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Safety and efficacy of the new, oral, small-molecule, GLP-1 receptor agonists orforglipron and danuglipron for the treatment of type 2 diabetes and obesity: systematic review and meta-analysis of randomized controlled trials

Paschalis Karakasis [a,*], Dimitrios Patoulias [b,c], Konstantinos Pamporis [d], Panagiotis Stachteas [a], Konstantinos I. Bougioukas [d], Aleksandra Klisic [e], Nikolaos Fragakis [a], Manfredi Rizzo [f]

[a] Second Department of Cardiology, Aristotle University of Thessaloniki, General Hospital "Hippokration", Greece
[b] Outpatient Department of Cardiometabolic Medicine, Aristotle University of Thessaloniki, General Hospital "Hippokration", Greece
[c] Second Department of Internal Medicine, European Interbalkan Medical Center, Thessaloniki, Greece
[d] Department of Hygiene, Social-Preventive Medicine & Medical Statistics, Medical School, Aristotle University of Thessaloniki, University Campus, Thessaloniki, Greece
[e] Primary Health Care Center, Faculty of Medicine, University of Montenegro, Podgorica, Montenegro
[f] Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties, School of Medicine, University of Palermo, Italy

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ABSTRACT

Aims: The present systematic review aimed to synthesize available data from recently published randomized trials (RCTs) investigating the efficacy and safety of the novel, orally administered, small-molecule glucagon-like peptide 1 receptor agonists (GLP-1RAs) orforglipron and danuglipron for the treatment of type 2 diabetes mellitus (T2DM), obesity or both.

Methods: Literature search was performed through Medline (via PubMed), Cochrane Library and Scopus until August 16, 2023. Double-independent study selection, data extraction and quality assessment were performed. Evidence was pooled with random effects meta-analysis.

Results: Totally, 1037 patients among seven RCTs were analyzed. All RCTs had low risk of bias according to the Cochrane Collaboration tool (RoB2). Novel GLP-1RAs led to significant reduction in HbA1c in patients with T2DM compared to controls (MD = −1.03 %; 95 % CI = [−1.29, −0.77]; P < 0.001). A significantly greater weight reduction was also noted both in patients with T2DM or obesity compared to controls (MD = −3.26 kg; 95 % CI = [−4.79, −1.72]; P < 0.001 and MD = −7.52 kg; 95 % CI = [−14.63, −0.41]; P = 0.038, respectively; P for subgroup differences = 0.25). Regarding safety, novel GLP-1RAs showed a neutral effect on the odds of severe hypoglycemia or serious adverse events (OR = 0.34; 95 % CI = [0.09, 1.31]; P = 0.11 and OR = 0.95; 95 % CI = [0.39, 2.34]; P = 0.91, respectively) and significantly higher odds of gastrointestinal, treatment-emergent adverse events (OR = 2.57; 95 % CI = [1.49, 4.42]; P < 0.001) and adverse events leading to discontinuation (OR = 2.89; 95 % CI = [1.22, 6.87]; P = 0.016).

Conclusion: Preliminary evidence supports that orforglipron and danuglipron are efficient in glycemic control and weight reduction in T2DM, obesity or both. More longitudinal research is warranted in order to provide deeper insights into their efficacy, safety and tolerability before their potential incorporation in the pharmacological arsenal against T2DM or obesity.

Abbreviations and acronyms: T2DM, type 2 diabetes mellitus; GLP-1RAs, glucagon-like peptide 1 receptor agonists; HbA1c, glycated hemoglobin A1c; FPG, fasting plasma glucose; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

* Corresponding author at: Second Cardiology Department, Hippokration General Hospital, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece.

E-mail address: pakar15@hotmail.com (P. Karakasis).

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1. Introduction

The escalating issue of type 2 diabetes mellitus (T2DM) has emerged as a significant public health concern, with a notable projected increase in the number of diagnosed individuals over the upcoming two decades [1]. Amidst alternate options in the effort to attain euglycemia, glucagon-like peptide 1 receptor agonists (GLP-1RAs) constitute a drug class with multiple cardio-renal benefits and are recommended for the management of T2DM, considering patient's glycemic needs, co-morbidities, and baseline risk factors [2,3]. Presently, all available GLP-1RAs are in the form of peptidic agonists, and most of them require subcutaneous administration [4]. However, this route of administration may not be convenient or suitable for some patients, leading to reduced uptake, adherence, and persistence, as patients generally prefer oral medications [5,6]. To date, the only oral peptidic GLP-1RA with indication for T2DM is semaglutide. Nevertheless, it necessitates rigorous fasting prior to and following each administration [7].

Obesity, another medical condition closely interconnected with T2DM, represents a substantial burden on patients, health care systems, and the economy in general, affecting >1 billion people worldwide [8]. Current clinical guidelines recommend the use of weight-management medications for individuals with obesity and those who are overweight with weight-related co-morbidities. The increasing use of GLP-1RAs as part of obesity treatment is mainly attributed to their long-term effectiveness, which has been demonstrated in trials focusing on excess weight management with injectable GLP-1RAs [9–11].

The newly developed, orally administered, small-molecule GLP-1RAs are being investigated as an adjunct to diet and exercise to improve glycemic control and weight management in T2DM [12]. Moreover, a recent trial reported that orforglipron, a novel GLP-1RA, leads to improvement in all prespecified weight-related and cardiometabolic measures in obese individuals without baseline T2DM [13].

Several phase 1 and phase 2 randomized controlled trials (RCTs) have been recently published, addressing the effect of small-molecule, oral GLP-1RAs on various cardiometabolic outcomes of interest in individuals with T2DM, obesity or both. The present systematic review and meta-analysis aimed to summarize the available evidence on the efficacy and safety of orforglipron and danuglipron in patients with T2DM, obesity or both.

2. Material and methods

The present study was conducted following the principles of the Cochrane Handbook for systematic reviews [14] and reported according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) 2020 guidelines [15]. The protocol of this meta-analysis was prepared a priori and registered in Open Science Framework (https://osf.io/rmu7q/). Amendments to the original protocol with rationale are outlined in Supplemental Table 1.

2.1. Search strategy

Two researchers independently performed the literature search in MEDLINE (via PubMed), Scopus and the Cochrane database of Systematic Reviews covering the period from inception to August 16, 2023, without language restrictions. The basic terms used in the search strings were small-molecule oral GLP-1RAs, danuglipron, orforglipron, type 2 diabetes mellitus and obesity in both free text and Medical Subject Headings format. Searches were supplemented with manual searching on Epistemonikos database and Google Scholar search engine Searches and by backward and forward citation chasing using the {citationchaser} R package [16]. The comprehensive search strategy is outlined in Supplemental Tables 2–4.

2.2. Eligibility criteria

2.2.1. Inclusion criteria

Eligible were RCTs of phase 1 or above investigating the efficacy and safety of small-molecule oral GLP-1RAs compared to placebo or other antidiabetic agents in adult patients (>18 years) with T2DM, obesity or both conditions.

2.2.2. Exclusion criteria

Studies with the following characteristics were excluded:

- Including pediatric population, patients with Type 1 diabetes or healthy controls
- Case reports/case series, narrative reviews
- Editorials, letters, commentaries, expert opinions, clinical practice guidelines, conference abstracts, dissertations, protocols
- Including animals and/or in vitro studies
- Not retrievable full text
- Observational studies
- Experimental studies
- Including animals

2.3. Outcomes

In terms of efficacy endpoints, the difference in absolute change in the percentage of HbA1c from baseline between small-molecule oral GLP-1RAs and control groups was considered as the primary outcome of interest. Secondary efficacy endpoints were the differences of absolute changes from baseline in fasting plasma glucose (FPG), body weight, body mass index (BMI), systolic (SBP) and diastolic blood pressure (DBP) and heart rate (HR).

