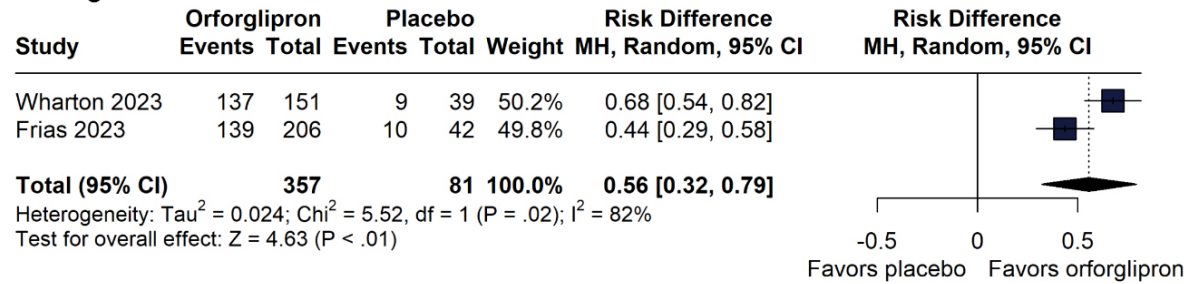
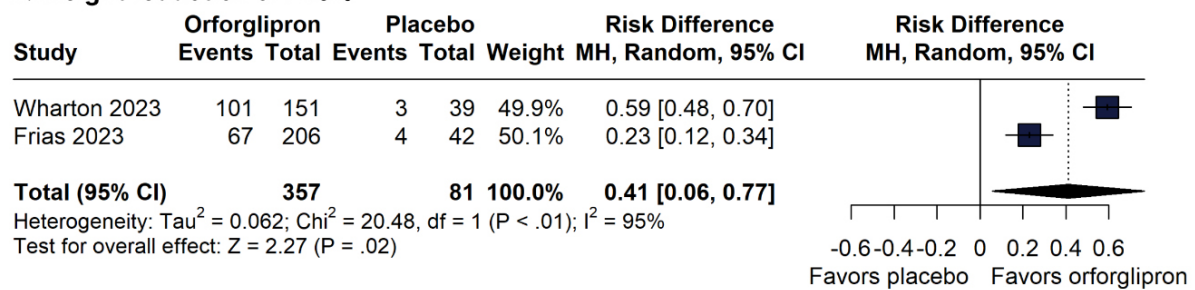
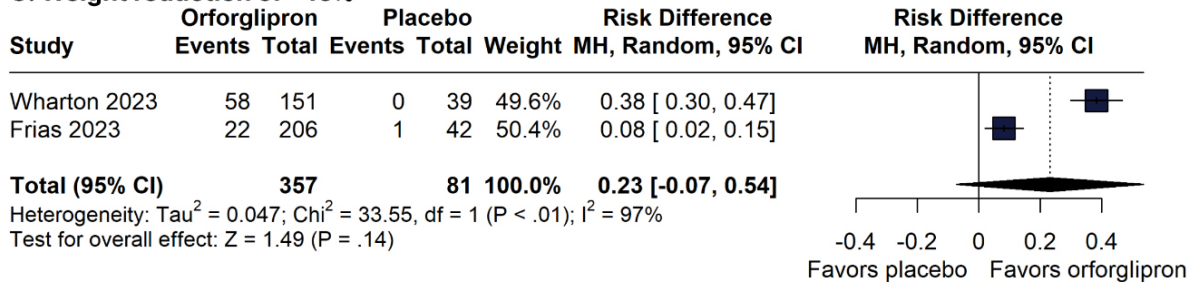
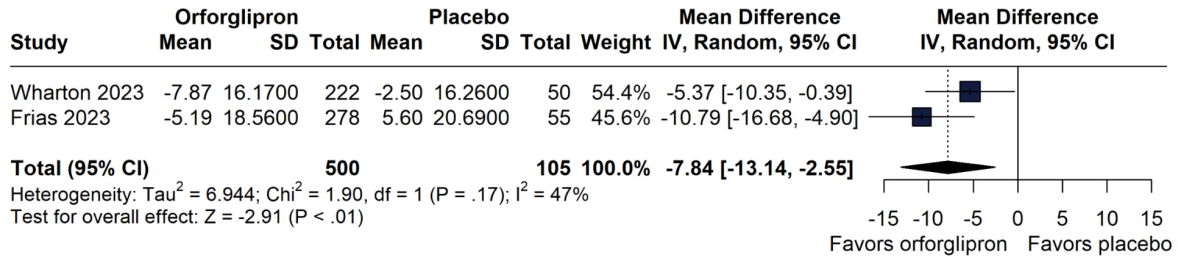
