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Effect of semaglutide versus other glucagon-like peptide-1 receptor agonists on cardio-metabolic risk factors in patients with type 2 diabetes: A systematic review and meta-analysis of head-to-head, phase 3, randomized controlled trials

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ABSTRACT

Introduction: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as a cornerstone treatment for type 2 diabetes mellitus (T2DM). The aim of the present meta-analysis was to assess whether semaglutide exerts greater effects on glycemia and other cardio-metabolic risk factors compared to other GLP-1RAs.
Methods: PubMed and Cochrane Library databases, along with grey literature sources, were searched form inception to 8th February 2023, in order to retrieve head-to-head, phase 3 randomized controlled trials (RCTs) assessing the effect of semaglutide versus other GLP-1RAs on glycemia and other cardio-metabolic risk factors in T2DM.
Results: We finally pooled data from 5 RCTs in a total of 3760 randomized participants. Semaglutide compared to other GLP-1RAs provided a significantly greater reduction in HbA1c levels by 0.44 %, in fasting plasma glucose by 0.48 mmol/L, in body weight by 2.53 kg and in body mass index by 0.91 kg/m^2. Subjects receiving semaglutide experienced significantly greater odds for achieving target and optimal HbA1c, along with significantly greater odds for weight loss >5 % and 10 %. However, subjects randomized to semaglutide also experienced significantly greater odds for gastrointestinal adverse events and treatment discontinuation.
Conclusion: Semaglutide is more effective than rest GLP-1RAs, in terms of improvement in glycemia and other cardio-metabolic risk factors, among individuals with T2DM.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a global pandemic of the 21st century, with the projections regarding its prevalence being pessimistic, due to the population's ageing in high-income countries and the population's growth in low- and middle-income countries.[1] Interconnection of T2DM with co-morbidities like atherosclerotic cardiovascular disease, chronic kidney disease, heart failure, obesity and non-alcoholic fatty liver disease, is well established, and therefore, we have moved towards a personalized treatment approach for individuals with T2DM.[2] However, according to recent evidence generated by hallmark cardiovascular or renal outcome randomized controlled trials (RCTs), treatment algorithms of T2DM have incorporated newer antidiabetic drug classes, namely sodium-glucose cotransporter-2 (SGLT-2) inhibitors and

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glucagon-like peptide-1 receptor agonists (GLP-1RAs), which have been prioritized for broader cardiorenal protection of individuals with T2DM, either with established or at high risk for cardio-renal disease.[3,4] Of course, it has to be admitted that some, but not all GLP-1RAs, have been shown to exert significant cardiovascular benefits for subjects with T2DM (mainly liraglutide, semaglutide, albiglutide, dulaglutide and efpeglenatide, but not exenatide and lixisenatide).[5,6]

According to a recent meta-analysis of the hallmark, cardiovascular outcome RCTs with GLP-1RAs in T2DM, cardiovascular benefits of this drug class are mainly attributed to the achieved reduction in glycated hemoglobin (HbA1c) levels, while body weight reduction is not associated with any surrogate, cardiovascular or renal outcome.[7] A former meta-analysis has demonstrated that semaglutide, a potent GLP-1RA that can be administered either subcutaneously or orally, provides a significant, robust reduction in HbA1c and improvement in other cardio-metabolic risk factors among subjects with T2DM.[8] Indeed, the former meta-analysis provided preliminary results supportive of a greater anti-hyperglycemic effect of semaglutide versus other GLP-1RAs, such as dulaglutide, exenatide and liraglutide.[8] Of course, besides improvement in glycemia and body weight, cardiovascular benefits observed with this class can be partially explained by their demonstrated anti-atherosclerotic effects, involving beneficial impact on low-grade inflammation, oxidative stress and endothelial dysfunction, among others.[9–11]

Therefore, we aimed to update those results, by assessing the effect of semaglutide directly compared to other GLP-1RAs in head-to-head RCTs on glycemia and other cardio-metabolic risk factors, along with safety endpoints, among individuals with T2DM, aiming at clarifying whether semaglutide should be preferred over other currently, commercially available GLP-1RAs.

2. Methods

The present systematic review and meta-analysis was conducted according to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[12] Manuscript has been registered at PROSPERO database (CRD42023397912).

2.1. Databases

PubMed and Cochrane Library databases were searched form inception to 8th February 2023, in order to retrieve eligible head-to-head, phase 3 RCTs assessing the effect of semaglutide versus other GLP-1RAs (regardless of dosing regimen) on glycemia and other cardio-metabolic risk factors in subjects with T2DM. In addition, references of potentially eligible trials and grey literature sources were searched for identification of eligible trials.

2.2. Inclusion criteria

Inclusion criteria were a. head-to-head, phase 3 RCTs, b. enrollment of adult individuals aged ≥18 years, c. randomly assigned either to semaglutide or other GLP-1RA, d. assessment of at least one cardio-metabolic parameter of interest and e. duration of intervention of at least 12 weeks. We excluded a. observational studies, b. case series, c. RCTs enrolling children or adolescents. In addition, unpublished RCTs and phase 2 dose-finding RCTs were excluded from our systematic review.

2.3. Search strategy

We applied the following search strategy in both databases: (((semaglutide) OR (wegovy)) OR (ozempic)) OR (rybelsus)) AND (type 2 diabetes mellitus [MeSH Terms]). We used both MeSH terms and free-text words, combined with the use of Boolean operators AND and OR. We did not imply any filter regarding study setting, sample size, publication language, or publication date. In addition, we did not impose any filter regarding the route of administration of semaglutide.

2.4. Outcomes of interest

After de-duplication and assessment of potentially eligible studies for inclusion at the title and abstract level, two independent reviewers (D.P. and Dj.P.) extracted data of interest from the eligible reports. We set as the primary efficacy outcome the change in HbA1c (%) with semaglutide versus other GLP-1RAs. We set as secondary efficacy outcomes the corresponding changes in the following cardio-metabolic indices: body weight (in kg), BMI (in kg/m^2), fasting plasma glucose (FPG, in mmol/L or mg/dL), office systolic blood pressure (SBP, in mm Hg), office diastolic blood pressure (DBP, in mm Hg), office pulse rate (PR, in beats/min), total cholesterol levels (TC, in mmol/L), low-density lipoprotein cholesterol levels (LDL-C, in mmol/L), high-density lipoprotein cholesterol levels (HDL-C, in mmol/L) and triglycerides levels (TRG, in mmol/L). We also assessed the effect of semaglutide versus other GLP-1RAs on the odds for achieving HbA1c reduction below 7 % and 6.5 %, and body weight loss >5 % and 10 %, compared to baseline. We also planned to conduct a subgroup analysis for the main efficacy endpoints according to the type of GLP-1RA compared to semaglutide (liraglutide, dulaglutide, albiglutide, exenatide, lixisenatide, etc.). Major safety endpoints were also assessed.

2.5. Measurement of outcome

concerning continuous variables, we calculated mean differences (MD) for prespecified outcomes of interest, with 95 % confidence interval (CI), after implementation of the Mantel-Haenszel (M-H) random effects formula, while, regarding dichotomous variables, we calculated odds ratio (OR) with 95 % CI, after implementation of the M-H random effects formula Statistical heterogeneity among studies was assessed by using I^2 statistics. All analyses were performed at the 0.05 significance level, while they were undertaken with RevMan 5.4.1 software.

2.6. Risk of bias assessment

D.P. and Dj.P. evaluated the quality of the included RCTs, by using the RoB 2.0 tool for the primary efficacy outcome.[13] RoB 2.0 tool assesses bias across randomization process, deviation from the intended intervention, missing outcome data, measurement of the outcome and selection of the reported results. The risk-of-bias judgments for each domain are “low risk of bias,” “some concern,” or “high risk of bias.”. Possible disagreements between reviewers were solved by discussion, consensus, or arbitration by a senior reviewer.

2.7. Publication bias assessment

We assessed publication bias by visual inspection of the corresponding funnel plot for the primary efficacy outcome (change in HbA1c).

