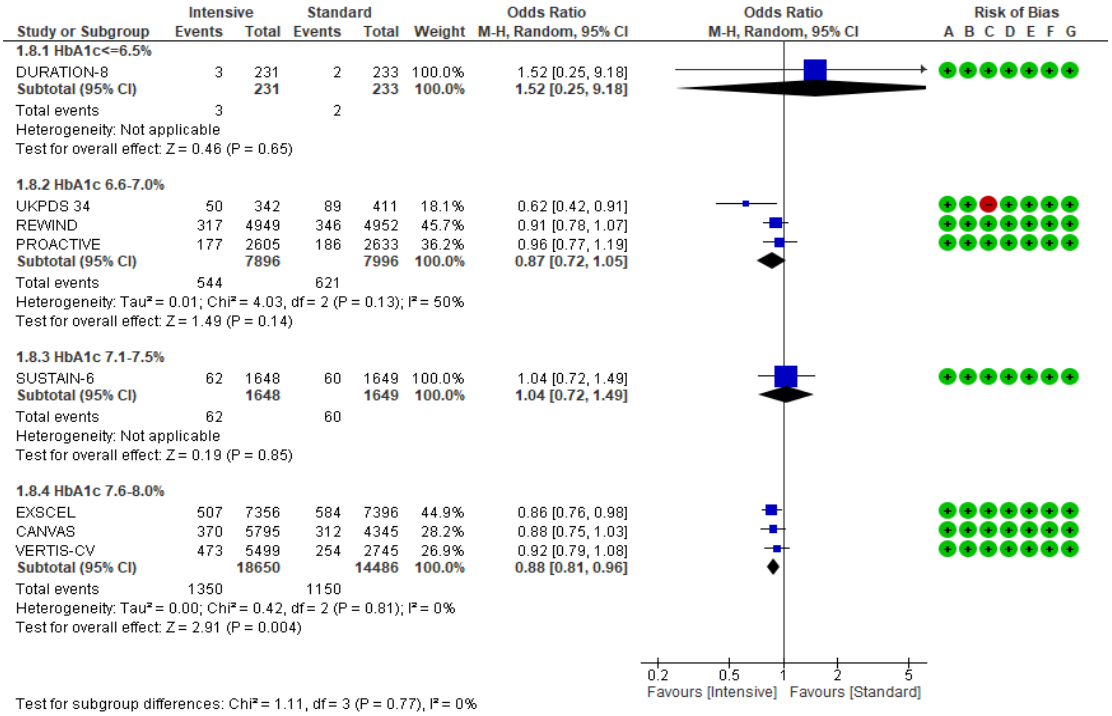
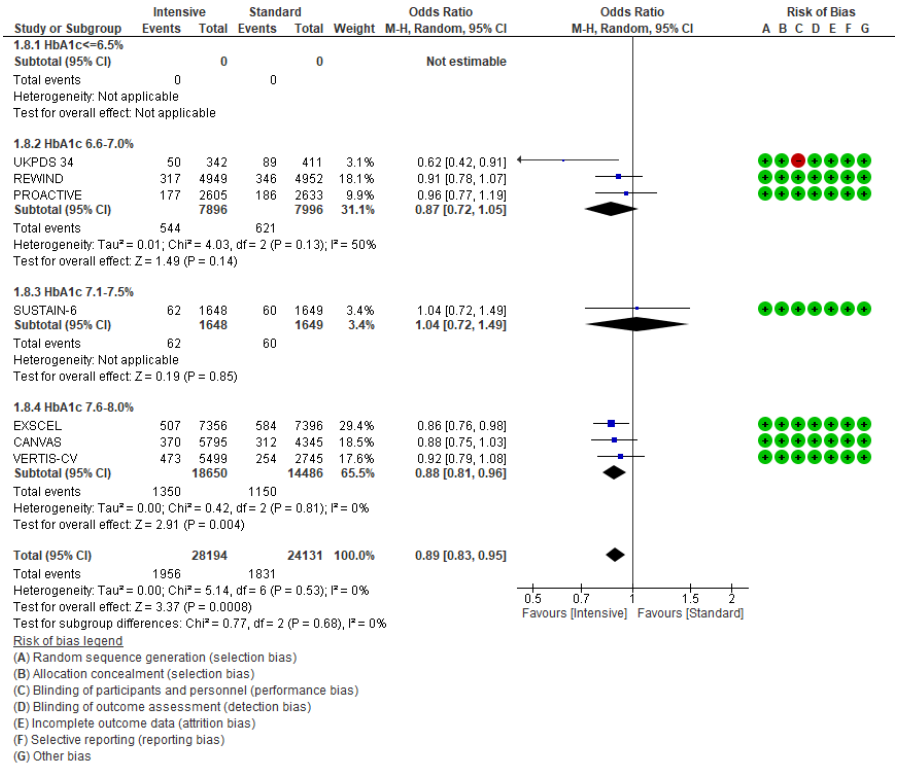


Figure 2 – Forest plot for trials comparing the effects of intensive glycemic control (using drugs associated with hypoglycemia) and standard care on all-cause mortality.



All-cause mortality

Figure 3 – Forest plot for trials comparing the effects of intensive glycemic control (using drugs associated with hypoglycemia) and standard care on all-cause mortality.



GRADE evidence

Table 1

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%)*											
464 (1 RCTs)	not serious	not serious	not serious[c]	very serious	none	⨁⨁◯◯ LOW	4/231 (1.7%)	4/233 (1.7%)	OR 1.01 (0.25;4.08)	-	-
All-cause mortality *For HbA1c ≤48 mmol/mol (6.5%)*											
464 (1 RCTs)	not serious	not serious	not serious[c]	very serious	none	⨁⨁◯◯ LOW	3/231 (1.3%)	2/233 (0,85%)	OR 1.52 (0.25 to 9.18)	-	-

Pharmacoeconomic evaluations

The search for pharmaeconomic studies has been updated without retrieving further studies for any of the questions included. Please see the previous version of the guidelines[1,2].