Safety outcomes of interest were the following: rates of nausea, constipation, dyspepsia, treatment-emergent adverse events, serious adverse events, adverse events leading to treatment discontinuation and any or severe hypoglycemia events. We adopted the definitions of adverse events as outlined per single SR.

2.4. Study selection

Initially, the records obtained from the aforementioned search strategy underwent independent title and abstract screening by two authors. To enhance the sensitivity of our study selection process, any disagreements in this phase did not lead to exclusions. Following this, the same authors individually conducted full-text evaluations of the identified studies. Discrepancies were resolved by means of discussions or by including a third author with more experience in the field. The online software Abstrackr [17] was used for the screening of the first phase. Subsequently, for the full text-screening, Mendeley Desktop was used for reference management.

2.5. Data extraction

A preliminary data extraction form was developed and tested on a subset of three studies through pilot extraction. Following discussions, training, and calibration exercises, a definitive standardized data extraction form was formulated. This process was performed independently and in duplicate, and any discrepancies were addressed through discussions or involvement of a third author with greater expertise in the field. In case of missing evidence or discrepant data we contacted the authors of the primary studies. In each study, data regarding sample size, major clinical and demographic characteristics, and changes in HbA1c, fasting plasma glucose, body weight/ BMI, blood pressure, heart rate or any other efficacy or safety outcome reported were extracted.

2.6. Risk of bias (ROB) assessment

The risk of bias in the included studies was evaluated independently by two authors, considering all predefined domains outlined in the revised version of the Cochrane Collaboration tool (RoB 2) [18]. Any disagreements were settled through discussion or with involvement of a third author with greater expertise.

2.7. Data analysis

All analyses were performed using R Statistical Software (v. 4.2). Categorical variables are presented as frequencies with percentages (%), while continuous variables as mean with standard deviation (SD) when normally distributed, otherwise as median with interquartile range (IQR). To estimate differences between intervention and control groups, the mean difference (MD) was used for continuous outcomes and the odds ratio (OR) for dichotomous outcomes. Effect estimates and 95 % confidence intervals (CIs) were calculated using DerSimonian-Laird random effects models. In case of zero events in any arm, continuity correction was applied. Difference in HbA1c between intervention and control groups was expressed as percentage (%), in FPG as mg/dl, in weight as kg, in BMI as kg/m^2, in blood pressure as mmHg and in HR as beats per minute (bpm). Additionally, subgroup analysis was performed based on the type of underlying condition (diabetes vs obesity without diabetes). Differences between subgroups were tested using the Cochran's Q test. For summary treatment effect estimates, a two-tailed p value <0.05 was considered statistically significant. All results were visually summarized using forest plots.

The percentage of total variability due to between-study heterogeneity was estimated using the I^2 value, that quantifies the inconsistency across studies, and formally tested with the Cochran's Q test. I-squared values range from zero to one, with values closer to one indicating larger heterogeneity between studies. Roughly, cut-off values of 25 %, 50 %, and 75 % indicate low, moderate, and high heterogeneity respectively. Investigation on small study effect (including investigation on publication bias) was represented graphically with contour enhanced funnel plots of effect size versus standard error and formally tested with the Egger's test.

To address the facts of missing standard deviations and that some studies did not report or pooled results for the whole population treated with small-molecule oral GLP-1RAs, but only for subgroups following different titration algorithms and to avoid including multiple comparisons from the same study in a single random effects model, following the recommendations of Cochrane, the outcomes for different subgroups were combined into a single group, using the suggested formulae [19].

Random effects meta-analyses were also performed to investigate the possible dose-response relationship between the different doses of GLP1-RAs and both HbA1c and weight change from baseline. For this purpose, we used the R package 'doseresmeta' and fitted restricted cubic splines with knots at the 10th, 50th, and 90th percentiles of the GLP1-RAs doses reported in RCTs [20]. Goodness-of-fit was assessed using de-correlated residuals versus exposure plots and the coefficient of determination [20].

2.8. Sensitivity analysis

Multiple leave-one-out meta-analyses were performed by excluding successively one study at each analysis to investigate the influence of each study on the overall effect size estimate and to identify influential studies.

2.9. Certainty of evidence

Assessments on certainty of evidence for each outcome were conducted using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) checklist via the GRADEpro [21]. Adhering to Cochrane's recommendation, assessments were planned only for limited outcomes of interest that were deemed as highly significant, rather than all secondary safety endpoints [22].

3. Results

3.1. Study selection and characteristics

The study selection process is summarized in Supplemental Fig. 1. A total of 2485 records were initially identified and screened on title and abstract level and, of those, 2460 were excluded. Consequently, 25 records were selected for full-text evaluation and 7 studies met the eligibility criteria [13,23–28]. A list of excluded studies with reasoning is provided in Supplemental Table 5.

The main characteristics of included RCTs are summarized in Table 1. Seven studies using the novel, small-molecule GLP1-RAs were identified. Patients' demographic and clinical characteristics are summarized in Table 2. In total, 1037 patients received the intervention under investigation, of which 793 (76.5 %) had baseline T2DM and 244 (23.5 %) were obese individuals without T2DM. These patients were compared to 230 controls treated with placebo (174 [75.7 %] with diabetes and 56 [24.3 %] with obesity/non-diabetes). The median diabetes duration was 9.1 years. Most participants in the intervention group were males (34.2 % to 85.7 %) and their mean age ranged from 54.2 to 59 years. All patients with T2DM had a baseline HbA1c above the target range, between 7.8 % and 8.4 %, whereas the median total follow-up was 16 weeks.

The overall and domain-specific risk of bias was low for all included RCTs, according to the RoB2 assessment tool (Supplemental Fig. 2).

3.2. Efficacy

Overall, the 789 T2DM patients treated with small-molecule oral GLP-1RAs had a greater, significant change in the percentage of HbA1c from baseline compared to controls (MD = −1.03 %; 95 % CI = [−1.29, −0.77]; P < 0.001; I^2 = 88 %; P < 0.001; Fig. 1A). The symmetrical contour- enhanced funnel plot of effect size versus standard error, revealed no evidence of small study effect, including publication bias (Supplementary Fig. 3).

Based on subgroup analysis the benefit in terms of HbA1c reduction was significantly higher in T2DM compared to the obese patients without T2DM (MD = −0.46 %; 95 % CI = [−0.75, −0.17]; P for subgroup differences <0.01; Fig. 1A).

Similarly, both T2DM patients and those with obesity without T2DM experienced a significantly greater reduction in FPG compared to controls (MD = −28.53 mg/dl; 95 % CI = [−34.04, −23.02]; P < 0.001; I^2 = 15 %; P = 0.32 and MD = −6.74 mg/dl; 95 % CI = [−12.78, −0.7], respectively; P for subgroup differences <0.01; Fig. 1B).

Regarding the weight change, a significant reduction was observed both in T2DM (MD = −3.26 kg; 95 % CI = [−4.79, −1.72]; P < 0.001; I^2 = 92 %; P < 0.01; Fig. 2A) and obesity without T2DM groups receiving small-molecule GLP-1RAs compared to controls (MD = −7.52 kg; 95 % CI = [−14.63, −0.41]; P = 0.038; I^2 = 91 %; P < 0.01; Fig. 2A). The test for subgroup differences was not significant (P for subgroup differences = 0.25). Furthermore, a similar significant reduction in BMI was also noted compared with the control group (MD = −2.87 kg/m^2; 95 % CI = [−4.65, −1.1]; P = 0.002; I^2 = 93 %; P < 0.01; Fig. 2B).