3. Results

Our search strategy initially yielded 1161 results. Searching grey literature sources did not yield any additional RCTs results, which could be included in the present quantitative synthesis. After de-duplication and screening at title and abstract level, we assessed 86 reports as potentially eligible for inclusion in the present systematic review and meta-analysis. Finally, we included 5 RCTs in our synthesis, in a total of 3760 randomized individuals.[14–18] Study selection process is depicted in the corresponding flow diagram (Fig. 1). A detailed summary of participants’ baseline characteristics is provided in Table 1. As demonstrated, all RCTs enrolled subjects with a mean age ranging from 56 to 60 years, with a mean T2DM duration ranging from 7 to 10 years, mainly

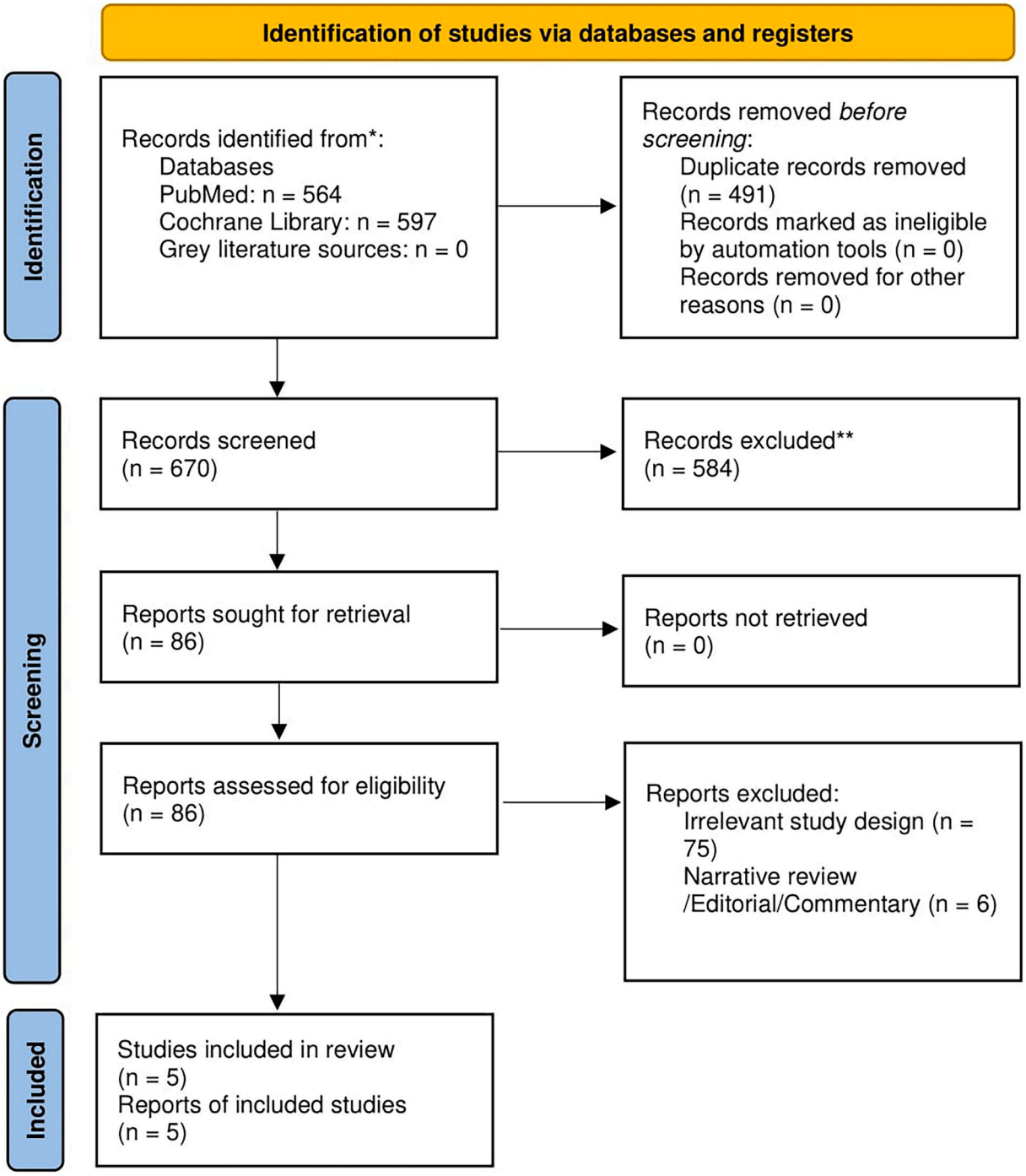

Fig. 1. Flow diagram depicting the study selection process.

men and mostly overweight or obese. Enrolled subjects had inadequately controlled T2DM, with a mean HbA1c >8 %, with all of them treated with metformin at baseline, while none of them treated with insulin prior to inclusion in each RCT. Of note, in 3 out of 5 RCTs, subjects were treated with SGLT-2 inhibitors at baseline, with utilization rates ranging from 17 % to 26 %.

One RCT compared once-weekly subcutaneous semaglutide with once-weekly subcutaneous exenatide for extended release.[14] Two RCTs compared semaglutide with once-daily liraglutide.[15,16] Capehorn and colleagues utilized once-weekly subcutaneous semaglutide, while Pratley and colleagues utilized once-daily oral semaglutide. Finally, two RCTs compared semaglutide with once-weekly subcutaneous dulaglutide.[17,18] Pratley and colleagues utilized once-weekly subcutaneous semaglutide, while Yabe and colleagues utilized once-daily oral semaglutide.

3.1. Glycemia

Concerning glycemia, semaglutide was found to be superior to other GLP-1RAs, providing a significantly greater reduction in HbA1c levels by 0.44 % (MD = −0.44, 95 % CI; −0.63 to −0.25, I^2 = 63 %, p < 0.00001), as shown in Fig. 2. Of note, no subgroup difference was documented ($p_{subgroup}$ = 0.10). In addition, semaglutide use was associated with a significantly greater reduction in FPG by 0.48 mmol/L (MD = −0.48, 95 % CI; −0.80 to −0.15, I^2 = 82 %, p = 0.004), as shown in Fig. 3. For this comparison, semaglutide was not superior to

Table 1
Participants' baseline characteristics across the eligible RCTs, included in the present meta-analysis.