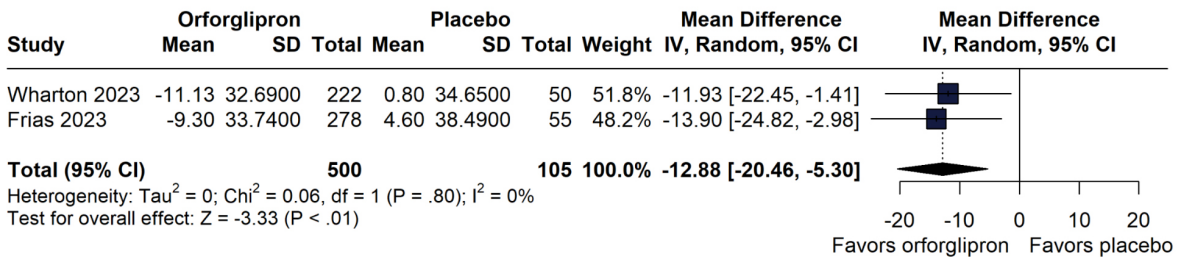
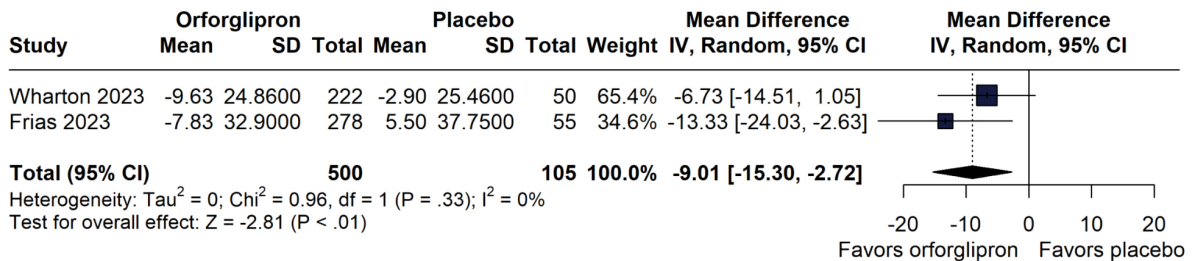
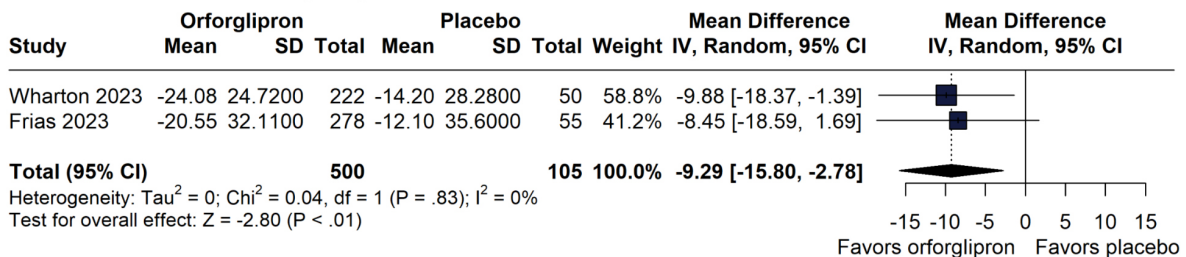