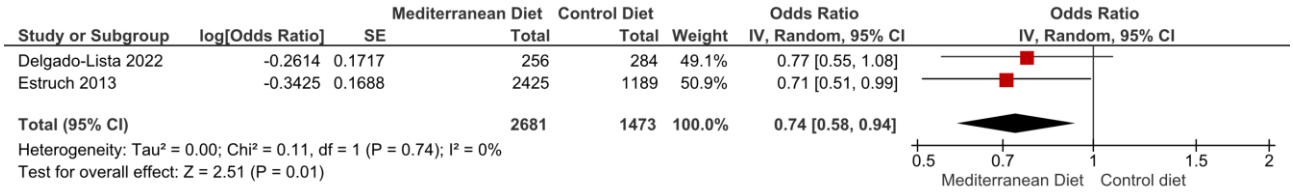
RECOMMENDATION # 2: NUTRITIONAL THERAPY.

Pharmacoeconomic evaluations

The search for pharmaeconomic studies has been updated without retrieving further studies for any of the questions included. Please see the previous version of the guidelines[1,2].

2.2 Low carbohydrate vs balanced (Mediterranean) diet

Figure 4 – Effects of Mediterranean diet in comparison with other standard diets on the risk of incident MACE.

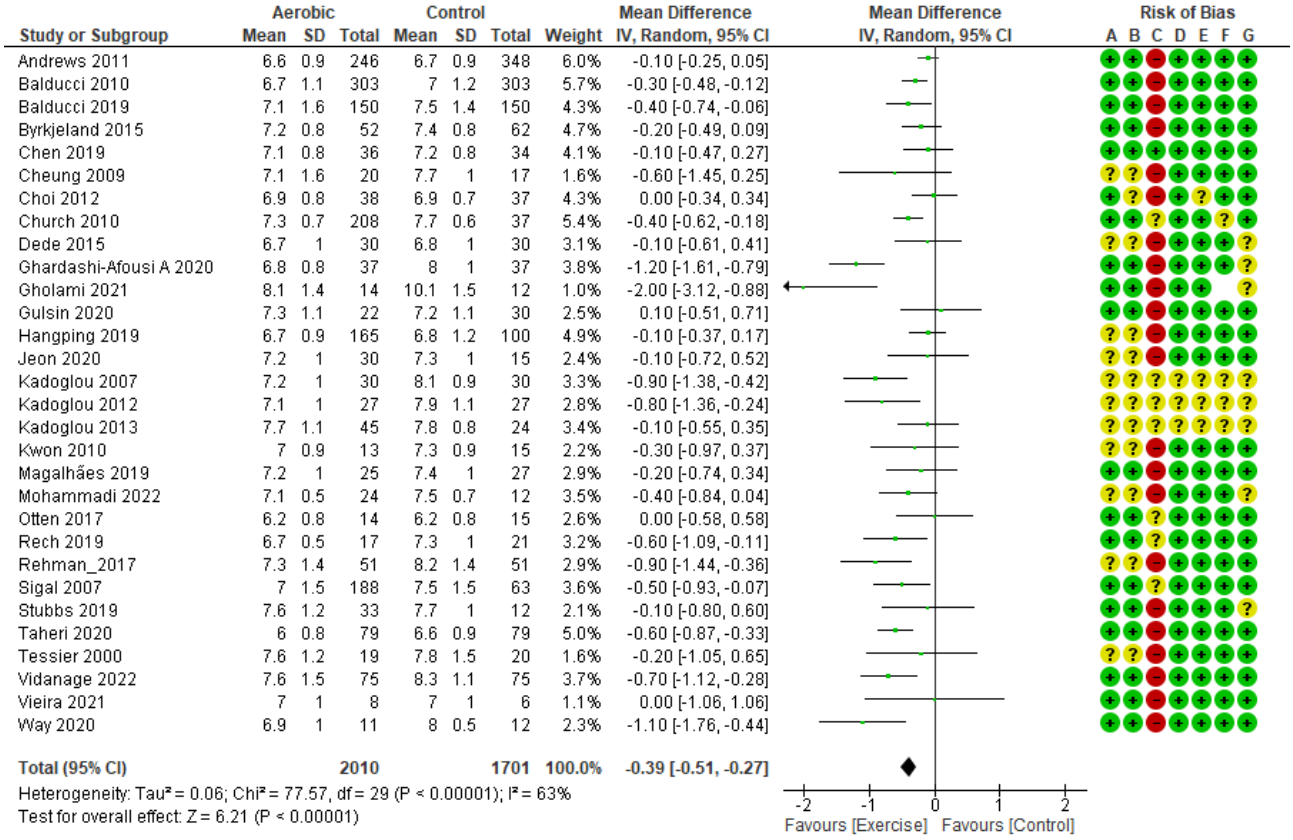


RECOMMENDATION # 3: PHYSICAL EXERCISE.

3.1. Regular physical exercise

HbA1c

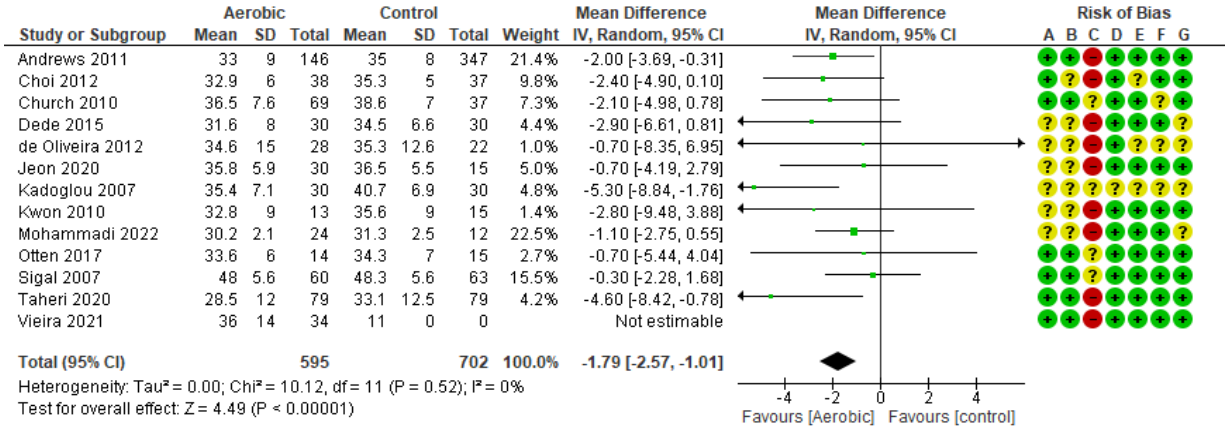
Figure 5 – Forest plot for trials comparing the effects of regular physical exercise and no intervention on HbA1c (%) at endpoint.