	Ahmann et al[14]	Capehorn et al[15]	Pratley et al[18]	Pratley et al[16]	Yabe et al[17]
Study design	Parallel group	Parallel group	Parallel group	Parallel group	Parallel group
Number of randomized subjects (n)	813	577	1201	711	458
Treatment duration (weeks)	56	30	40	26	52
Route of semaglutide administration	Subcutaneous	Subcutaneous	Subcutaneous	Oral	Oral
Dose of semaglutide	1.0 mg	1.0 mg	0.5 mg & 1.0 mg	14 mg	3 mg, 7 mg & 14 mg
Comparator	Exenatide 2 mg	Liraglutide 1.2 mg	Dulaglutide 0.75 mg & 1.5 mg	Liraglutide 1.8 mg	Dulaglutide 0.75 mg
Age (years)	Semaglutide: 56.4 (20–82)	Semaglutide: 60.1 (10.5)	Semaglutide 0.5 mg: 56 (10.9) Semaglutide 1.0 mg: 55 (10.6)	Semaglutide: 56 (10)	Semaglutide 3 mg: 59 (10) Semaglutide 7 mg: 58 (11) Semaglutide 14 mg: 57 (10)
	Exenatide: 56.7 (21–83)	Liraglutide: 58.9 (10.0)	Dulaglutide 0.75 mg: 55 (10.4) Dulaglutide 1.5 mg: 56 (10.6)	Liraglutide: 56 (10)	Dulaglutide: 61 (9)
Male to female ratio	Semaglutide: 219/185	Semaglutide: 160/130	Semaglutide: 331/270	Semaglutide: 147/138	Semaglutide: 290/103
	Exenatide: 228/177	Liraglutide: 167/120	Dulaglutide: 331/267	Liraglutide: 149/135	Dulaglutide: 51/14
Type 2 diabetes duration (years)	Semaglutide: 9.0 (0.4–37.1)	Semaglutide: 9.6 (6.1)	Semaglutide 0.5 mg: 7.7 (5.9) Semaglutide 1.0 mg: 7.3 (5.7)	Semaglutide: 7.8 (5.7)	Semaglutide 3 mg: 9.4 (6.3) Semaglutide 7 mg: 9.3 (6.3) Semaglutide 14 mg: 9.1 (6.4)
	Exenatide: 9.4 (0.3–54.0)	Liraglutide: 8.9 (5.7)	Dulaglutide 0.75 mg: 7.0 (5.5) Dulaglutide 1.50 mg: 7.6 (5.6)	Liraglutide: 7.3 (5.3)	Dulaglutide: 9.9 (6.3)
Body mass index (kg/m^2)	Semaglutide: 34.0 (21.0–72.8)	Semaglutide: 33.7 (6.6)	Semaglutide 0.5 mg: 33.7 (7.1) Semaglutide 1.0 mg: 33.6 (6.5)	Semaglutide: 32.5 (5.9)	Semaglutide 3 mg: 25.8 (4.5) Semaglutide 7 mg: 26.8 (5.0) Semaglutide 14 mg: 26.3 (5.2)
	Exenatide: 33.6 (21.2–55.8)	Liraglutide: 33.7 (7.0)	Dulaglutide 0.75 mg: 33.6 (6.9) Dulaglutide 1.50 mg: 33.1 (6.6)	Liraglutide: 33.4 (6.7)	Dulaglutide: 26.0 (4.0)
HbA1c (%)	Semaglutide: 8.4 (6.7–11.1)	Semaglutide: 8.2 (0.9)	Semaglutide 0.5 mg: 8.3 (0.9) Semaglutide 1.0 mg: 8.2 (0.9)	Semaglutide: 8.0 (0.7)	Semaglutide 3 mg: 8.2 (0.9) Semaglutide 7 mg: 8.3 (0.9) Semaglutide 14 mg: 8.4 (1.0)
	Exenatide: 8.3 (6.5–11.2)	Liraglutide: 8.3 (1.0)	Dulaglutide 0.75 mg: 8.2 (0.9) Dulaglutide 1.50 mg: 8.2 (0.9)	Liraglutide: 8.0 (0.7)	Dulaglutide: 8.4 (0.9)
Biguanides, n (%)	Semaglutide: 391 (96.8)	Semaglutide: 279 (96.2)	All included subjects (100 % in both arms) were on metformin treatment	All included subjects (100 % in both arms) were on metformin treatment	All included subjects (100 % in all arms) were on metformin treatment
	Exenatide: 390 (96.3)	Liraglutide: 268 (93.4)			
Sulfonylureas, n (%)	Semaglutide: 181 (44.8)	Semaglutide: 136 (46.9)	0 (0)	0 (0)	Semaglutide: 126 (32)
	Exenatide: 208 (51.4)	Liraglutide: 134 (46.7)			Dulaglutide: 21 (32)
Thiazolidinediones, n (%)	Semaglutide: 13 (3.2)	Semaglutide: 0 (0)	0 (0)	0 (0)	Semaglutide: 68 (17)
	Exenatide: 6 (1.5)	Liraglutide: 0 (0)			Dulaglutide: 11 (17)
Insulin, n (%)	Semaglutide: 0 (0)	Semaglutide: 0 (0)	0 (0)	0 (0)	0 (0)
	Exenatide: 1 (0.2)	Liraglutide: 0 (0)			
SGLT-2 inhibitors, n (%)	Semaglutide: 0 (0)	Semaglutide: 73 (25.2)	0 (0)	Semaglutide: 74 (26)	Semaglutide: 67 (17)
	Exenatide: 0 (0)	Liraglutide: 69 (24.0)		Liraglutide: 73 (26)	Dulaglutide: 11 (17)
Clinicaltrials.gov registration number	NCT01885208	NCT03191396	NCT02648204	NCT02863419	NCT03015220

Data is presented as mean (standard deviation) or n (relative frequency), unless otherwise stated.

dulaglutide; however, semaglutide produced a significantly greater reduction in FPG compared to either exenatide or liraglutide. Test for subgroup differences remained marginally non-significant ($p = 0.05$).

In addition, we showed that subjects treated with semaglutide compared to other GLP-1RAs had significantly greater odds for achieving the target of HbA1c < 7 % (OR = 2.10, 95 % CI; 1.40 to 3.14, $I^2 = 87$ %, $p = 0.003$), as depicted in Fig. 4, and for achieving a HbA1c < 6.5 % (OR = 2.16, 95 % CI; 1.52 to 3.07, $I^2 = 83$ %, $p < 0.0001$), as shown in Fig. 5. For both comparisons, semaglutide was superior to both dulaglutide and exenatide; however, subjects treated either with semaglutide or liraglutide had no significant difference in the odds for achieving a target or an intensive reduction in HbA1c levels.

3.2. Body weight

Semaglutide was shown to provide a significantly greater reduction in body weight compared to other GLP-1RAs among subjects with T2DM, equal to 2.53 kg (MD = −2.53, 95 % CI; −3.31 to −1.75, $I^2 = 86$ %, $p < 0.00001$), as depicted in Fig. 6. In addition, we documented that semaglutide compared to other GLP-1RAs resulted in a significantly greater reduction in BMI by 0.91 kg/m^2 (MD = −0.91, 95 % CI; −1.18 to −0.63, $I^2 = 85$ %, $p < 0.0001$), as shown in Fig. 7. For both comparisons, a significant subgroup difference was documented. Of note, individuals treated with semaglutide versus other GLP-1RAs had significantly greater odds for achieving a body weight loss >5 % (OR = 3.70, 95 % CI; 2.71 to 5.06, $I^2 = 73$ %, $p < 0.00001$) and >10 % (OR = 4.39, 95 % CI; 3.27 to 5.90, $I^2 = 20$ %, $p < 0.00001$), compared to baseline, as shown in Figs. 8 and 9, respectively.

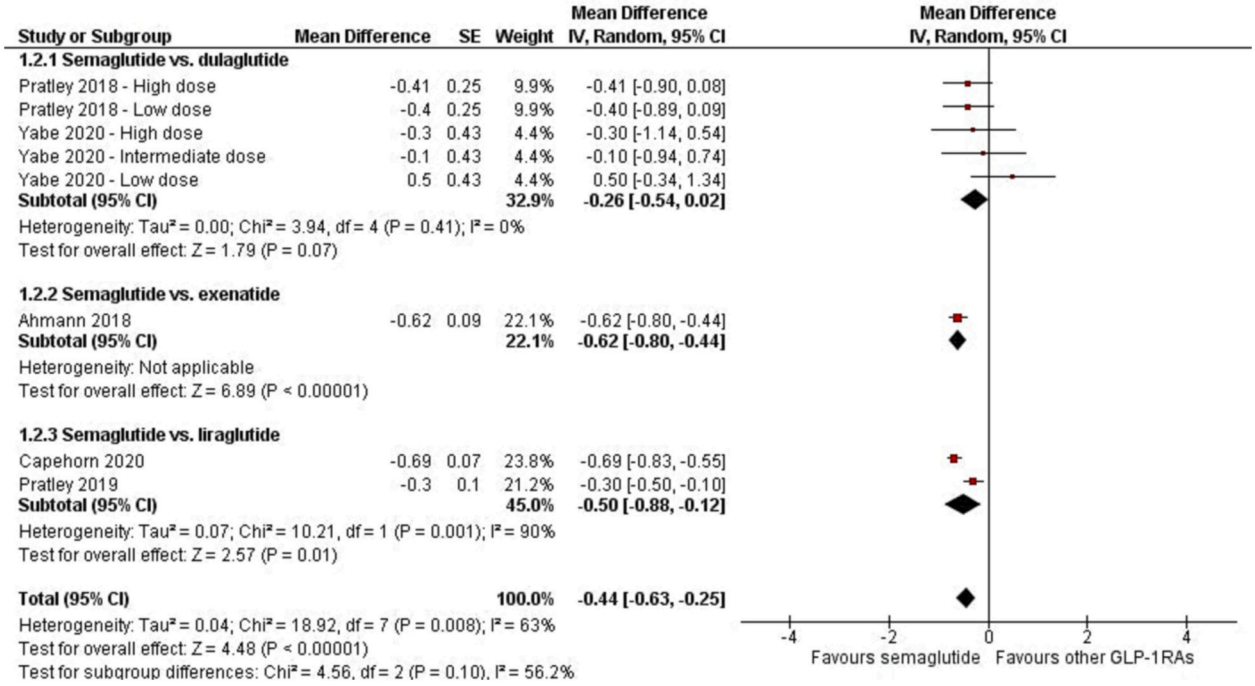

Fig. 2. Effect of semaglutide versus other GLP-1RAs on HbA1c levels.