SUPPLEMENTARY MATERIALS

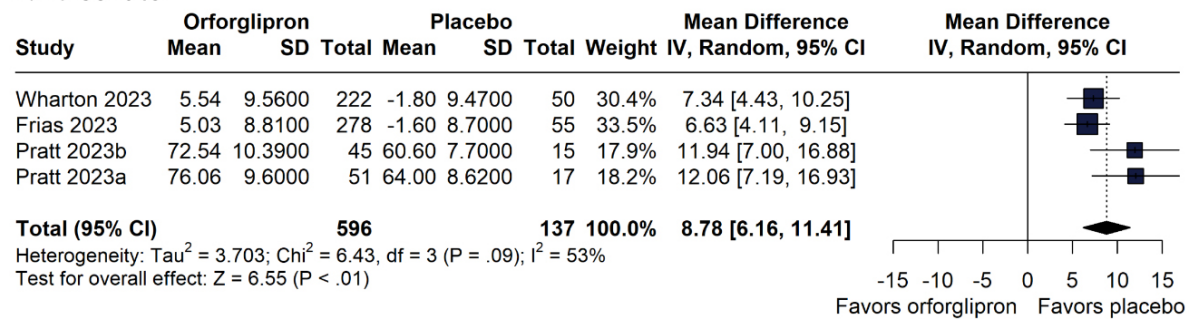
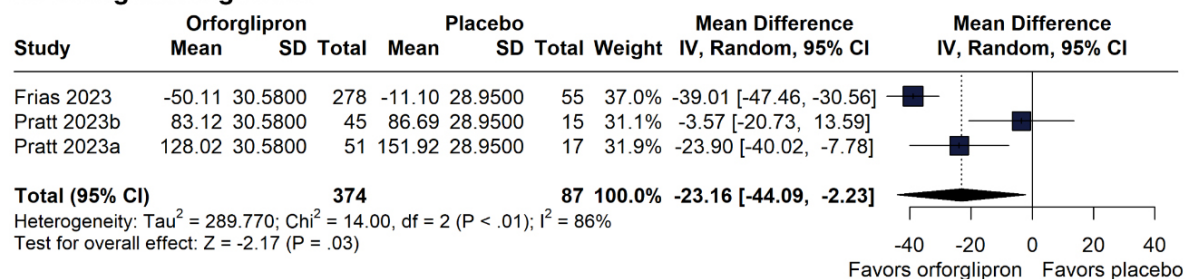
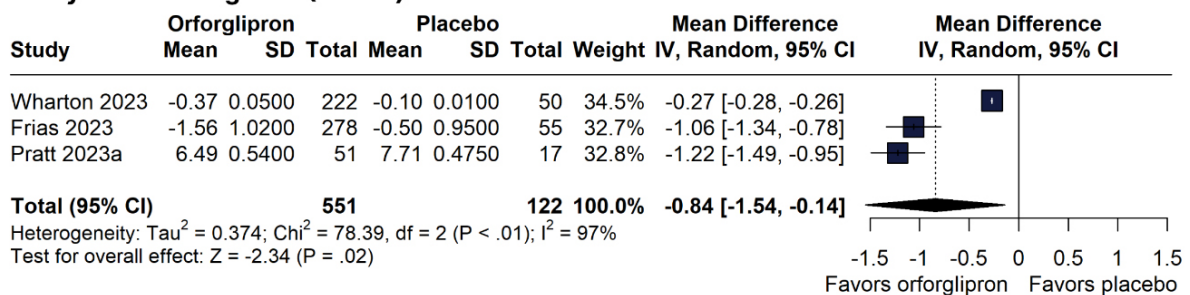
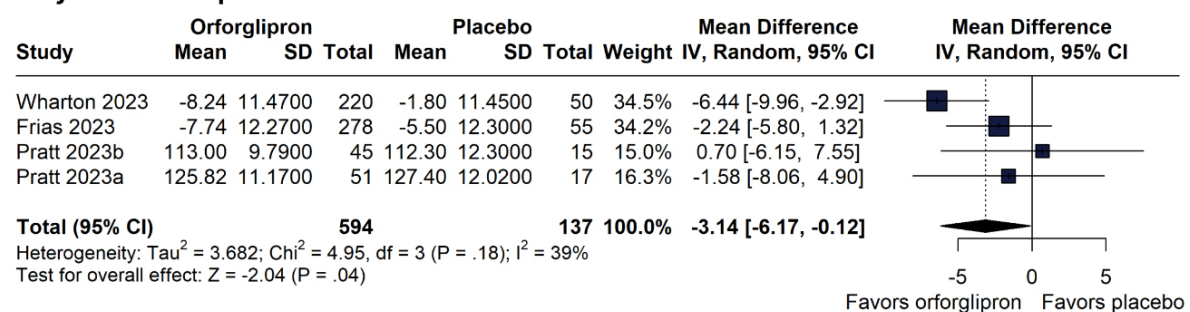
Supplementary Material 1