Patients receiving small-molecule GLP-1RAs had a significant reduction in SBP compared to controls (MD = −3.48 mmHg; 95 % CI = [−6.2, −0.76]; P = 0.012; I^2 = 52 %; P = 0.13; Fig. 3A), whereas the effect on DBP and heart rate was not significant (MD = 0.3 mmHg; 95 % CI = [−0.84, 1.45]; P = 0.6; I^2 = 0 %; P = 0.89; Fig. 3B and MD = 4.27 beats per minute; 95 % CI = [−1, 9.54]; P = 0.11; I^2 = 93 %; P < 0.01; Fig. 3C, respectively).

Table 1
Characteristics of included studies.

First author	Publication Year	Phase	Treatment duration (weeks)	Total follow-up (weeks)	Population	Intervention	Comparator	Primary outcome	Secondary efficacy outcome	Safety outcome
Wharton [13]	2023	2	36	38	Adults 18 to 75 years without diabetes with obesity (BMI $\geq$ 30) or overweight (BMI, 27 to<30 kg/m2) with one of the following: HTN, DLD, CV disease, or OSA	Orforglipron 12 mg, 24 mg, 36 mg, or 45 mg OD	Placebo	Percentage change from baseline in BW at week 26	Percentage change from baseline in body weight at week 36, the absolute change from baseline in body weight, BMI, and waist circumference at week 26 and week 36; weight reductions of at least 5 % and at least 10 % by week 26 and week 36, weight reduction of at least 15 % by week 26 and week 36	AEs, BP, the pulse, safety-related laboratory measures, pharmacokinetic measures, and patient-reported outcomes
Saxena [24]	2023	2a	12	16	Adults (18–75 years old) with T2D (stable metformin dose, HbA1c $\geq$ 7 % and $\leq$ 10.5 %) or obesity (BMI $\geq$ 30 kg/m2 and weight $>$ 50 kg) without diabetes	Danuglipron 80 mg bid with low (5 mg) and high (10 mg) starting dose, 120 mg bid with low and high starting dose and 200 mg bid	Placebo	Primary outcome was the Incidence and severity of TEAEs	Change from baseline in HbA1c (T2D population), FPG (T2D population) and BW (both populations) at weeks 2, 4, 6, 8, 10 and 12	Secondary safety outcome included treatment-emergent laboratory abnormalities, vital sign and ECG abnormalities and mental health assessments
Saxena [23]	2023	2b	16	16	Adults (aged 18–75 years) with T2D treated with diet and exercise, having HbA1c between 7 % and 10.5 %, BW $>$ 50 kg and BMI between 22.5 (Asia) or 24.5 (North America and Europe) to 45.4 kg/m2	Danuglipron 2.5, 10, 40, 80 or 120 mg bid	Placebo	Change from baseline in HbA1c at week 16.	Change from baseline in HbA1c at weeks 2, 4, 6, 8, and 12, patients achieving HbA1c $<$ 7 %(at week 16), and changes from baseline in FPG and BW at all time points	TEAEs, hypoglycemia, treatment-emergent clinical laboratory, vital sign or ECG abnormalities
Saxena [25]	2021	1	4	4	Patients with T2D receiving metformin	Danuglipron 10 mg bid, 15 mg bid, 50 mg bid, 70 mg bid, 120 mg bid, 120 mg bid slow titration, 120 mg OD and 200 mg OD	Placebo	Pharmacodynamic and pharmacokinetic profiles of multiple ascending doses	N/A	TEAEs
Ono [28]	2023	1	8	12	Japanese adults (20–70 years) with T2DM treated by	Danuglipron 40, 80 or 120 mg bid	Placebo	Evaluation of safety and tolerability of danuglipron	N/A	AEs, TEAEs

(*continued on next page*)

Table 1 (*continued*)

First author	Publication Year	Phase	Treatment duration (weeks)	Total follow-up (weeks)	Population	Intervention	Comparator	Primary outcome	Secondary efficacy outcome	Safety outcome
					diet and exercise alone, HbA1c between 7 % and 10.5 %, BW >50 kg and BMI = 22.5–45.4 kg/m2					
Pratt [27]	2023	1b	12	12	Adults (18–70 years) with T2D for at least 6 months, treated with diet and exercise alone or a stable dose of metformin for at least 3 months. Patients should have HbA1c between 7.0 % -10.5 %, BMI between 18.5 and 45 kg/m2 and stable BW for theprevious 3 months	Orforglipron 6, 12 and 21 mg OD	Placebo	Safety and tolerability of multiple oral doses of orforglipron	N/A	TEAEs and SAEs
Frias [26]	2023	2	26	28	Adults >18 years with T2D and HbA1c between 7·0–10·5 %, treated with diet and exercise +/− metformin for at least 3 months, BMI > 23 kg/m^2 and stable BW in the previous 3 months	Orforglipron 3 mg, 12 mg, 24 mg, 36 mg (two subgroups), or 45 mg OD	Placebo and dulaglutide 1,5 mg	Change from baseline in HbA1c at week 26	Change from baseline in HbA1c at week 26, percentage of participants with HbA1c < 7 % and less than or equal to 6·5 %, change from baseline in FPG and BW, BW percentage and percentage of participants with 5 % or more and 10 % or more BW reduction	Participant-reported and investigator-reported AEs, rate and incidence of hypoglycaemia events, change in safety laboratory variables, ECG and vital signs

Abbreviations: BMI, Body Mass Index; HTN, hypertension; DLD, dyslipidemia; CV, cardiovascular; OSA, obstructive sleep apnea; BP, blood pressure; T2D, type 2 diabetes; HbA1c, glycated hemoglobin; AE, adverse event; TEAE, treatment emergent adverse event; SAE, serious adverse event; ECG electrocardiogram; bid, twice daily; OD, once daily; N/A, not available.

3.3. Safety

Considering the safety of small-molecule GLP-1RAs, non-significant differences were observed for the number of patients with severe or any hypoglycemic events (OR = 0.34; 95 % CI = [0.09, 1.31]; P = 0.11; I^2 = 0 %; P = 0.97 and OR = 1.41; 95 % CI = [0.55, 3.6]; P = 0.48; I^2 = 0 %; P = 0.95; Fig. 4A and B, respectively) and serious adverse events compared to controls (OR = 0.95; 95 % CI = [0.39, 2.34]; P = 0.91; I^2 = 0 %; P = 0.72; Fig. 4C).

Regarding the gastrointestinal symptoms, GLP-1RAs were associated with increased odds of nausea (OR = 7.95; 95 % CI = [4.79, 13.21]; P < 0.001; I^2 = 0 %; P = 0.88; Supplemental Fig. 4A), constipation (OR = 3.68; 95 % CI = [1.87, 7.23]; P < 0.001; I^2 = 0 %; P = 0.88; Supplemental Fig. 4B), vomiting (OR = 7.07; 95 % CI = [3.64, 13.74]; P < 0.001; I^2 = 0 %; P = 0.76; Supplemental Fig. 4D) and diarrhea (OR = 1.92; 95 % CI = [1.18, 3.13]; P < 0.001; I^2 = 0 %; P = 0.55; Supplemental Fig. 5A) compared to control group.

Finally, significantly higher odds of treatment emergent adverse event and adverse event leading to treatment discontinuation were observed in intervention group compared to controls (OR = 2.57; 95 % CI = [1.49, 4.42]; P < 0.001; I^2 = 54 %; P = 0.04 and OR = 2.89; 95 % CI = [1.22, 6.87]; P = 0.016; I^2 = 24 %; P = 0.24; Supplemental Fig. 5B and C, respectively).

Table 2
Demographic and clinical characteristics.