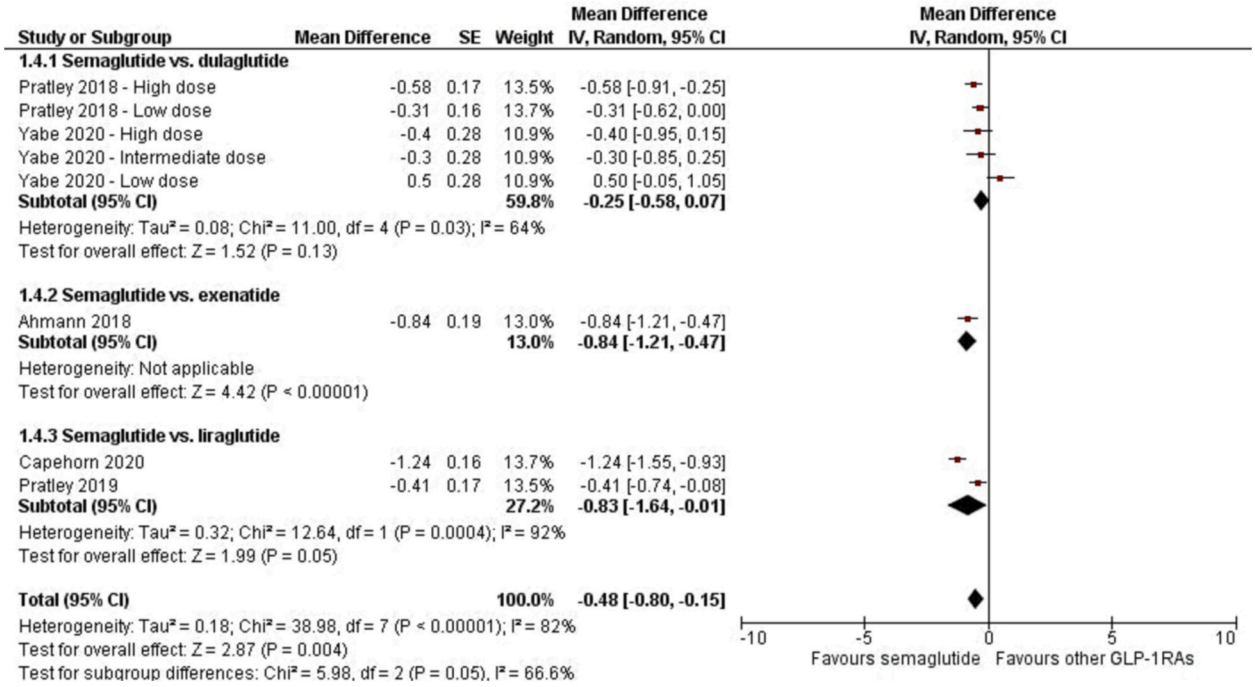

Fig. 3. Effect of semaglutide versus other GLP-1RAs on fasting plasma glucose levels.

3.3. Waist circumference

We also found that semaglutide was superior to other GLP-1RAs concerning waist circumference reduction, producing a significant decrease by 2.04 cm among individuals with T2DM (MD = −2.04, 95 % CI; −2.49 to −1.60, I^2 = 40 %, p < 0.00001), as shown in Fig. 10.

3.4. Blood pressure & heart rate

Subjects treated with semaglutide versus other GLP-1RAs experienced a significantly greater reduction in office SBP by 1.20 mm Hg (MD = −1.20, 95 % CI; −2.05 to −0.34, I^2 = 0 %, p = 0.006), as shown in Supplementary Fig. 1, and in office DBP by 0.67 mm Hg (MD = −0.67, 95 % CI; −1.18 to −0.16, I^2 = 0 %, p = 0.01), as shown in Supplementary Fig. 2. Regarding office SBP, the results were primarily driven by the comparison between semaglutide and exenatide, while, regarding office DBP, the results were mainly driven by the comparison between semaglutide and dulaglutide. However, no significant subgroup difference for none of the above-mentioned comparisons was shown.

Regarding office HR, no significant difference between semaglutide

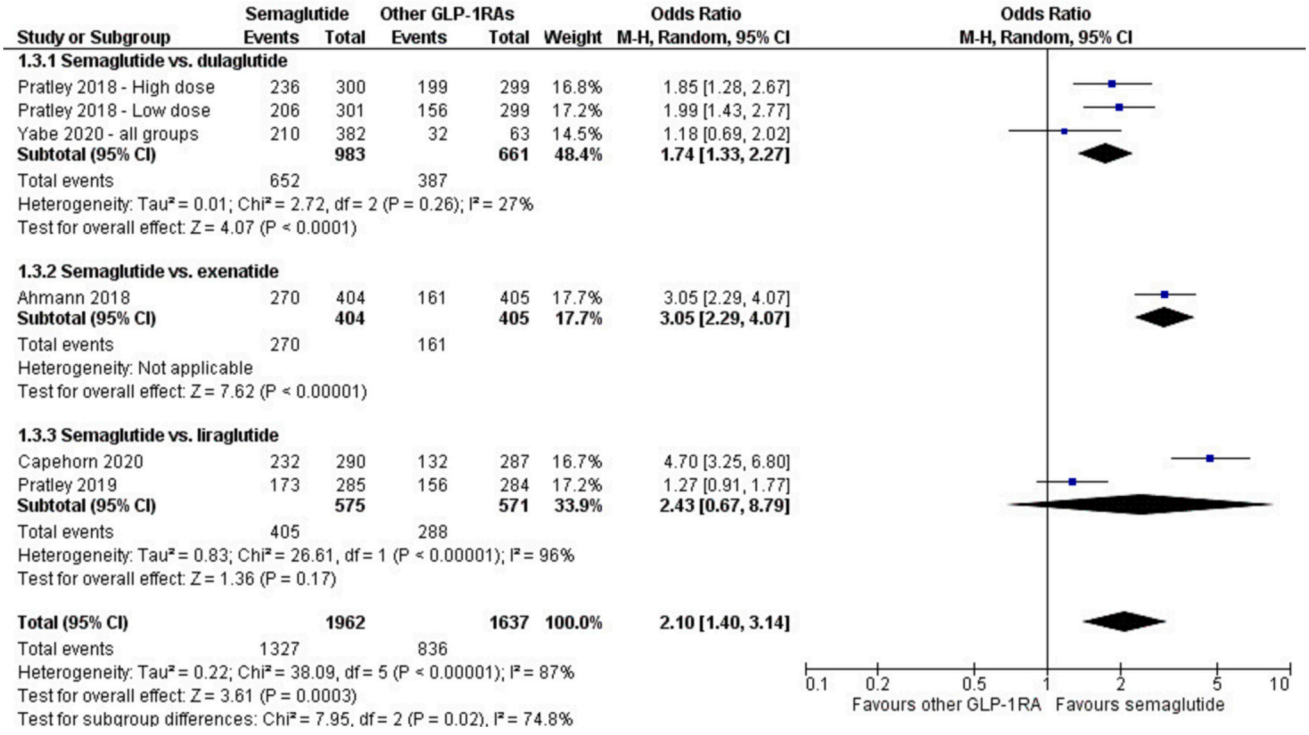

Fig. 4. Effect of semaglutide versus other GLP-1RAs on the odds for achieving HbA1c levels lower than 7 %.