A. Weight reduction of $\geq 5\%$ B. Weight reduction of $\geq 10\%$ C. Weight reduction of $\geq 15\%$ 

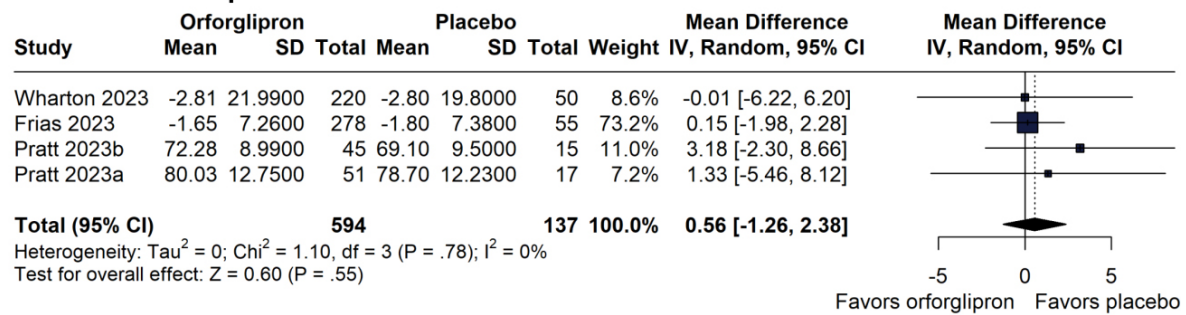
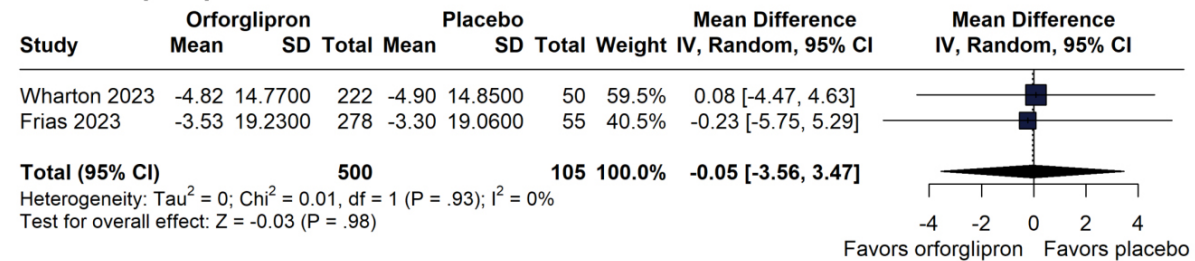
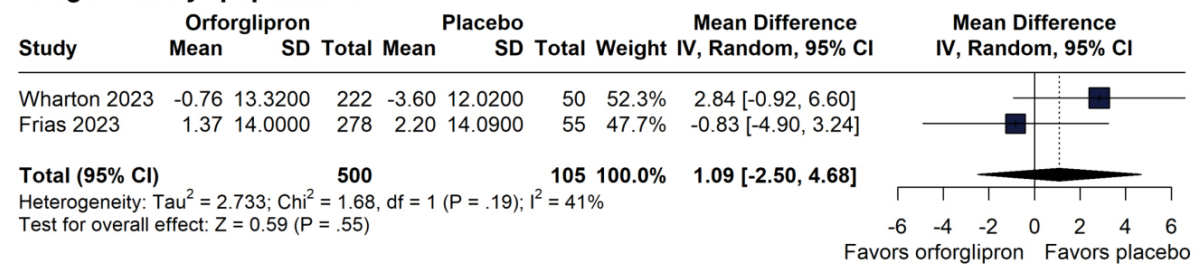
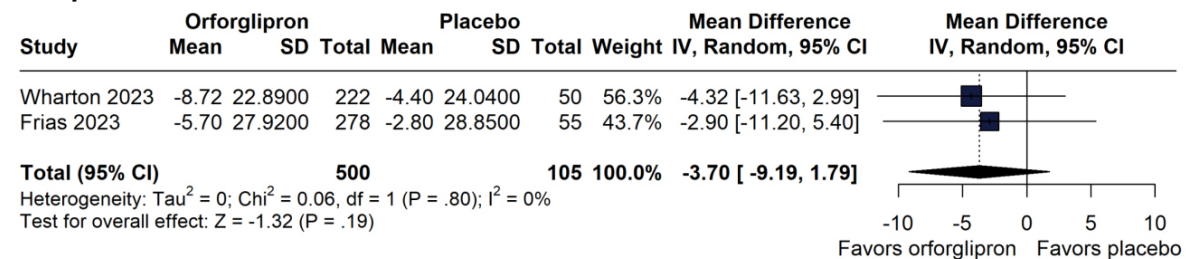
Supplementary Figure 1. Forest plots of pooled comparisons between orforglipron and placebo, with risk differences. **(A)** Weight reduction of $\geq 5\%$. **(B)** Weight reduction of $\geq 10\%$. **(C)** Weight reduction of $\geq 15\%$.