First Author	Year	Participants' number (n)			Male sex (%)		Age, years (SD)		Diabetes duration, years (SD)		SBP, mmHg (SD)		HbA1c (%)		BMI, kg/m2 (SD)		FPG (mg/dl)		Metformin use (%)	
		Total	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C
Wharton [13]	2023	272	222	50	34.2	42	54.2 (11.1)	54 (8.8)	N/R	N/R	129.5 (11.5)	128.5 (9.5)	5.6 (0.4)	5.6 (0.4)	37.9 (7.02)	37.8 (6.5)	96 (11.3)	97.2 (10.2)	N/R	N/R
Saxena [24]	2023	151	129	22	37.7	45.4	57.2 (10.8)	52.7 (8.4)	9.4 (6.6)	8.15 (7.6)	N/R	N/R	7.8 (1.4)	7.6 (1.2)	34.3 (5.5)	35.8 (5.1)	160 (53.3)	146.8 (46.5)	83	73
Saxena [23]	2023	411	345	66	50.9	50	58.8 (9.1)	57.9 (10.3)	8.7 (6.6)	8.8 (6.9)	N/R	N/R	8 (0.9)	8.24 (0.9)	32.8 (5.3)	32.5 (5.1)	168.6 (41.2)	173 (43.8)	91.4	94
Saxena [25]	2021	98	73	25	53.4	48	57.4 (7.1)	57.6 (7.7)	9.8 (5.7)	8.5 (6.6)	N/R	N/R	8.4 (0.8)	8 (0.8)	32.8 (4.2)	33.2 (4.5)	182.5 (34.4)	167.6 (32.5)	100	100
Ono [28]	2023	37	28	9	85.7	88.9	54.9 (8.5)	58.6 (8.8)	5.8 (6)	5.5 (4.1)	N/R	N/R	8.4 (1.1)	8.3 (1.2)	28.5 (3.6)	25.9 (2.7)	17.1 (36.1)	182.9 (36.3)	N/R	N/R
Pratt [27]	2023	68	51	17	62.7	58.8	58.5 (6.3)	56 (6)	11.1 (7.6)	8.6 (4.9)	N/R	N/R	8 (0.9)	8.1 (0.75)	30.9 (4.1)	31.3 (4.9)	N/R	N/R	90.2	88.2
Frias [26]	2023	383	278	105	60.3	51	59 (9.3)	58.3 (9.5)	6.8 (5.8)	8.1 (6.5)	133.5 (12.8)	135.2 (14.6)	8.1 (0.8)	8.1 (0.9)	35 (6.9)	35.8 (6.2)	166.1 (38.4)	172 (42.9)	N/R	N/R

Abbreviations: I, intervention; C, Controls; SD, standard deviation; SBP, systolic blood pressure; HbA1c, glycated hemoglobin; BMI, body mass index; FPG, fasting plasma glucose; DPP4i, dipeptidyl peptidase-4 inhibitors; SGLT2i, Sodium-glucose cotransporter-2 inhibitors; N/R, not reported.

3.4. Sensitivity analysis

The sensitivity analysis, using the leave-one-out approach did not reveal outlying or influential studies for the association between the novel, small-molecule GLP1RAs and HbA1C (Supplemental Fig. 6). On the contrary, the study by Wharton et al. was identified as influential for the effect on weight reduction; nevertheless, the association remained significant even after omitting the aforementioned study (Supplemental Fig. 7).

3.5. Dose-response meta-analysis

The restricted cubic splines models revealed a significant non-linear association between GLP1-RAs dosage and HbA1c change, compared to placebo ($P < 0.001$; $P_{non\text{-}linearity} < 0.001$ for both Danuglipron and Orforglipron, Fig. 5A and B, respectively). Regarding the effect on weight change, a significant linear association was observed for Danuglipron ($P < 0.001$; $P_{non\text{-}linearity} = 0.86$, Fig. 6A), whereas a significant non-linear association was noted for Orforglipron ($P = 0.002$; $P_{non\text{-}linearity} < 0.001$, Fig. 6B).

3.6. GRADE assessment

The assessment of the reported findings based on the GRADE checklist is illustrated in the Supplemental Table 6. Briefly, the strength of evidence was estimated as high for the effect of small-molecule GLP-1RAs on SBP. The level of evidence in the relationship between small-molecule GLP-1RAs and HbA1c, FPG, weight, severe hypoglycemic or serious adverse events was downgraded to moderate, due to serious inconsistency or imprecision.

4. Discussion

This is the first systematic review and meta-analysis of RCTs addressing the safety and efficacy of currently available oral, small-molecule, GLP-1RAs, namely orforglipron and danuglipron, for the treatment of T2DM, obesity, or both. Herein we have demonstrated that those new agents resulted in a significant improvement in glycemic control, by decreasing HbA1c and FPG, and in body weight, by producing a significant reduction, compared with placebo. In addition, a numerically small, but significant, reduction in SBP levels was also shown. Concerning safety endpoints of interest, we have demonstrated that oral, small-molecule GLP-1RAs did not result in significantly higher odds of any serious adverse event, while they also did not increase the odds for any or severe hypoglycemic event. In symphony with other GLP-1RAs, those new agents led to a significant increase in the odds of gastrointestinal adverse events, mainly nausea, vomiting, diarrhea and constipation. It has also to be noted that oral, small-molecule GLP-1RAs had a neutral effect on HR, although evidence was based on only 3 eligible RCTs providing relevant data for synthesis.

Last, but not least, utilization of oral, small-molecule GLP-1RAs was associated with significantly increased odds of treatment discontinuation due to gastrointestinal adverse events, a finding that is compatible with what has been observed in large trials with currently available GLP-1RAs. Of importance, the odds of treatment discontinuation with GLP-1RAs compared to control was not significant among subjects with T2DM, whereas it was significant for those with obesity without T2DM at baseline. Unfortunately, we do not have data from currently available trials concerning the impact of treatment discontinuation on cardio-metabolic parameters of interest in the enrolled patients, such as glycemia, body weight, or blood pressure levels. However, according to relevant evidence from trials with commercially available GLP-1RAs, a negative impact on cardio-metabolic indices after discontinuation should rather be expected [29].

The glucose-lowering efficacy of GLP-1RAs in T2DM is well-established over the last years [30–32], leading to the modification of