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

Body fat

Figure 6 – Forest plot for trials comparing the effects of regular physical exercise and no intervention on body fat (%) at endpoint.



Risk of bias legend
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(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
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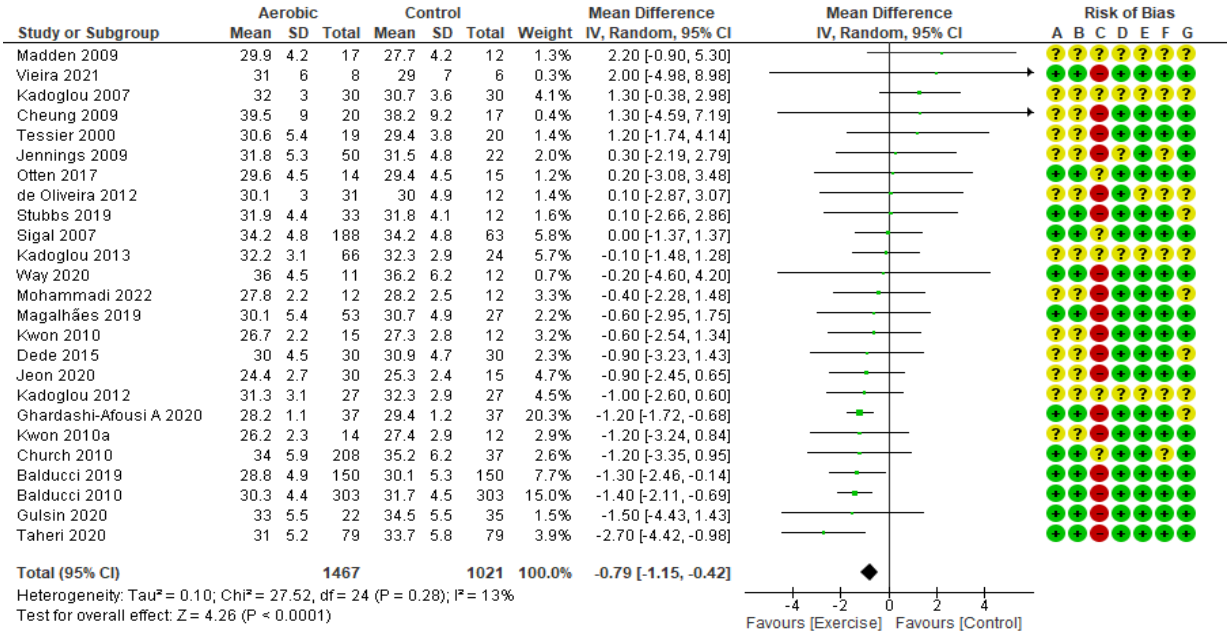
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

BMI

Figure 7 – 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
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(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