A. Total cholesterol**B. Triglycerides****C. Low-density lipoprotein (LDL)****D. Alanine transaminase (ALT)**

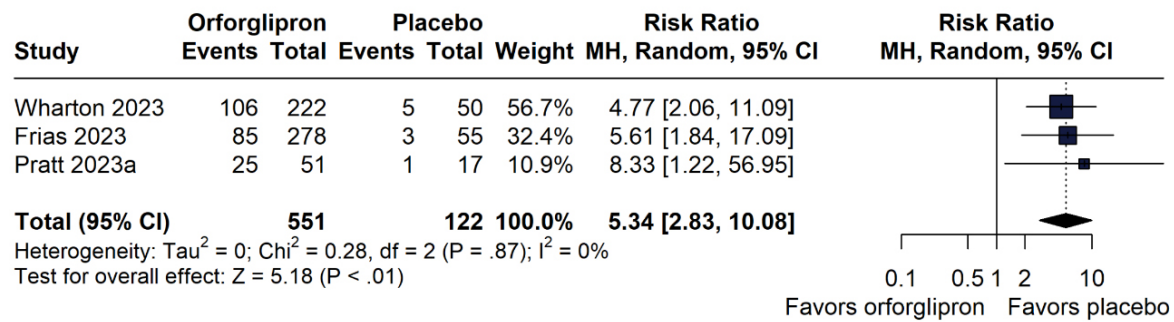
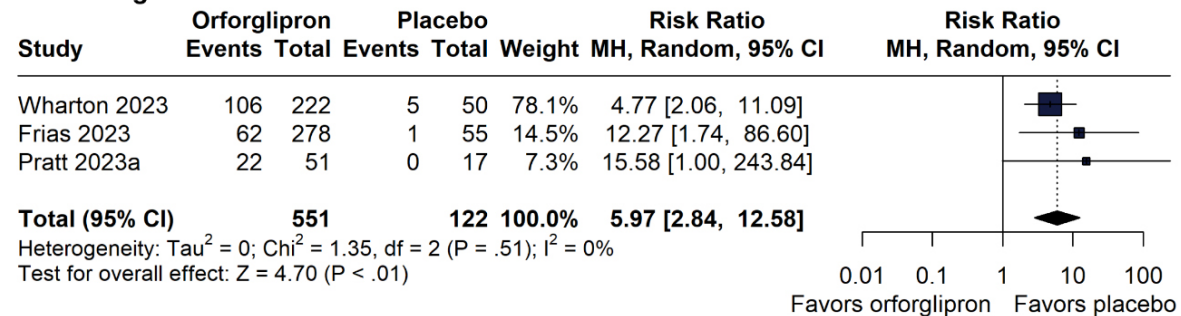
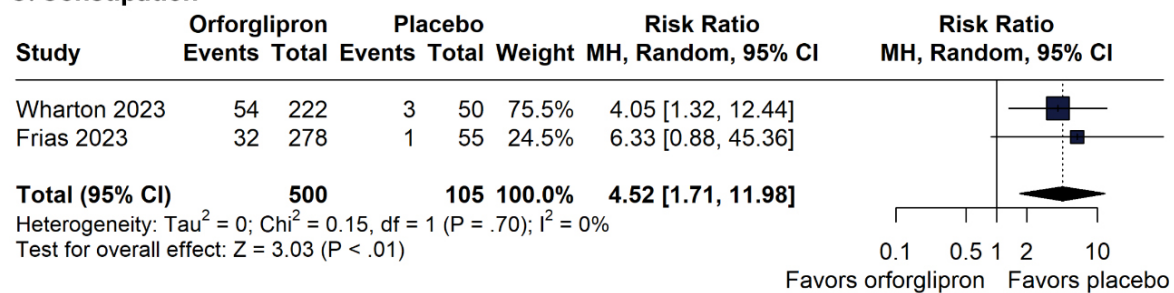
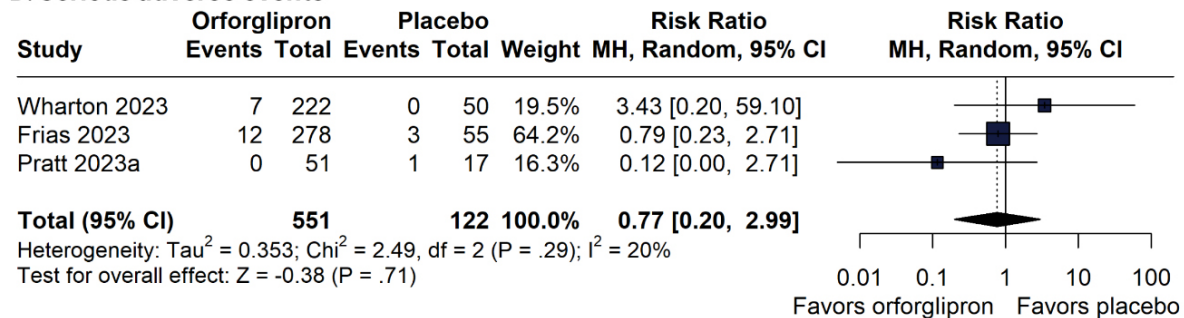
Supplementary Figure 2. Forest plots of pooled comparisons between orforglipron and placebo. (A) Total cholesterol. (B) Triglycerides. (C) Low-density lipoprotein (LDL) cholesterol. (D) Alanine transaminase (ALT).