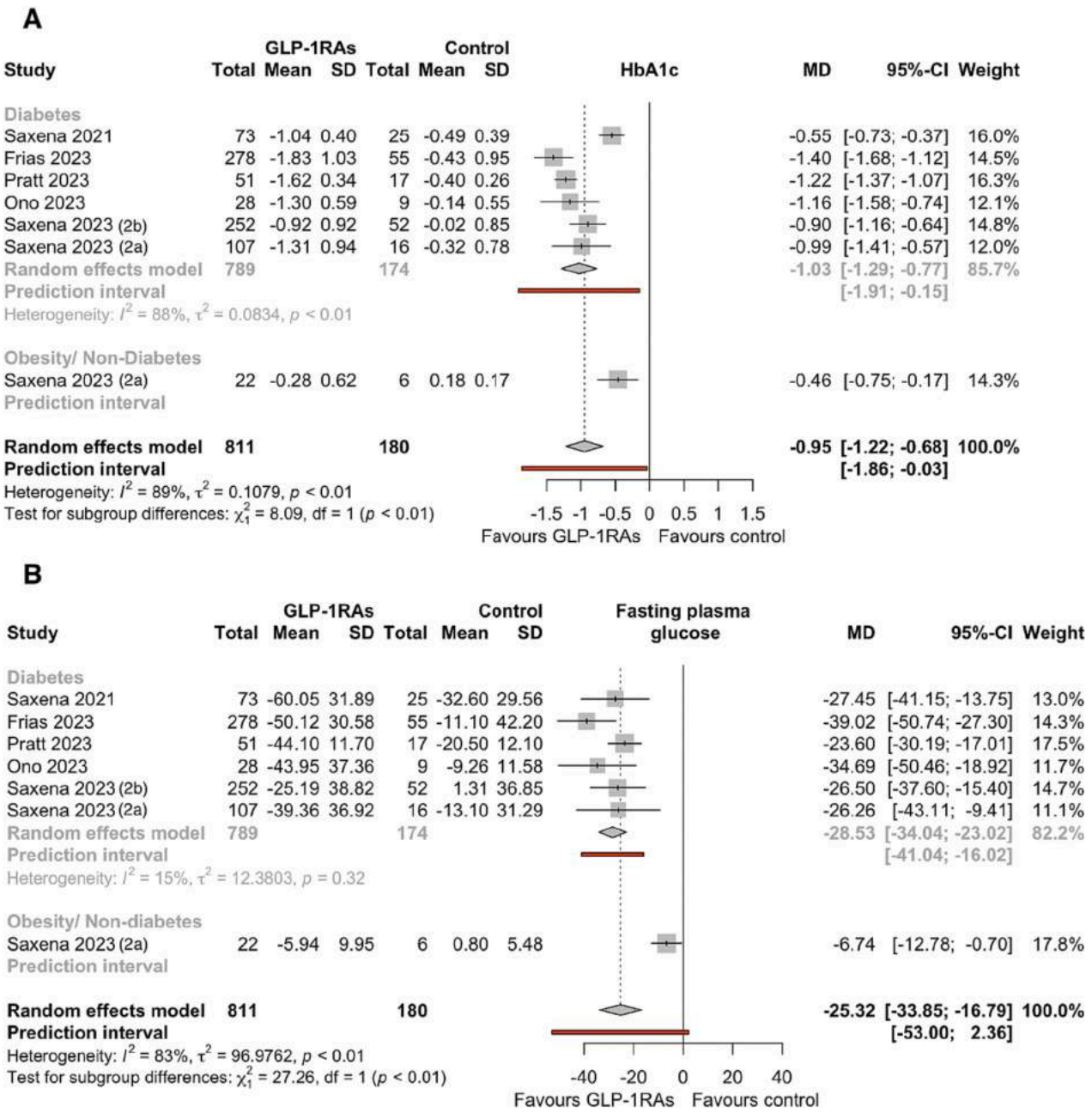

Fig. 1. Forest plots of the effect of small-molecule oral GLP-1RAs vs control: Mean difference in the absolute change from baseline in the percentage of HbA1c (A) and in fasting plasma glucose (B).
Abbreviations: CI, Confidence Interval; MD, Mean Difference.

treatment strategy, as reflected in the recently published guidelines [3]. Of course, their use has been prioritized in the treatment of T2DM due to their impressive cardio-renal benefits, especially for subjects with established or at high risk for atherosclerotic cardiovascular disease (ASCVD), besides the undoubted improvement in glycemic control [30,33]. Apart from their glucose-lowering efficacy, GLP-1RAs have proven to be a powerful tool to tackle the progression of the obesity pandemic, when administered in subjects with obesity without baseline T2DM, based on the significant weight loss they produce, especially when administered in higher doses than those recommended for the treatment of T2DM [34,35].

GLP-1RAs are mainly administered subcutaneously, with the dosing regimen varying from once-daily to once-weekly. The development of oral semaglutide, the first GLP-1RA designed for once-daily, oral administration, was a revolution in the field. Indeed, oral semaglutide has proven to be effective in reducing blood glucose levels and body weight in subjects with T2DM, while it might also exert a beneficial effect on SBP levels, at the cost of increasing the odds for gastrointestinal adverse events, mainly nausea, vomiting and diarrhea [36,37]. In addition, subjects assigned to oral semaglutide versus control had significantly higher odds for achieving adequate and ideal glycemic control [37].

According to the most recent, relevant evidence, semaglutide 7 mg and 14 mg once-daily resulted in a significant reduction in HbA1c by 1.06 % and 1.1 %, respectively, compared with placebo, when given in subjects with T2DM [38]. In addition, the above doses resulted in a significant decrease in HbA1c by 0.26 % and 0.38 %, respectively, when compared with other antidiabetic drug classes [38]. As far as body weight is concerned, semaglutide 7 mg led to a significant decrease by 1.18 kg, compared with placebo, and by 1.47 kg, compared with other

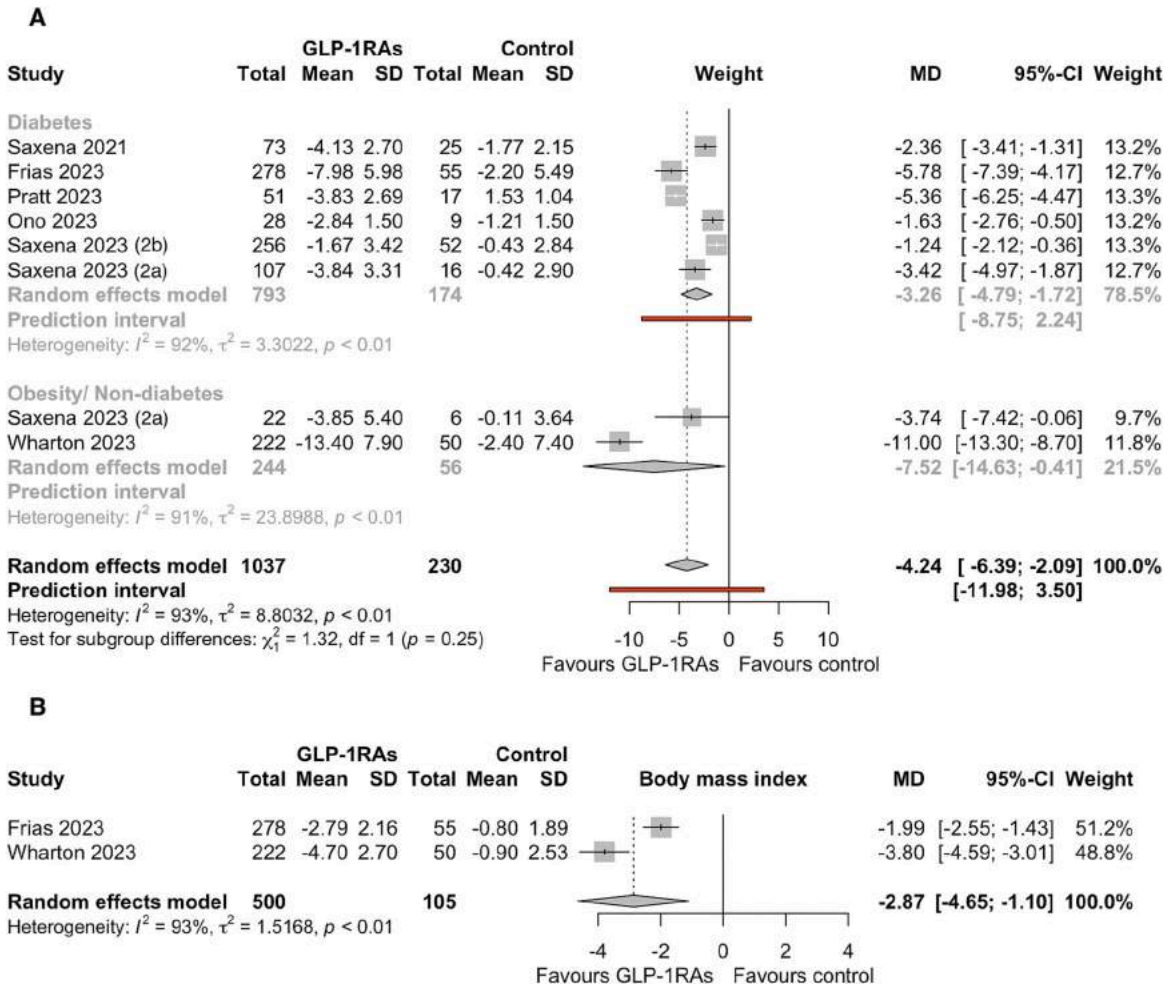

Fig. 2. Forest plots of the effect of small-molecule oral GLP-1RAs vs control: Mean difference in the absolute change from baseline in weight (A) and in body mass index (B).
Abbreviations: CI, Confidence Interval; MD, Mean Difference.

antidiabetic agents. Accordingly, semaglutide 14 mg resulted in a significant decrease by 2.96 kg, compared with placebo, and 1.78 kg, compared with other antidiabetic drug classes, when administered in subjects with T2DM [38].