GRADE evidence table

Table 2

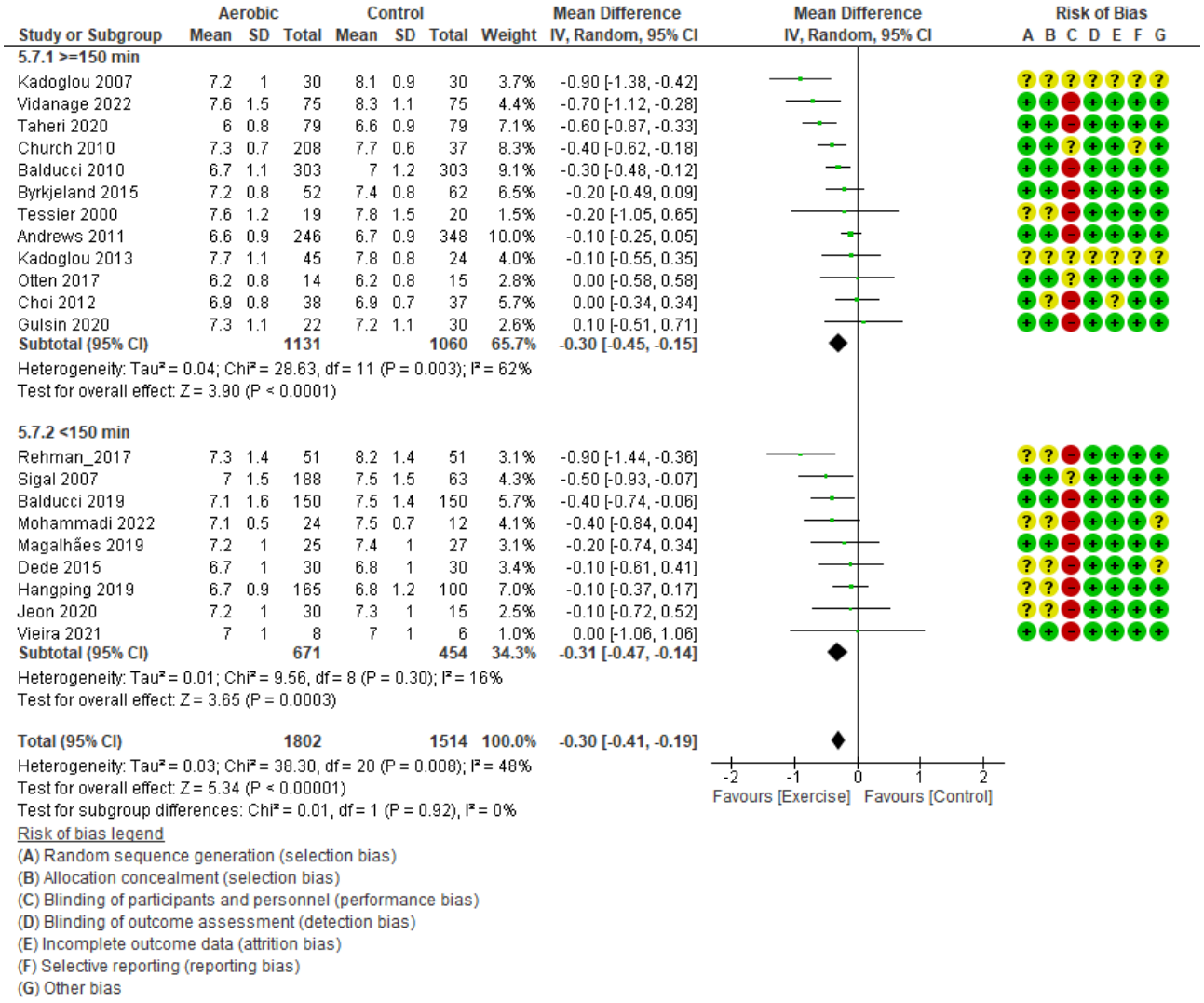
Certainty assessment							Summary of findings		
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Relative effect** (95%, CI)	**Anticipated absolute effects**	
								Control	**Intervention**
HbA1c (%)									
3711 (30 RCT)	serious[a]	not serious	not serious	not serious	Strong association	⨁⨁⨁⨁ HIGH	**-0.39 [-0.51, -.27]**	Mean HbA1c at endpoint: 7.4 %	**MD 0.39 % lower** (from 0.51 lower to 0.27 lower)
Body fat percentage at endpoint (%)									
1297 (13 RCT)	serious[a]	not serious	not serious	not serious	Strong association; possible publication bias	⨁⨁⨁◯ MODERATE	**-1.79 [-2.57, -1.01]**	Mean body fat at endpoint:: 34.7%	**MD 1.79 % lower** (2.57 lower to 1.01 lower)
BMI (Kg/m^2)									
2488 (25 RCT)	serious[a]	not serious	not serious	serious[b]	Strong association; possible publication bias	⨁⨁⨁⨁ HIGH	**-0.79 [-1.15,-0.42]**	Mean BMI at endpoint: 31.0 Kg/m^2	**MD 0.8 Kg/m^2 lower** (da 1.1 a 0.4 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.

3.2. Duration of aerobic exercise

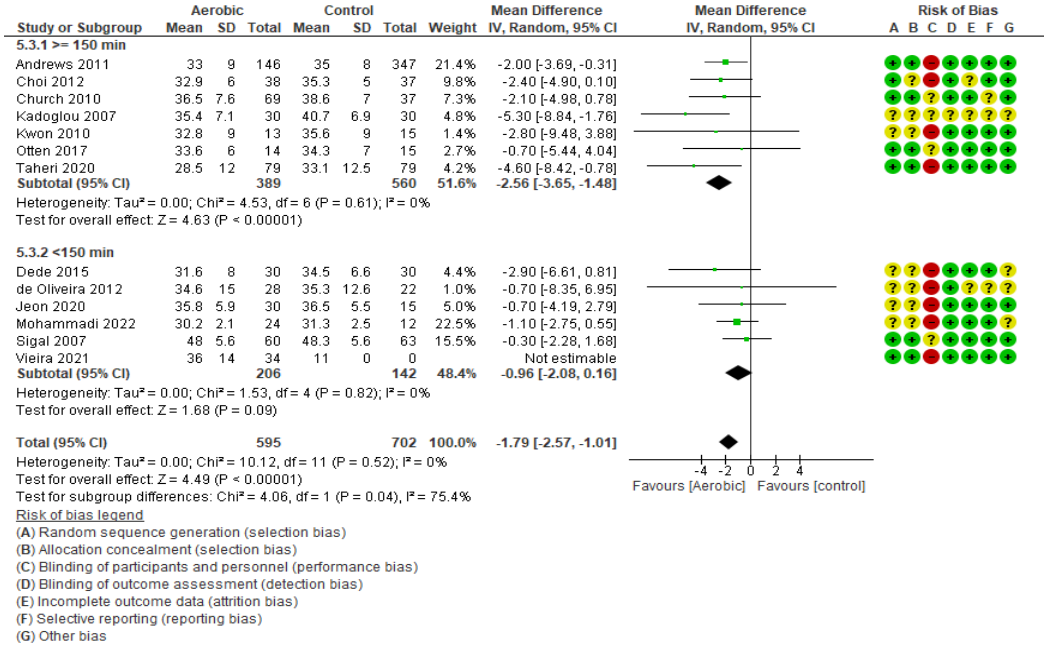
HbA1c

Figure 8 – 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.