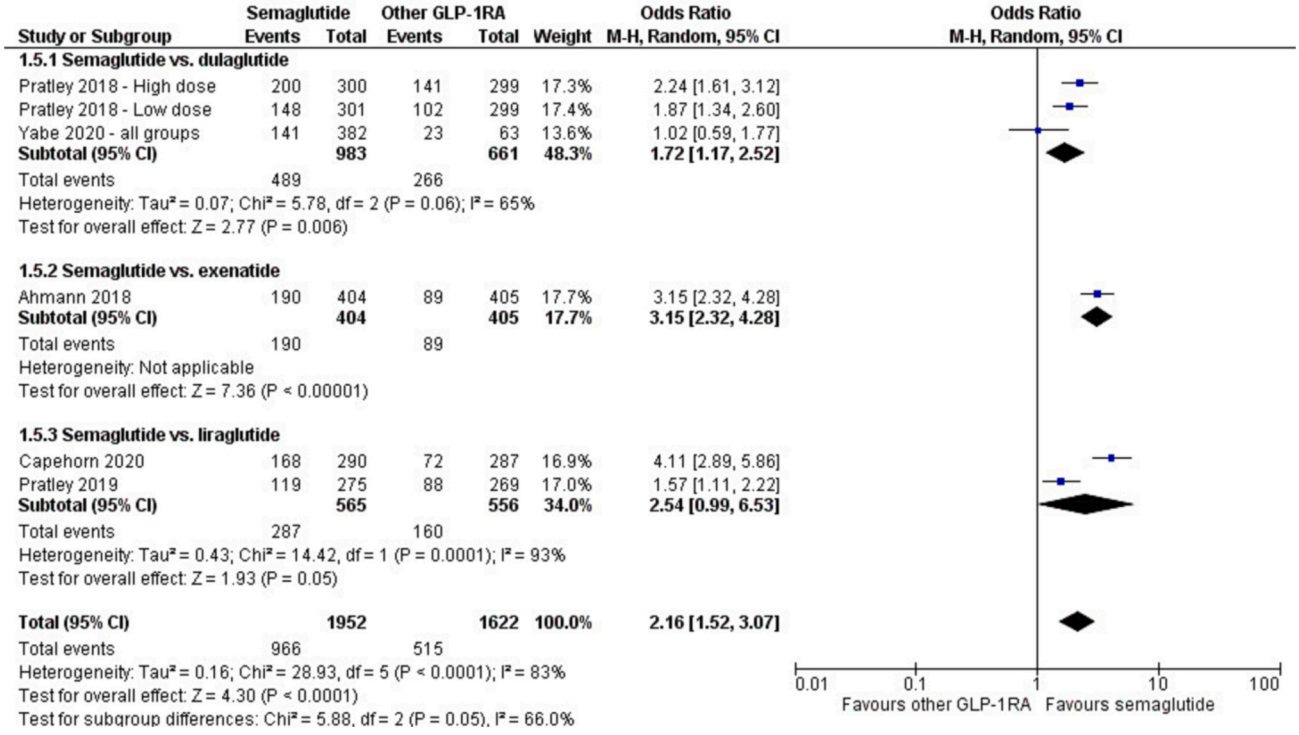

Fig. 5. Effect of semaglutide versus other GLP-1RAs on the odds for achieving HbA1c levels lower than 6.5 %.

and other GLP-RAs was shown, as depicted in Supplementary Fig. 3 (MD = 0.22, 95 % CI; −0.59 to 1.03, I^2 = 47 %, p = 0.59).

3.5. Lipid profile parameters

Regarding lipid profile parameters, all eligible RCTs provided estimated treatment ratios instead of absolute numeric differences between the different treatment arms. As shown in Supplementary Figs. 4–6, semaglutide did not significantly affect total cholesterol, HDL-cholesterol, and LDL-cholesterol levels, compared to other GLP-1RAs. However, the mean difference in the estimated treatment ratio for triglycerides levels was significant in favor of semaglutide compared to other GLP-1RAs, as depicted in the Supplementary Fig. 7.

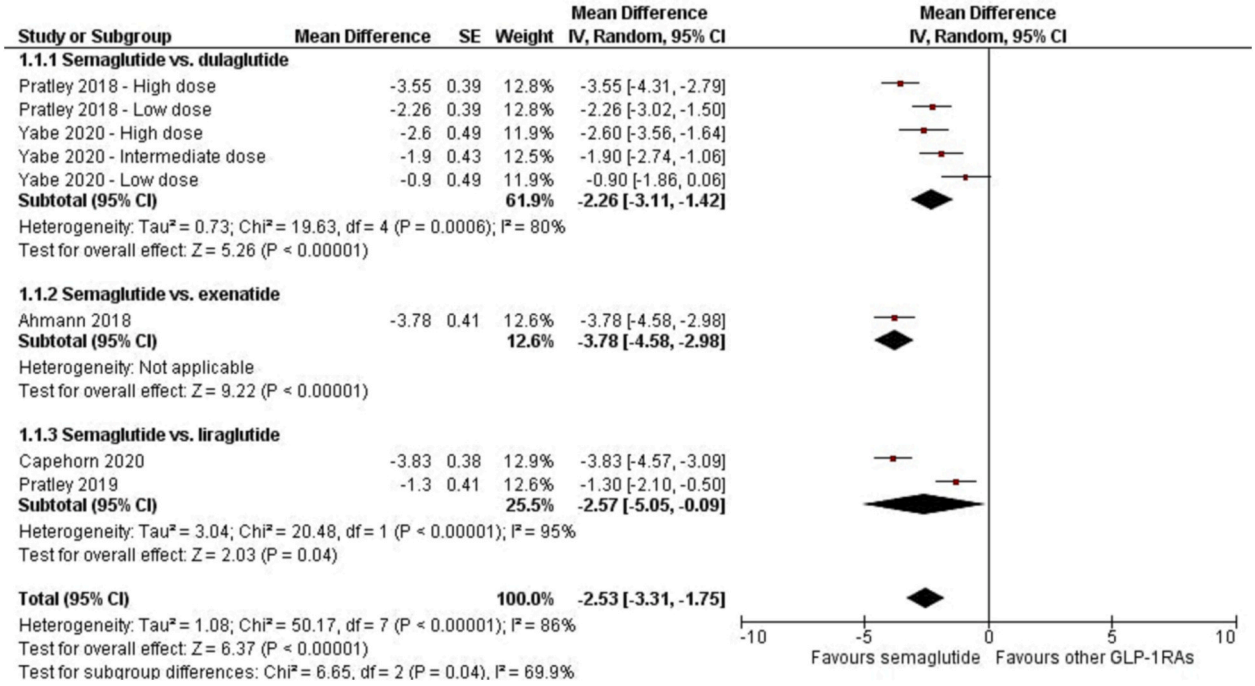

Fig. 6. Effect of semaglutide versus other GLP-1RAs on body weight.

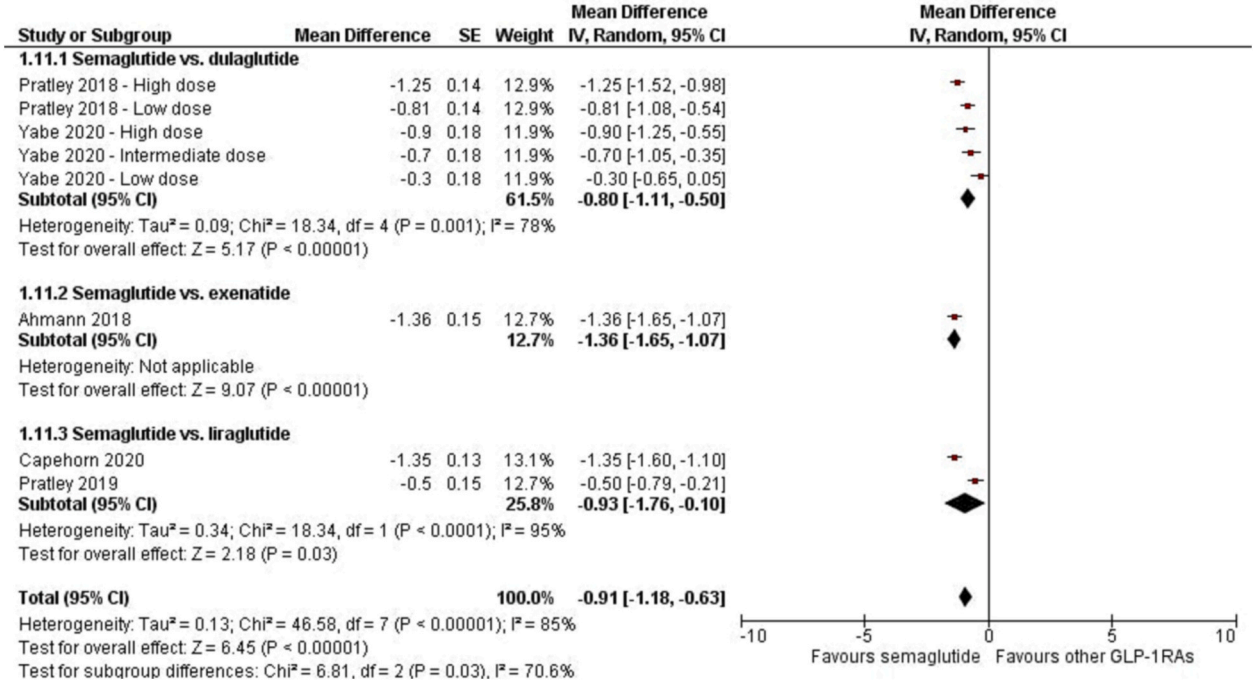

Fig. 7. Effect of semaglutide versus other GLP-1RAs on body mass index.