Of interest, the recently published PIONEER PLUS trial [39] documented that oral semaglutide at even greater doses, equal to 25 mg and 50 mg once daily, were even more efficacious in decreasing HbA1c among subjects with uncontrolled T2DM, with an estimated treatment difference of −0.27 % between semaglutide 25 mg and 14 mg, and of −0.53 % between semaglutide 50 mg and 14 mg. Of course, subjects assigned to higher semaglutide doses achieved significantly greater weight loss, also having significantly greater odds for achieving optimal and ideal glycemic control, defined as HbA1c lower than 7 % and 6.5 %, respectively [39]. Similar to T2DM, in the field of obesity, the recently published OASIS 1 trial [40] showed that semaglutide 50 mg once daily, compared with placebo, resulted in a significant decrease in body weight by 15.1 % at week 68, at the cost of the higher incidence of the well-known gastrointestinal adverse events. Therefore, it appears that oral formulations of GLP-1RAs can also "work well" in subjects with T2DM, obesity, or both, with higher dosing regimens potentially resulting in greater reduction in blood glucose levels and body weight. The question that inevitably arises is what the new, oral, small-molecule GLP-1RAs can offer in the field of "diabesity".

Orforglipron and danuglipron are novel, non-peptide GLP-1RAs, designed for oral administration, biased toward G protein activation over β-arrestin recruitment at the GLP-1 receptor [41]. Indeed, these agents are selective against other, class B, G protein–coupled receptors, with a pharmacokinetic profile favorable for oral route of administration [41]. This action may be therapeutically beneficial, since β-arrestin proteins are associated with receptor internalization, intracellular trafficking, and desensitization [42]. Such a profile of action might, in fact, enhance the efficacy of GLP-1 receptor agonism [43]. The molecular and structural basis of their biological action is discussed elsewhere in detailed reviews [44–46].

Indeed, according to our meta-analysis, those novel, oral GLP-1RAs resulted in a significant decrease in HbA1c by 1.03 %, in FPG by 28.53 mg/dL, in body weight by 4.3 kg and in SBP by 3.48 mmHg. These results seem to be comparable with those achieved with the "classic" doses of oral semaglutide (7 and 14 mg), as shown in the most updated meta-analysis of oral semaglutide in T2DM [10]. Of course, to date, there is no head-to-head RCT to directly compare the efficacy and safety of those novel agents with oral semaglutide in the setting of T2DM, or even of obesity without underlying T2DM.

In addition, we have demonstrated that the use of these novel, oral GLP-1RAs was not associated with increased odds for any serious adverse event and for any adverse event requiring hospitalization, while their use was also not linked with increased odds for any and severe hypoglycemia, similar to other, widely used GLP-1RAs. Of course, as with the "classic" GLP-1RAs, use of those agents was associated with significantly increased odds for gastrointestinal adverse events, mainly vomiting and constipation.

It has to be emphasized that the results of this systematic review and

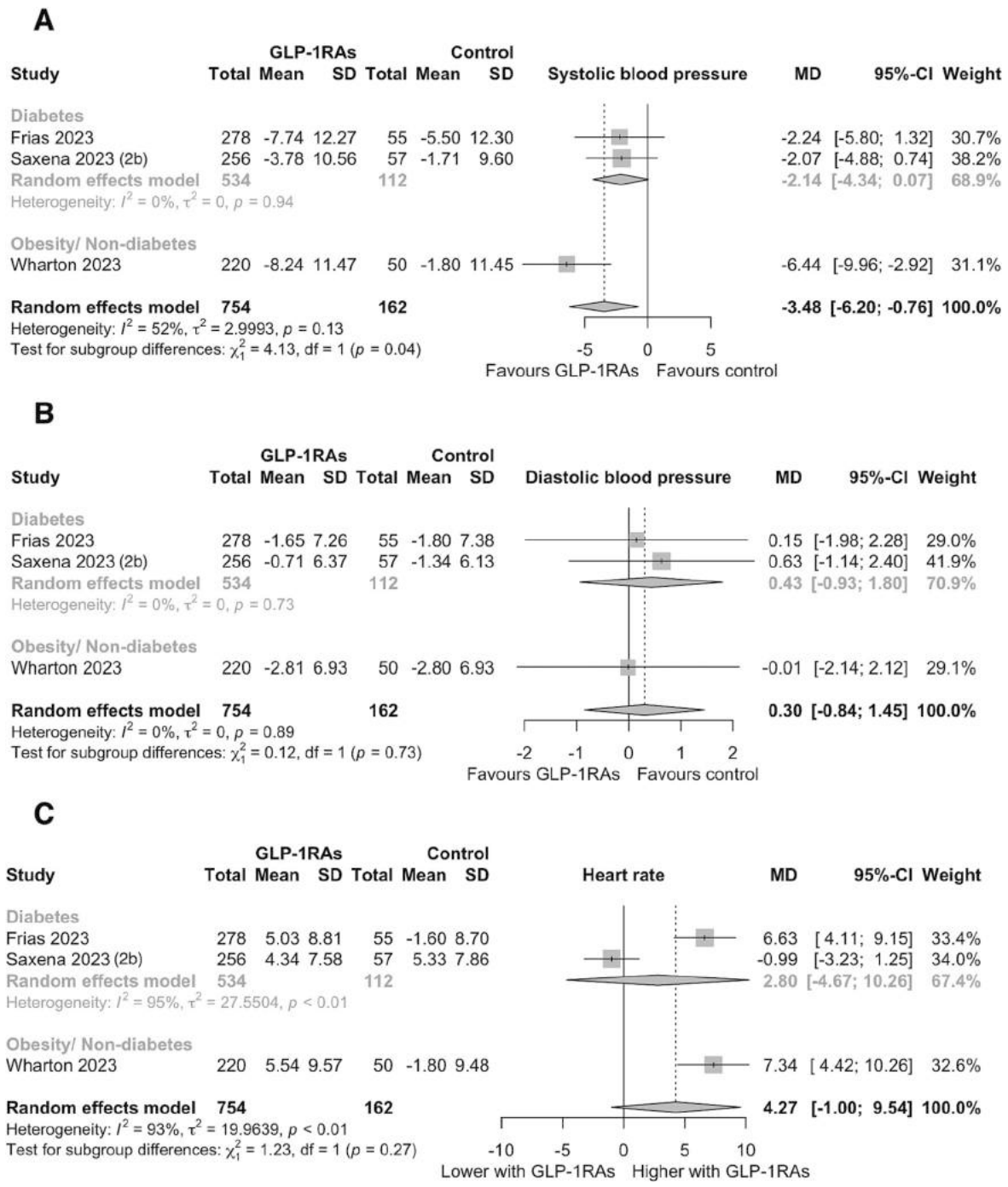

Fig. 3. Forest plots of the effect of small-molecule oral GLP-1RAs vs control: Mean difference in the absolute change from baseline in systolic blood pressure (A), in diastolic blood pressure (B) and in heart rate (C).
Abbreviations: CI, Confidence Interval; MD, Mean Difference.

meta-analysis are rather preliminary, than confirmatory. Two major issues that have to be further addressed are, first, whether those novel oral GLP-1RAs are superior to other, either oral or injectable, GLP-1RAs, which has to be assessed in dedicated, head-to-head RCTs, and, second, whether those novel GLP-1RAs are, at least safe, if not efficacious, in terms of surrogate cardiovascular endpoints, similar to semaglutide, based on the results of the hallmark PIONEER 6 trial [47]. In addition, future RCTs should also address the renal safety of those novel, oral GLP-1RAs, since "classic", injectable GLP-1RAs have established reno-protective effects [48].