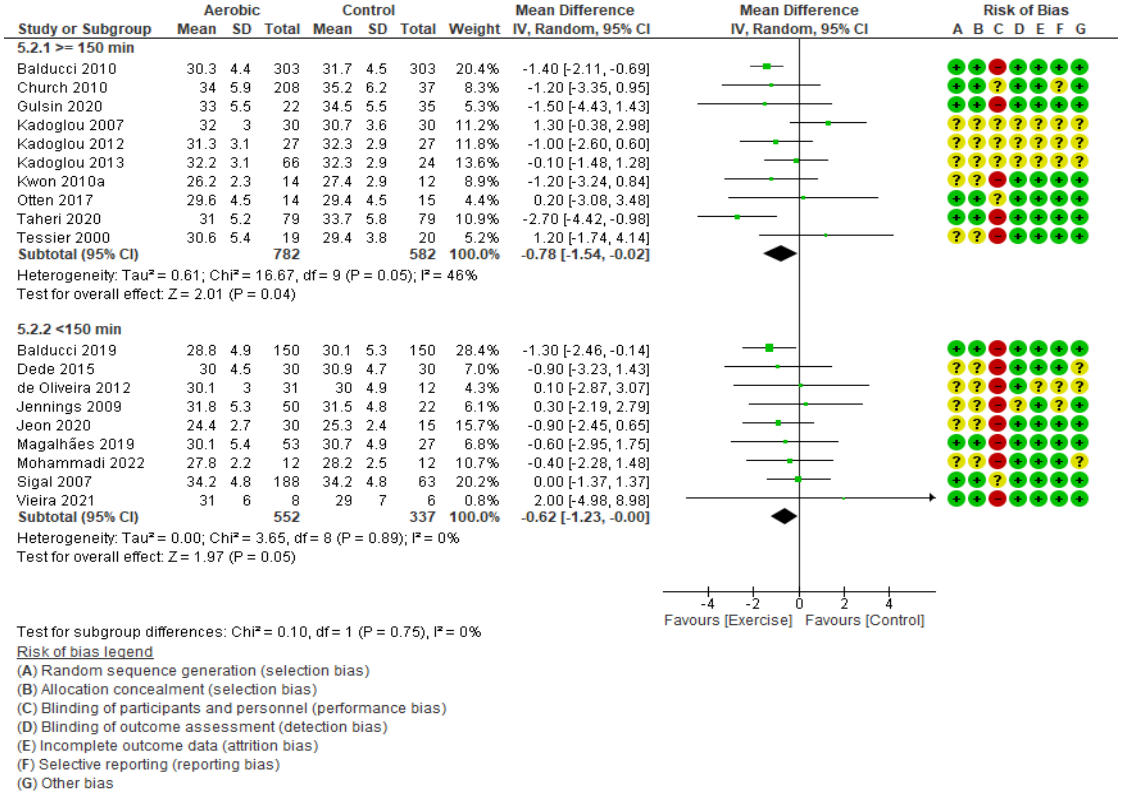
Body fat

Figure 9 – 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.



BMI

Figure 10 –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.



GRADE evidence

Table 3

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									
1125 (9 RCT)	serious[a]	not serious	not serious	serious[b]	publication bias[c]	⨁◯◯◯ VERY LOW	**-0.30** [-0.47;-0.14]	-	MD **0.31 lower** (from 0.47 lower to 0.14 lower)
HbA1c (Kg/m^2) for RCT with physical exercise >150 min/week									
2191 (12 RCT)	serious[a]	not serious	not serious	serious[b]	publication bias[c]	⨁◯◯◯ VERY LOW	**-0.30** [-0.45;-0.15]	-	MD **0.3 lower** (from 0.45 lower to 0.15 lower)
Massa grassa (%) for RCT with physical exercise ≤ 150 min/week									
348 (6 RCT)	serious[a]	not serious	not serious	serious[b]	publication bias[c]	⨁◯◯◯ VERY LOW	-1.20 [-2.70;0.29]	-	MD 1.2 % lower (from 2.7 lower to 0.3 more)
Massa grassa (%) per gli studi dii durata >150 min/ settimana									
921 (6 RCT)	serious[a]	not serious	not serious	serious[b]	publication bias[c]	⨁◯◯◯ VERY LOW	**-2.56** [-3.65; -1.48]	-	**MD 2.56 lower (3.66 lower 7o 1.46 lower)**

Indice di massa corporea (Kg/m^2) per gli studi dii durata ≤150 min/ settimana

1364 (10 RCT)	serious[a]	not serious	not serious	serious[b]	publication bias[c]	⊕◯◯◯ VERY LOW	-0.78 [-1.54;-0.02]	-	**MD 0.78 lower (1.54 lower to 0.02 lower)**

Indice di massa corporea (Kg/m^2) per gli studi dii durata >150 min/settimana

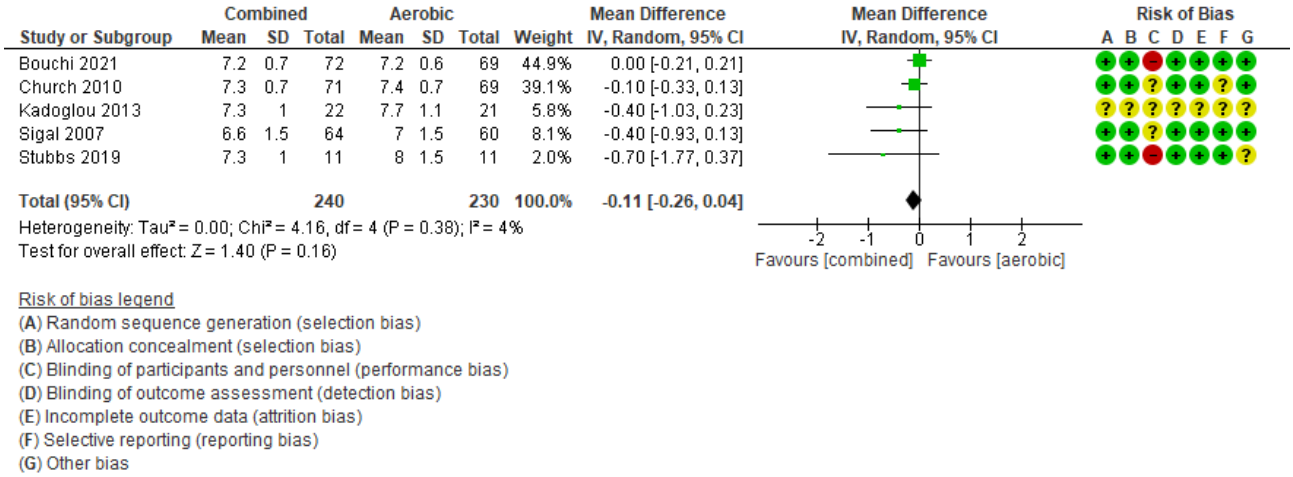
889 (9 RCT)	serious[a]	not serious	not serious	serious[b]	publication bias[c]	⊕◯◯◯ VERY LOW	-0.62 [-1.23;0.0]	-	MD **0.62 lower** (1.23 **lower** to 0)

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 Different modalities of physical exercise

HbA1c

Figure 11 – Forest plot for trials comparing the effects of combined exercise (aerobic and resistance) and aerobic exercise on HbA1c (%) at endpoint.