3.6. Safety

Semaglutide use compared to other GLP-1RAs was linked to a significant increase in the odds for nausea (OR = 1.43, 95 % CI; 1.08 to 1.88, $I^2 = 55$ %, p = 0.01) and vomiting (OR = 1.49, 95 % CI; 1.10 to 2.01, $I^2 = 19$ %, p = 0.01), as shown in Supplementary Figs. 8 and 9. However, semaglutide was not associated with significantly increased odds for diarrhea, compared with other GLP-1RAs (OR = 1.23, 95 % CI; 0.89 to 1.70, $I^2 = 54$ %, p = 0.21), as depicted in Supplementary Fig. 10. Semaglutide use was also not associated with a significant increase in the odds for acute pancreatitis (OR = 0.45, 95 % CI; 0.11 to 1.82, $I^2 = 0$ %, p = 0.26) and diabetic retinopathy (OR = 1.36, 95 % CI; 0.68 to 2.75, $I^2 = 0$ %, p = 0.39), as shown in Supplementary Figs. 11 and 12, respectively. Importantly, subjects randomized to semaglutide compared to other GLP-1RAs had significantly increased odds for premature treatment discontinuation, mainly due to gastrointestinal adverse events (OR = 1.48, 95 % CI; 1.15 to 1.91, $I^2 = 0$ %, p = 0.002), as shown in Supplementary Fig. 13.

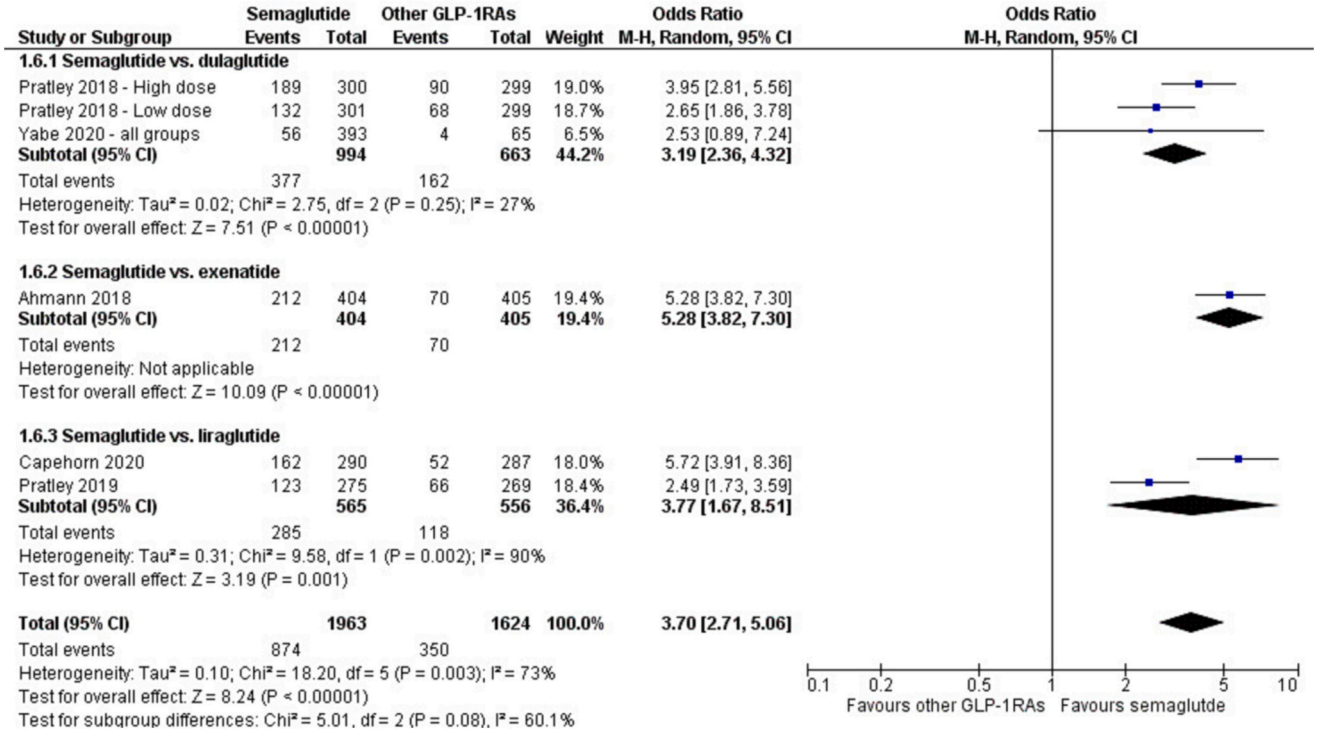

Fig. 8. Effect of semaglutide versus other GLP-1RAs on the odds for achieving weight loss >5 % compared to baseline.

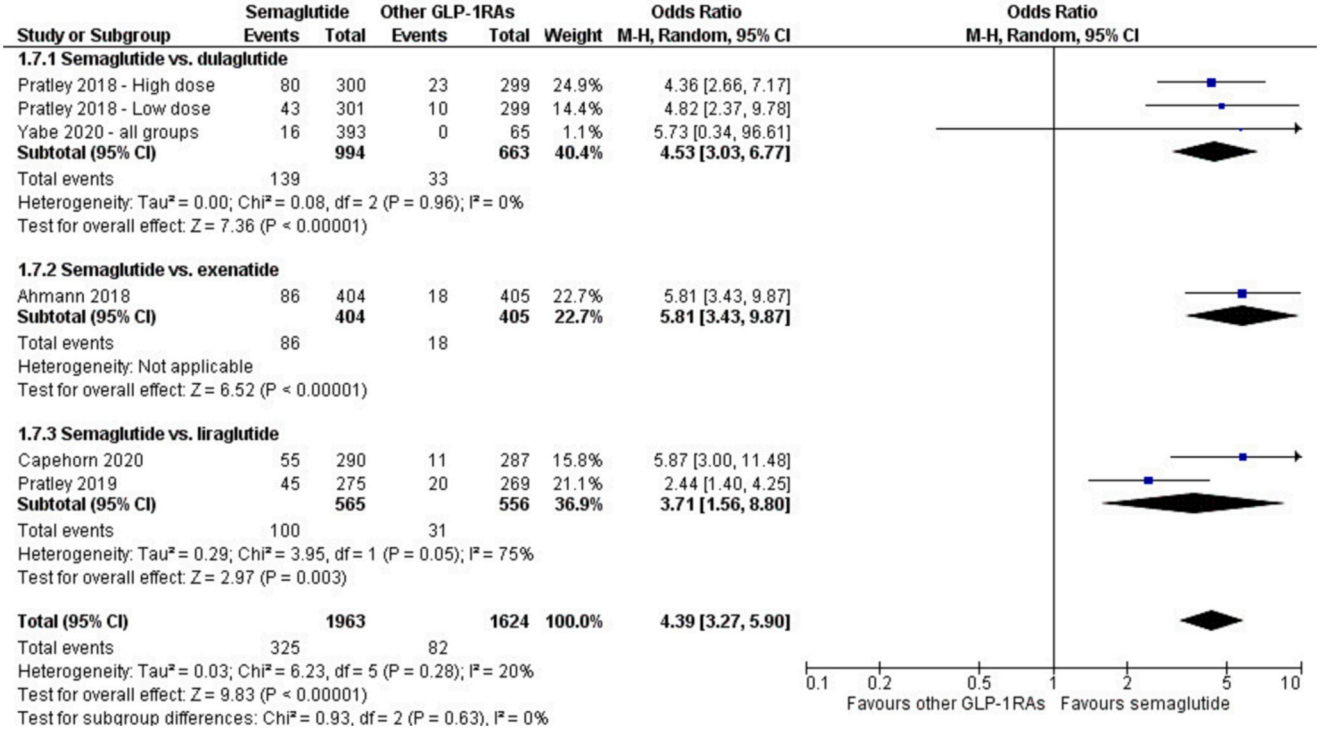

Fig. 9. Effect of semaglutide versus other GLP-1RAs on the odds for achieving weight loss >10 % compared to baseline.