Last, but not least, there has been a vivid and ongoing discussion over the last years regarding the risk for malignancy with GLP-1RAs; several, well-conducted systematic reviews and meta-analyses of RCTs, have documented that GLP-1RAs do not increase the risk for any type of cancer, including medullary thyroid and pancreatic cancer, despite initial concerns [49–52], while, synthesis of real-world evidence seems to generate similar results [53]. Thus, it has to be thoroughly assessed in the future RCTs, whether the use of these novel, oral GLP-1RAs is equally safe with "classic" GLP-1RAs, in terms of malignancy occurrence among subjects with T2DM and/or obesity.

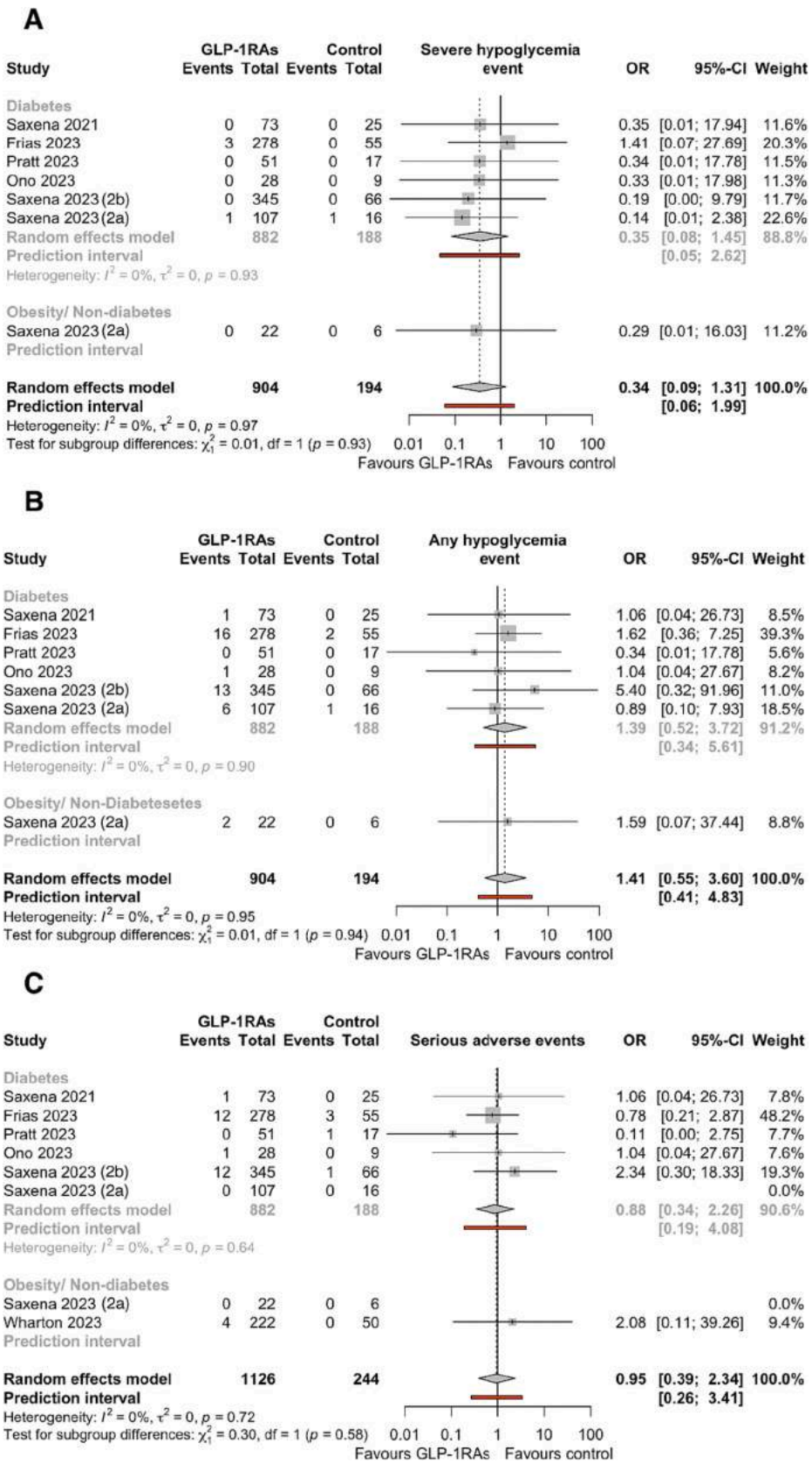

Fig. 4. Forest plots of the effect of small-molecule oral GLP-1RAs vs control: Odds ratio of severe hypoglycemia event (A), any hypoglycemia event (B) and serious adverse events (C).
Abbreviations: CI, Confidence Interval; OR, Odds Ratio.

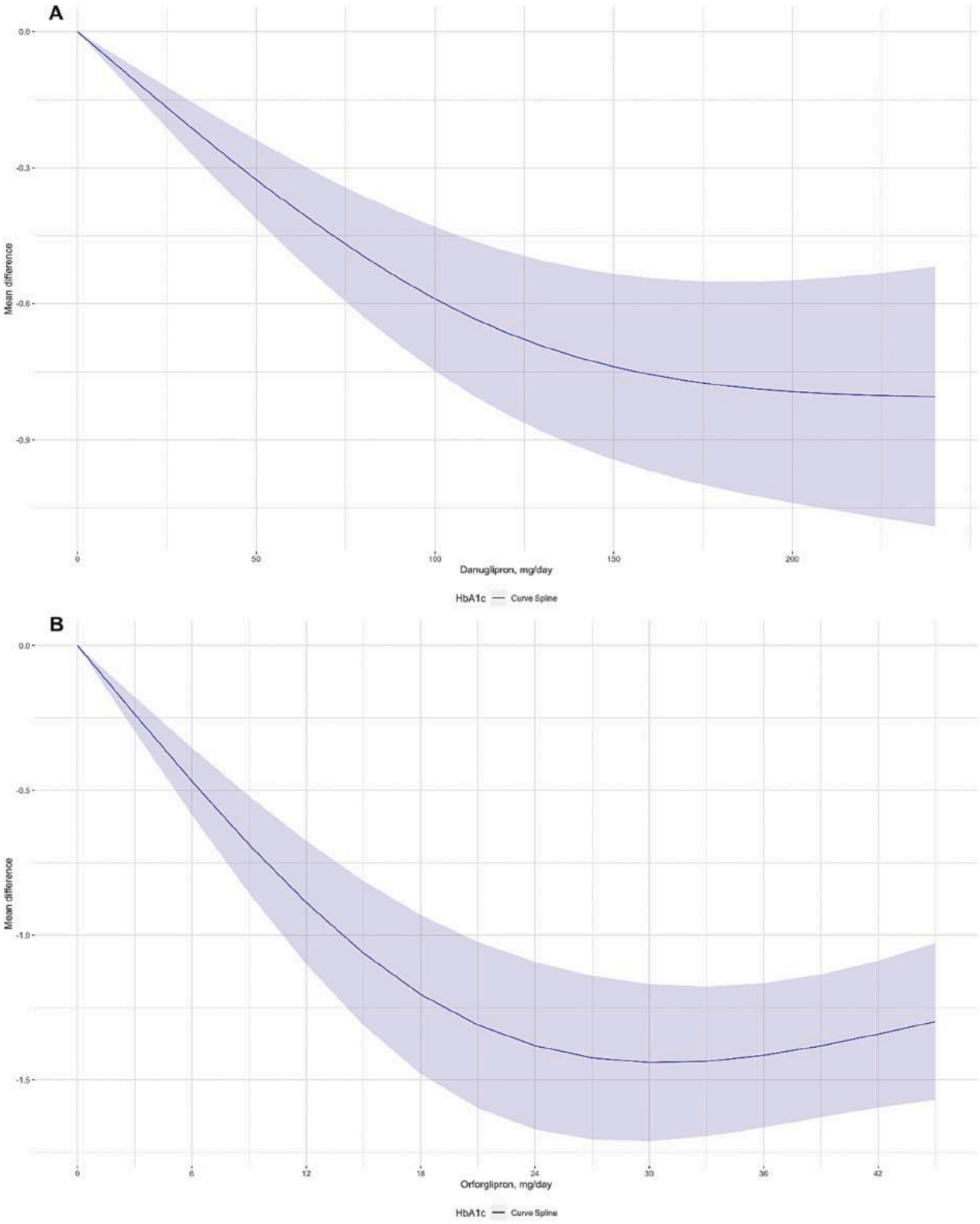

Fig. 5. Pooled dose-response association between Danuglipron (A), Orforglipron (B) and mean change in HbA1c (solid line), compared to placebo. GLP1-RAs dosage was modeled with restricted cubic splines in a random-effects model. Shaded areas represent the 95 % confidence intervals for the spline model.