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

GRADE evidence table

Table 4

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 (%)									
470 (5 RCTs)	serious[a]	not serious	not serious	serious[b]	Possible publication bias[c]	⨁◯◯◯ VERY LOW	**-0.11** [-0.26, 0.04]	Mean HbA1c at the end of the study: 7.2%	**MD 0.11 % lower** (from 0.26 lower to 0.4 higher)

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.

Pharmacoeconomic evaluations

The search for pharmaeconomic studies has been updated without retrieving further studies for any of the questions included. Please see the previous version of the guidelines[1,2].

RECOMMENDATION # 5: PHARMACOLOGICAL THERAPY.

Table 5 – New trials included after updating the previous version of guidelines (20/05/22) for glucometabolic control.

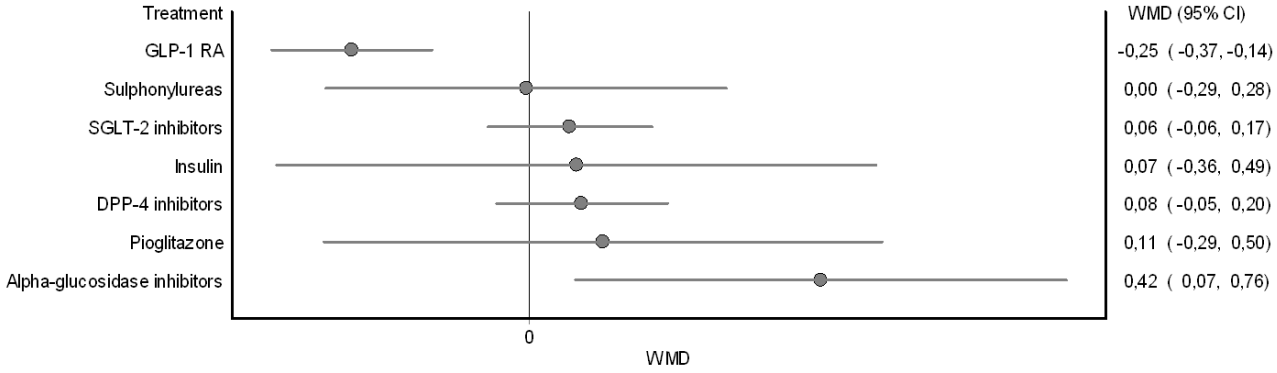
First name (Pub. year)	**Drug 1**	**Drug 2**	**Trial duration** (weeks)	**N. patients** Drug 1	**N. patients** Drug 2
Buse 2020[3]	Sitagliptin	Oral semaglutide	52	98	100
Weinstock 2015[4]	Sitagliptin	Dulaglutide	104	315	304
Pfutzner 2011[5]	Saxagliptin	Metformin	76	335	328
Khaloo 2019[6]	Sitagliptin	Pioglitazone	52	125	125
Handelsman 2017[7]	Omarigliptin	Glimepiride	54	376	375
Terauchi[8] 2017	Sitagliptin	Glimepiride	52	143	127
Jabbour 2020[9]	Dapagliflozin	Exenatide	104	230	227
Lingvay 2019[10]	Canagliflozin	Semaglutide	52	394	394
Rodbard 2019[11]	Empagliflozin	Semaglutide	52	410	411
Ridderstrale 2018[12]	Empagliflozin	Glimepiride	208	765	780
Kaku 2019[13]	Liraglutide	Degludec	52	273	271
Wang 2019[14]	Dulaglutide	Glargine	52	253	250
Zhang 2020[15]	Exenatide	Insulin	52	27	32

HbA1c

Figure 12 – RCTs comparing different glucose-lowering agents versus other active drugs, with a duration ≥ of 52 weeks[16].

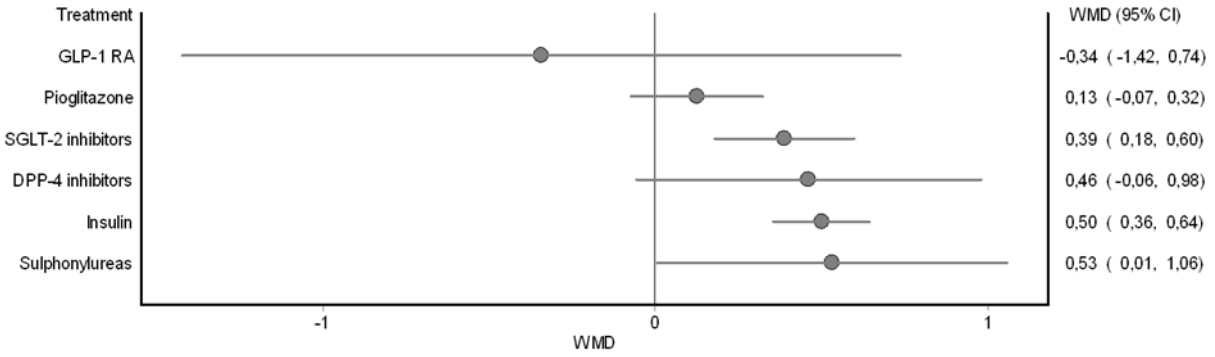
Network metanalysis of different glucose-lowering agents: forest plots of comparisons versus metformin. Panel A: 52 weeks; Panel B: ≥104 weeks. GLP-1 RA: Glucagon-Like Peptide-1 Receptor Agonists; SGLT-2: Sodium-Glucose Transporter-2; Sulfonylureas include also glinides.