3.7. Risk of bias

Overall risk of bias was assessed as low across RCTs included in the present systematic review and meta-analysis (Supplementary Table 1).

3.8. Publication bias

Visual evaluation of the funnel plot asymmetry for the primary outcome (alteration in HbA1c) did not suggest any asymmetry, a finding indicative of the absence of publication bias (Supplementary Fig. 14).

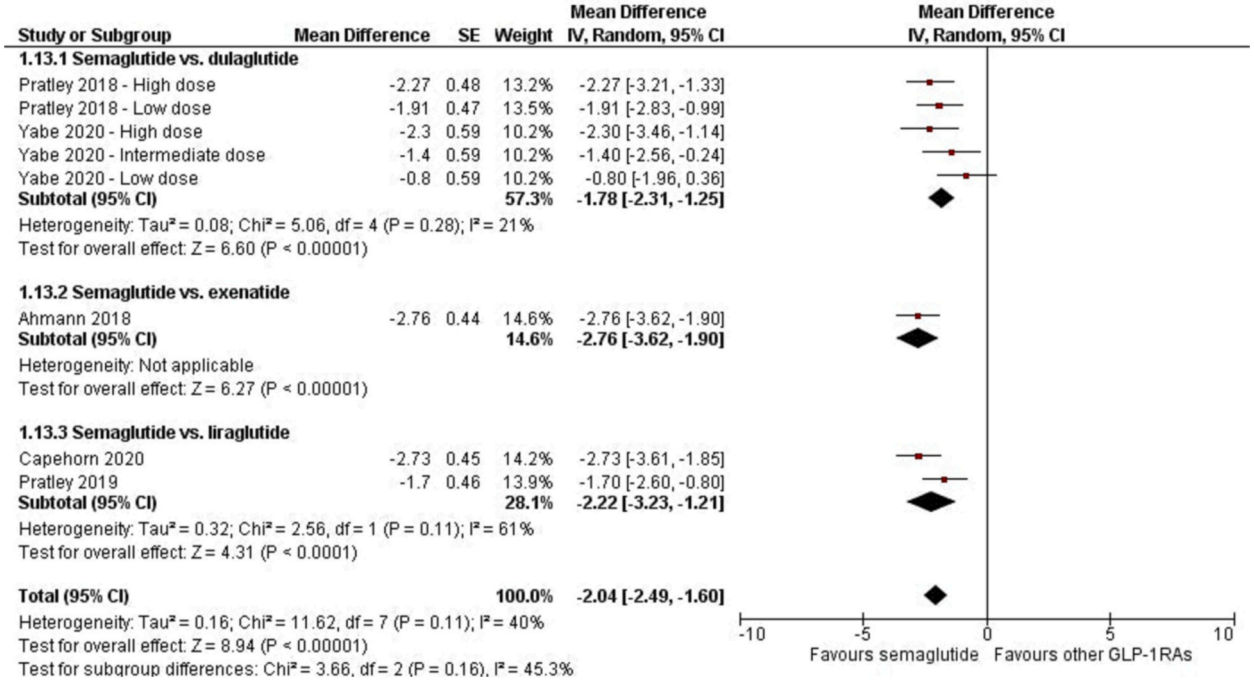

Fig. 10. Effect of semaglutide versus other GLP-1RAs on waist circumference.

4. Discussion

We aimed at comparing the effects of semaglutide and other commercially available GLP-1 RAs on glycemic control and other cardiometabolic risk factors, along with their safety profile assessment, in individuals with T2DM.Therefore, with this meta-analysis we aimed at elucidating if semaglutide should be preferred among the constantly growing GLP-1 RAs armamentarium.

Although all four drugs (exenatide, liraglutide, dulaglutide, and semaglutide) discussed in the present meta-analysis are under the same umbrella of GLP-1 RAs class, they have distinct molecular structures that might impact their interactions with biological targets. Exenatide is a synthetic exendin-4.[19] Exenatide has a 53 % homology to mammalian GLP-1 sequence, and was firstly approved for a twice daily regimen, but after the development of an extended release polymeric formulation, weekly dosing became possible.[20] Liraglutide is a peptide characterized by 97 % homology with the original GLP-1, slightly modified with a free fatty acid side chain attached, while intended for once daily dosing regimen.[21,22] Dulaglutide represents a bigger molecule, with two modified GLP-1 molecules attached to an immunoglobulin (Fc) fragment, initially purposed for once-weekly regimen.[21,23] Finally, semaglutide has a molecular structure very similar to that of liraglutide, but with alanine exchanged for α-amino butyric acid in amino acid position 2 and tighter binding of the fatty acid side chain, thus supporting its once-weekly dosing regimen.[21,24,25] Additionally, an oral preparation of semaglutide has been developed, which contains an absorption enhancer that prevents semaglutide degradation, via elevation of local pH.[21,26] However, this oral preparation of semaglutide is recommended to be administered once daily.[21] These variations in molecular structure certainly lead to disparities in the efficacy and safety profiles of different GLP-1 RAs.

With respect to achieved glycemia, our meta-analysis' results demonstrated that semaglutide provides a greater lowering of HbA1c and FPG levels and is associated with more than two times greater odds for achieving both targeted and intensive reduction in HbA1c levels compared to other GLP-1 RAs. However, absolute reduction in HbA1c and FPG levels accomplished with semaglutide is not superior to that achieved with dulaglutide, while the odds for achieving target and intensive HbA1c reductions with semaglutide are comparable with those achieved with liraglutide. One of the former meta-analyses evaluating clinical efficacy and safety of semaglutide compared with other therapeutic modalities in T2DM documented that semaglutide was more effective in terms of glycemic control, with a significant reduction of HbA1c by 0.47 %, compared to exenatide and dulaglutide, although high heterogeneity regarding studies' duration and administered dosages was reported.[26] Another relevant meta-analysis compared efficacy and safety of semaglutide to dipeptidyl peptidase-4 inhibitors or other GLP-1 RAs in T2DM.[27] Semaglutide 1 mg was significantly superior in reducing HbA1c, with a corresponding reduction by 0.38 % in comparison to other GLP-1 RAs, including liraglutide, exenatide and dulaglutide.[27] Another network meta-analysis showed that, among individuals with T2DM, semaglutide 1 mg was marginally more effective in reducing HbA1c (−0.37 %) than other GLP-1 RAs, including liraglutide, exenatide and dulaglutide.[6] Similarly, another network meta-analysis reported that semaglutide 1 mg was associated with a greater HbA1c reduction compared with all other commercially available GLP-1 RAs (albiglutide, dulaglutide, exenatide, liraglutide and lixisenatide) among T2DM subjects.[28] It was also suggested that even semaglutide 0.5 mg provided a significantly greater reduction in HbA1c compared to the majority of other GLP-1 RAs.[28] Finally, in the most specific network meta-analysis, which assessed long-term efficacy of semaglutide and liraglutide in T2DM, it was reported that semaglutide 1 mg produced a significantly greater reduction in HbA1c, compared to liraglutide 0.6 mg, 1.2 mg, 1.8 mg, equal to 0.56 %, 0.47 % and 0.30 %, respectively, while semaglutide 0.5 mg also provided a significantly greater reduction in HbA1c, compared to liraglutide 0.6 mg and 1.2 mg, equal to 0.25 % and 0.17 %, respectively.[29]