4.1. Strengths and limitations

While the current study was rigorously conducted following relevant methodological and reporting guidelines, as well as a predefined protocol, there are potential limitations that merit consideration. To begin with, for some outcomes the between-study heterogeneity was substantial, which could be partly attributed to fact that the sample size, length of follow-up and titration algorithms were variable among the identified RCTs. Secondly, investigation on small study effects (including publication bias) was performed only for the primary

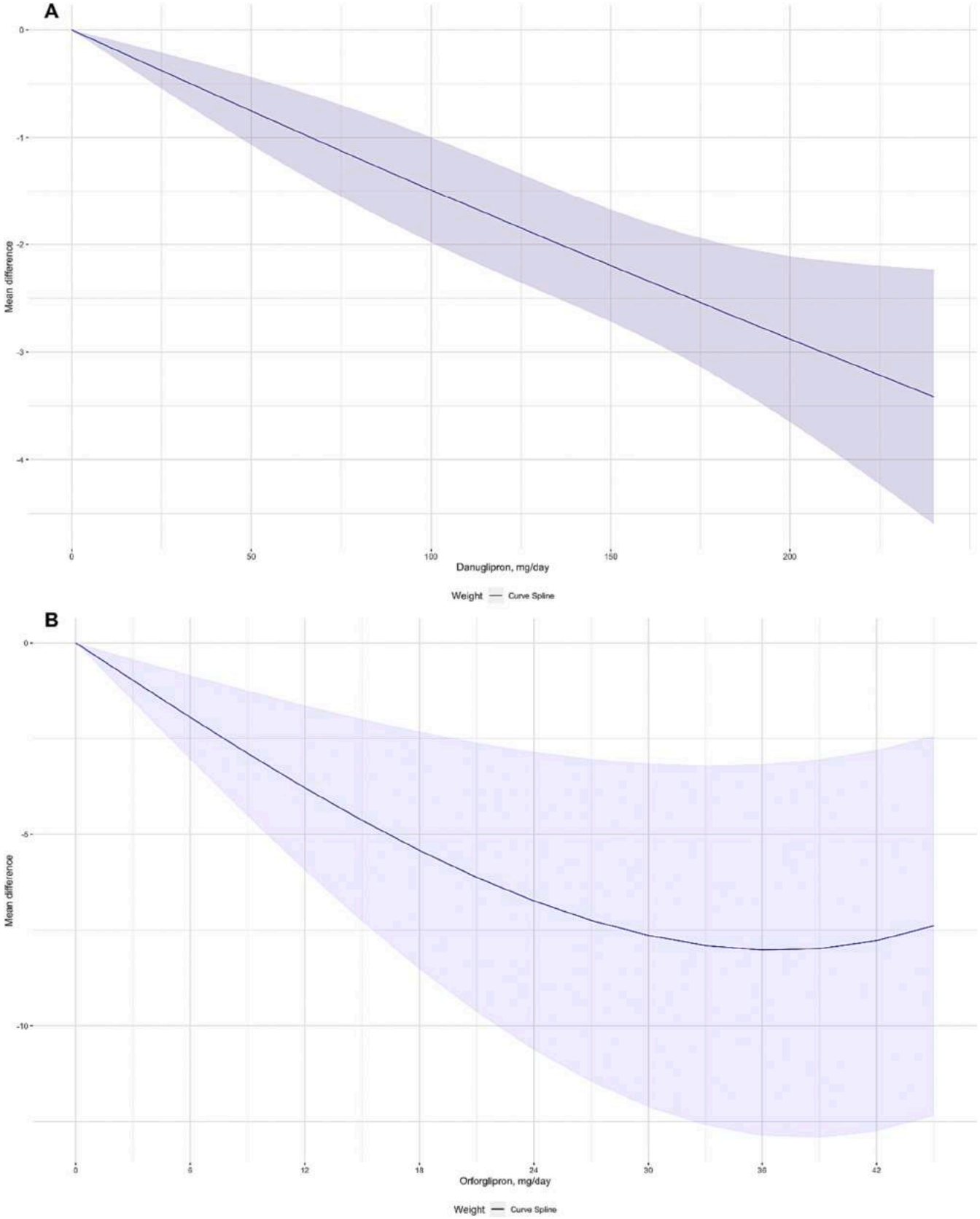

Fig. 6. Pooled dose-response association between Danuglipron (A), Orforglipron (B) and mean change in weight (solid line), compared to placebo. GLP1-RAs dosage was modeled with restricted cubic splines in a random-effects model. Shaded areas represent the 95 % confidence intervals for the spline model.

outcome due to the limited number of existing RCTs and should be interpreted with caution. Thirdly, due to the small number of primary studies, it was not feasible to account for the influence of concurrent hypoglycemic medications through meta-regression analysis.

5. Conclusions

Our preliminary findings suggest that the novel, small-molecule GLP1-RAs constitute an effective and safe option for glycemic management in subjects with T2DM. Notably, these agents lead to a significant weight reduction in patients with obesity, T2DM or both. Further and more longitudinal research is warranted in order to provide deeper knowledge regarding their efficacy, safety and tolerability, along with the assessment of presence of cardio-renal benefits in dedicated cardiovascular and renal outcome trials, similar to commercially available GLP-1RAs. Of course, cost-effectiveness analyses are also required before their potential incorporation in the pharmacological arsenal against T2DM or obesity. Last, but not least, head-to-head comparison between those novel GLP-1RAs and the currently, commercially available GLP-1RAs (especially oral semaglutide) would provide the most powerful insights into their place in the treatment armamentarium against the constantly growing pandemics of T2DM and obesity.

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Consent

Not applicable.

Protocol

The study protocol was prepared a priori and registered in OSF (https://osf.io/rmu7q/).

CRediT authorship contribution statement

Paschalis Karakasis: Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Visualization, Project administration, Writing -original draft, Writing - review & editing. **Dimitrios Patoulias**: Conceptualization, Methodology, Investigation, Project administration, Writing -original draft, Writing - review & editing. **Konstantinos Pamporis**: Writing -original draft, Writing - review & editing. **Panagiotis Stachteas**: Writing -original draft, Writing - review & editing. **Konstantinos I. Bougioukas:** Methodology, Validation, Writing - review & editing. **Alexandra Klisic**: Writing -original draft, Writing - review & editing. **Nikolaos Fragakis:** Methodology, Validation, Writing - review & editing. **Manfredi Rizzo:** Conceptualization, Methodology, Validation, Writing - review & editing, Supervision. **All authors read and approved the final manuscript. P.K. is the guarantor of this work.**

Declaration of competing interest

None declared.

Data availability

The data generated in this research will be shared on reasonable request to the corresponding author.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metabol.2023.155710.

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