A



Consistency H: 1.55

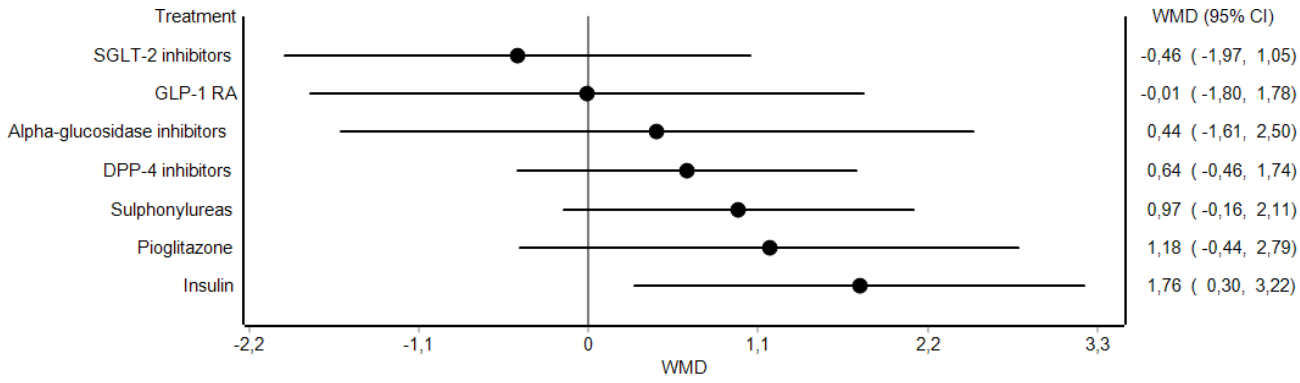
B



Consistency H:1.68

BMI

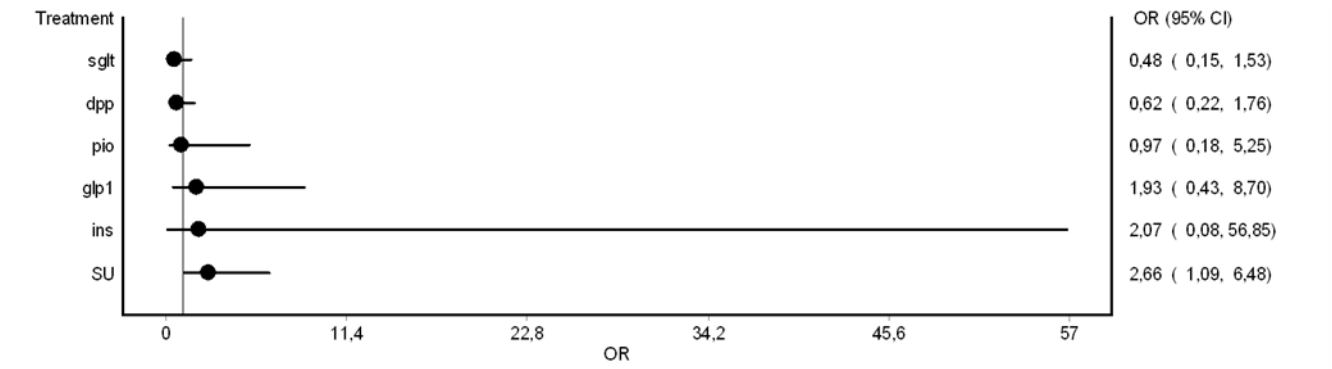
Figure 13 – Network metanalysis of different glucose-lowering agents: forest plots of comparisons versus metformin for BMI at endpoint [16].



Consistency H: 2.056

Severe hypoglycemia

Figure 14 – Network metanalysis of different glucose-lowering agents: forest plots of comparisons versus metformin for severe hypoglycemia[16].



Consistency H: 1.001

5.4. Pharmacoeconomic evaluations

The search for pharmaeconomic studies has been updated without retrieving further studies for any of the questions included. Please see the previous version of the guidelines[1,2].

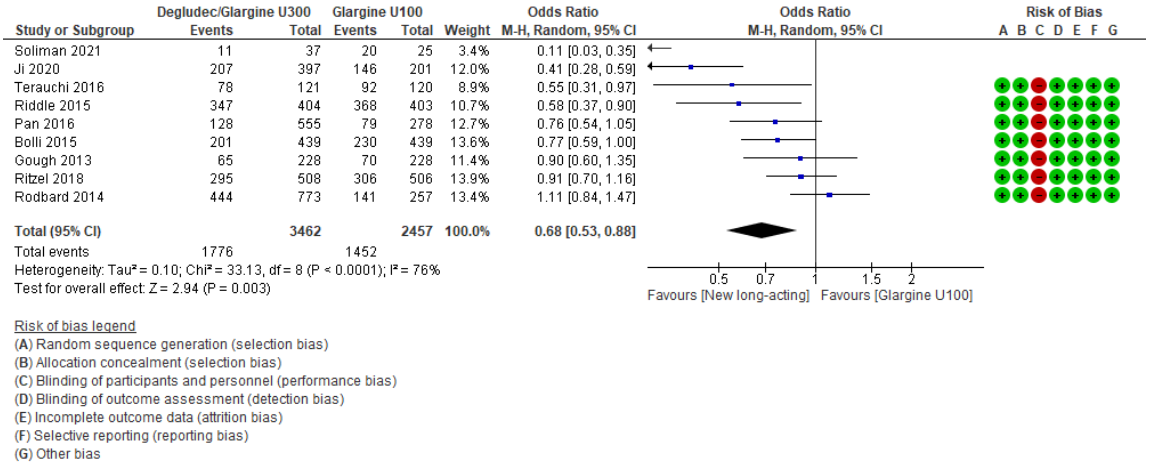
5.6. Long-acting basal analogues

EVIDENCES

This recommendation is based on results of an unpublished meta-analysis updated up to 01/05/2022.