Considering absolute weight loss, BMI reduction, and odds for achieving weight loss >5 % and 10 %, compared with baseline, semaglutide is more efficient than dulaglutide, exenatide and liraglutide, according to present results. At the same time, semaglutide use is associated with a greater decrease in WC compared to other GLP-1 RAs. In one of the previously mentioned network meta-analyses, semaglutide was associated with a significantly greater reduction in both body weight (−3.19 kg) and WC (−2.33 cm), compared to exenatide and dulaglutide.[26] Pooled results for change in body weight from the meta-

analysis by Mishriky and colleagues showed a statistically significant reduction (−2.5 kg) favoring semaglutide compared to other GLP-1 RAs (liraglutide, exenatide and dulaglutide).[27] Additionally, in the meta-analysis conducted by Andreadis and colleagues, semaglutide 1 mg was more efficacious in reducing body weight (−2.79 kg) than other GLP-1 RAs (liraglutide, exenatide and dulaglutide).[6] In the network meta-analysis by Witkowski et al, it was shown that semaglutide 1 mg was associated with a significantly greater reduction in body weight compared to all other GLP-1 RAs (albiglutide, dulaglutide, exenatide, liraglutide and lixisenatide), while semaglutide 0.5 mg also provided significantly greater reductions in body weight compared to most GLP-1 RAs.[28] On the other hand, in the network meta-analysis by Alsugair and colleagues, comparing semaglutide and liraglutide, semaglutide 0.5 mg and 1 mg use was associated with greater body weight reduction compared to liraglutide 0.6 mg (−2.42 kg and −3.06 kg, respectively) while no significant difference was found, when semaglutide was compared to either liraglutide 1.2 mg or liraglutide 1.8 mg.[29]

As far as office BP change is concerned, semaglutide use is accompanied with a greater reduction in both office SBP and DBP, compared to other GLP-1 RAs, according to the results of the present meta-analysis. At the same time, no difference in office HR was observed between individuals treated with semaglutide versus other GLP-1 RAs. The meta-analysis by Shi and colleagues showed a significantly greater reduction of both SBP (−1.60 mm Hg) and DBP (−1.04 mm Hg) with semaglutide in comparison to other GLP-1 RAs (exenatide and dulaglutide).[26] However, use of semaglutide was also associated with a significant increase in HR (1.03 bpm) when compared with other utilized GLP-1 RAs.[26] Pooled results from the meta-analysis by Mishriky and colleagues showed a significant reduction in both office SBP and DBP favoring semaglutide compared to other GLP-1RAs (liraglutide, exenatide and dulaglutide) (−1.60 mm Hg and −1.03 mm Hg, respectively).[27] Semaglutide 1 mg was more efficacious in reducing office SBP (−2.27 mm Hg), but was also associated with increased office HR (1.24 bmp), compared to other GLP-1 RAs (liraglutide, exenatide and dulaglutide) in the meta-analysis conducted by Andreadis and colleagues.[6] Finally, the network meta-analysis by Witkowski and colleagues showed that semaglutide 1.0 mg was associated with a greater reduction in office SBP against other GLP-1 RAs, except for dulaglutide 0.75 mg and liraglutide 1.2 mg, while semaglutide 0.5 mg was associated with an office SBP reduction comparable between all GLP-1 RAs (albiglutide, dulaglutide, exenatide, liraglutide and lixisenatide).[28]

Regarding the lipid profile parameters evaluated in our meta-analysis, the estimated treatment ratios for total cholesterol, LDL-cholesterol, and HDL-cholesterol did not differ between semaglutide and other GLP-1 RAs, while mean difference in the estimated treatment ratio for triglycerides is in favor of semaglutide compared to other GLP-1 RAs. With respect to their impact on lipids, GLP-1 RAs have been shown to modestly reduce total cholesterol, LDL- cholesterol, and triglycerides.[30] However, dedicated studies designed to compare the effect of different GLP-1 RAs on lipid profile parameters are lacking.

Concerning safety evens of particular interest in our meta-analysis, semaglutide use is associated with significantly increased odds for nausea and vomiting when compared to other GLP-1 RAs. On the other hand, semaglutide is not associated with increased odds for diarrhea, acute pancreatitis, and diabetic retinopathy. However, subjects randomized to semaglutide have increased odds for premature treatment discontinuation, mainly due to gastrointestinal adverse events. The meta-analysis by Shi and colleagues did not find an increased risk of gastrointestinal adverse events when comparing semaglutide and other GLP-1 RAs (exenatide and dulaglutide).[26] On the other hand, meta-analysis by Mishriky and colleagues found no statistically significant difference in the incidence of any or serious adverse events between semaglutide and other GLP-1RAs, but revealed that patients treated with semaglutide had a higher incidence of gastrointestinal adverse effects (nausea and vomiting) leading to drug discontinuation.[27]

Despite the fact that GLP-1RAs have emerged as cornerstone treatment options both for T2DM and overweight/obesity, even without underlying T2DM,[31] a dual GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist, named tirzepatide, has been approved as another treatment option for T2DM and obesity, while it might also confer a significant improvement in cardiovascular risk factors.[32,33] In addition, according to a recently published RCT directly comparing tirzepatide and semaglutide for subjects with T2DM, tirzepatide was shown to be superior to semaglutide in terms of glycemic control and body weight reduction.[34] Therefore, it is unclear whether this novel agent will overcome the very efficacious semaglutide in the treatment algorithm of T2DM, while we are eagerly waiting for results of the relevant cardiovascular outcome trial of tirzepatide, namely SURPASS-CVOT. It is also true that over the last decade there has been a significant progress in understanding the exact pathophysiologic mechanisms by which GLP-1RA treatment in T2DM results in such a substantial improvement in cardio-metabolic risk factors, also improving surrogate cardiovascular and renal endpoints in this population.[35,36] Similar research should be performed over the next years to elucidate whether tirzepatide also improves such cardio-metabolic risk factors, and if such an improvement is translated into significant cardio-renal benefits across surrogate endpoints.

We consider as the greatest strength of our meta-analysis the fact that it represents the most updated meta-analysis of head-to-head phase 3 RCTs, comparing the safety and efficacy of either subcutaneous or oral semaglutide to other GLP-1RAs among subjects with T2DM. Above-mentioned meta-analyses, despite being highly relevant, are mostly outdated, or are network meta-analyses, providing effect estimates based upon indirect treatment comparisons. Major limitations of our meta-analysis are the relatively small number of eligible head-to-head phase 3 RCTs and the lack of access to individual participants' data, which could enable further subgroup analyses for the pre-specified outcomes of interest (for example, assessment of outcomes of interest according to baseline SGLT-2 inhibitors' use).

5. Conclusion

Semaglutide seems to be more efficacious compared with the rest of commercially available GLP-1RAs, in terms of improvement in glycemia and other cardio-metabolic risk factors, among individuals with T2DM. However, it is also associated with significantly greater odds for treatment discontinuation, due to gastrointestinal adverse events, mainly nausea and vomiting. No other major safety issues emerged in the present meta-analysis. Generated results from relevant RCTs should be incorporated into daily clinical practice, by amending treatment algorithms used by involved physicians[37] and proposing appropriate treatment combinations, especially for subjects with concomitant cardio-renal disease.[38,39] The impact of semaglutide compared with other GLP-1RAs on surrogate endpoints, including all-cause mortality and cardiovascular morbidity and mortality, compared to other GLP-1RAs, remains unclear, and should be the focus of future RCTs.

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CRediT authorship contribution statement

DP and MR conceived and designed the study. DP and DjP performed the search, identified eligible studies, extracted data of interest, and performed the analyses. DP and DjP wrote the first draft of the report. APS, AJ, AS and MR critically reviewed the draft. All authors approved the final form of the manuscript.

Declaration of competing interest

This manuscript was written independently, and the authors did not

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Data availability statement

Data available upon reasonable request from authors.

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Appendix A. Supplementary data

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