Pubmed
("insulin detemir"[MeSH Terms] OR ("insulin"[All Fields] AND "detemir"[All Fields]) OR "insulin detemir"[All Fields] OR "detemir"[All Fields]) OR ("insulin glargine"[MeSH Terms] OR ("insulin"[All Fields] AND "glargine"[All Fields]) OR "insulin glargine"[All Fields] OR "glargine"[All Fields]) OR ("insulin degludec"[Supplementary Concept] OR "insulin degludec"[All Fields] OR "degludec"[All Fields]) OR aspart[All Fields] OR ("insulin lispro"[MeSH Terms] OR ("insulin"[All Fields] AND "lispro"[All Fields]) OR "insulin lispro"[All Fields] OR "lispro"[All Fields]) OR glulisine[All Fields] AND Randomized Controlled Trial[ptyp] AND (Randomized Controlled Trial[ptyp] AND "humans"[MeSH Terms])
Embase
'detemir'/exp OR detemir OR 'glargine'/exp OR glargine OR 'degludec'/exp OR degludec OR 'aspart'/exp OR aspart OR 'lispro'/exp OR lispro OR 'glulisine'/exp OR glulisine AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) AND 'randomized controlled trial'/de AND 'humans'/de.
Cochrane Library
Trials matching detemir or glargine or degludec or aspart or lispro or glulisine in Title Abstract Keyword - in Trials (Word variations have been searched) [Source: The International Clinical Trial Registry Platform].

Figure 15 – Forest plot for trials comparing the effects of long-acting basal insulin with longer vs. shorter duration on total hypoglycemic risk.



Risk of bias legend
(A) Random sequence generation (selection bias)
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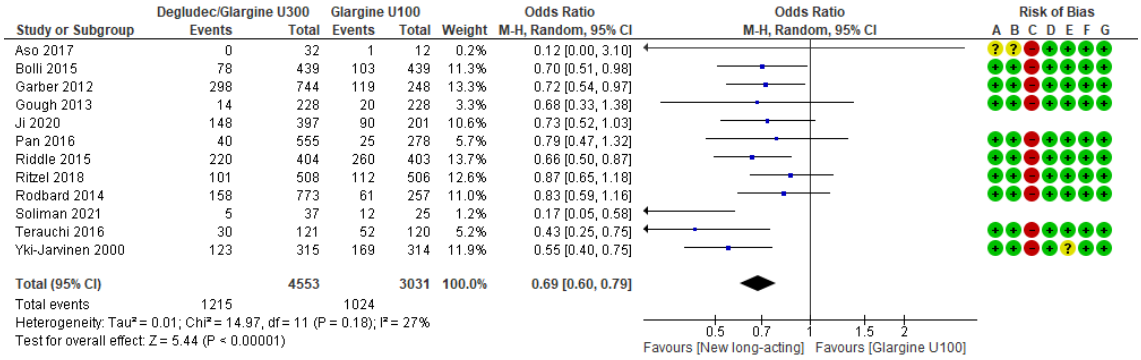
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 16 – Forest plot for trials comparing the effects of long-acting basal insulin with longer vs. shorter duration on nocturnal hypoglycemic risk.



Risk of bias legend
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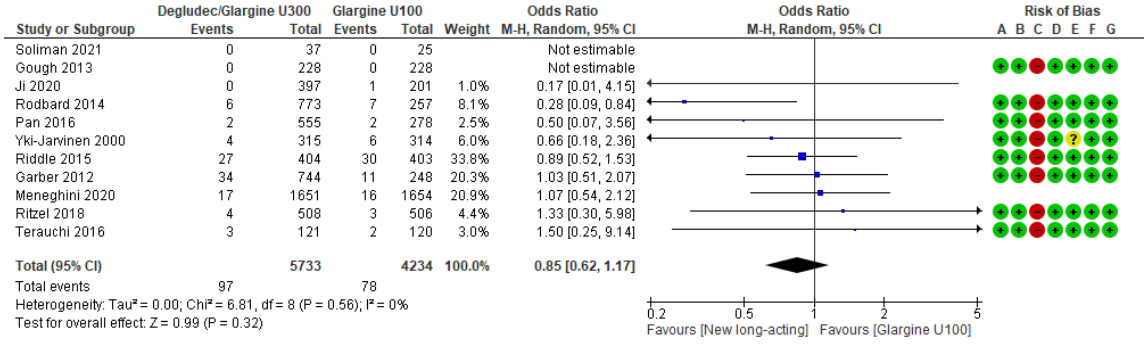
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 17 – Forest plot for trials comparing the effects of long-acting basal insulin with longer vs. shorter duration on severe hypoglycemic risk.



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

Grade of evidence

Table 6

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**
Total hypoglycemia									
5919 (9 RCT)	serious[a]	not serious	not serious	not serious	very stron association	⨁⨁⨁⨁ HIGH	**OR 0.68** (0.53;0.88)	600 per 1000	**88 lower per 1000** (from 139 to 37 lower)
Nocturnal hypoglycemia									
7584 (12 RCT)	serious[a]	not serious	not serious	not serious	very stron association	⨁⨁⨁⨁ HIGH	**OR 0.69** (0.60 a 0.79)	338 per 1.000	**77 lower per 1.000** (from 103 to 51 lower)
Severe hypoglycemia									
9967 (11 RCT)	serious[a]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	**OR 0.85** (0.62 a 1.17)	18 per 1.000	3 lower per 1.000 (from 7 lower to 3 higher)

CI: Confidence interval; **OR:** Odds Ratio; a. Randomization, allocation, and blinding procedures not adequately reported for the majority of included trials;

Pharmacoeconomic evaluations

The search for pharmaeconomic studies has been updated without retrieving further studies for any of the questions included. Please see the previous version of the guidelines[1,2].

REFERENCES

1. Mannucci E, Candido R, Delle Monache L, et al. Italian guidelines for the treatment of type 2 diabetes. Nutrition, metabolism, and cardiovascular diseases : NMCD 2022 (In eng). DOI: 10.1016/j.numecd.2022.01.027.
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3. Buse JB, Bode BW, Mertens A, et al. Long-term efficacy and safety of oral semaglutide and the effect of switching from sitagliptin to oral semaglutide in patients with type 2 diabetes: a 52-week, randomized, open-label extension of the PIONEER 7 trial. BMJ Open Diabetes Res Care 2020;8(2) (In eng). DOI: 10.1136/bmjdrc-2020-001649.
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