A. Pulse rate**B. Fasting serum glucose****C. Glycated hemoglobin (HbA1c)****D. Systolic blood pressure**

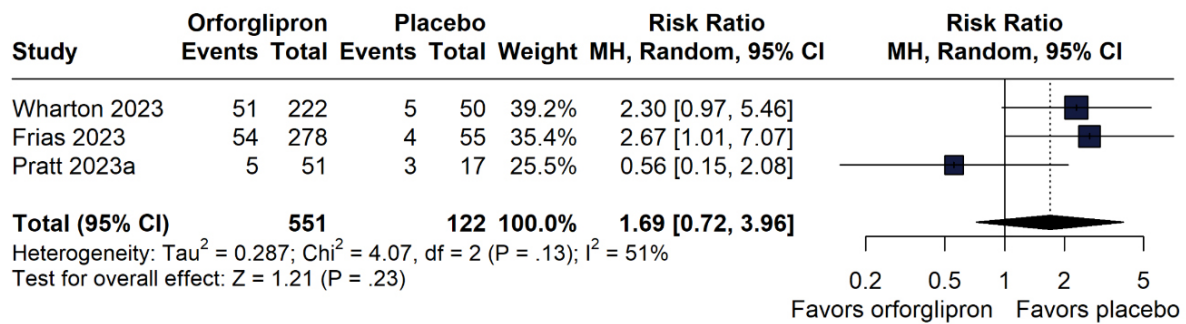
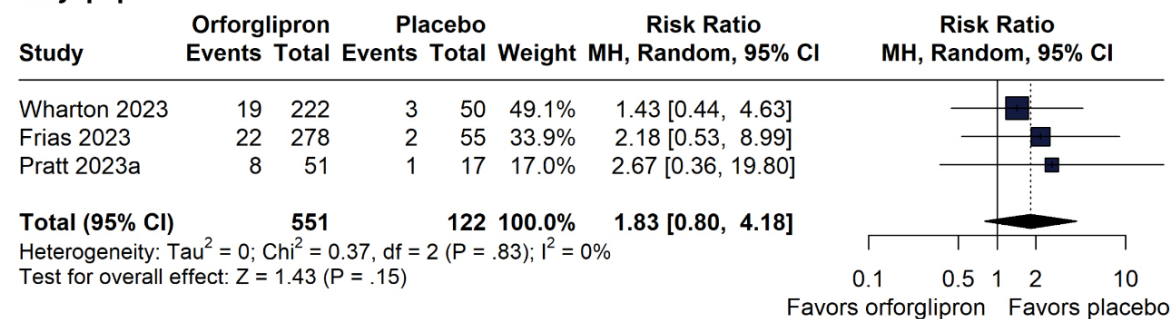
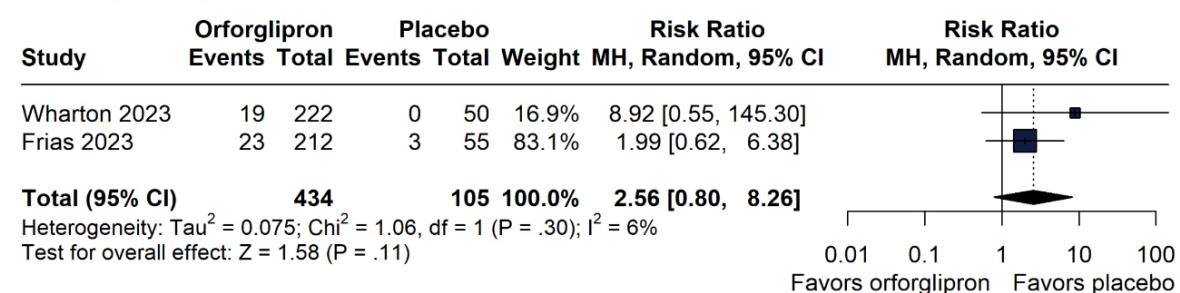
Supplementary Figure 3. Forest plots of pooled comparisons between orforglipron and placebo. (A) Pulse rate. (B) Fasting serum glucose. (C) Glycated hemoglobin (HbA1c). (D) Systolic blood pressure.

A. Diastolic blood pressure**B. Alkaline phosphatase****C. High-density lipoprotein (HDL)****D. Aspartate aminotransferase (AST)**

Supplementary Figure 4. Forest plots of pooled comparisons between orforglipron and placebo. **(A)** Diastolic blood pressure. **(B)** Alkaline phosphatase. **(C)** High-density lipoprotein (HDL) cholesterol. **(D)** Aspartate aminotransferase (AST).

A. Nausea**B. Vomiting****C. Constipation****D. Serious adverse events**

Supplementary Figure 5. Forest plots of pooled comparisons between orforglipron and placebo. (A) Nausea. (B) Vomiting. (C) Constipation. (D) Serious adverse events.

A. Diarrhea**B. Dyspepsia****C. Cardiac disorders****Supplementary Figure 6.** Forest plots of pooled comparisons between orforglipron and placebo. (A) Diarrhea. (B) Dyspepsia. (C) Cardiac disorders.

		Risk of bias domains					Overall
		D1	D2	D3	D4	D5	
Study	Wharton 2023	+	-	+	+	+	-
	Frias 2023	+	-	+	+	+	-
	Pratt 2023a	+	-	+	+	+	-
	Pratt 2023b	+	-	+	+	+	-

Domains:
 D1: Bias arising from the randomization process.
 D2: Bias due to deviations from intended intervention.
 D3: Bias due to missing outcome data.
 D4: Bias in measurement of the outcome.
 D5: Bias in selection of the reported result.

Judgement
 - Some concerns
 + Low

Supplementary Figure 7. Critical appraisal of randomized controlled trials according to the Cochrane Collaboration tool for assessing risk of bias in randomized trials.

Supplementary Material 2

Effects of Once-Daily Oral Orforglipron on Weight and Metabolic Markers: A Systematic Review and Meta-analysis of Randomized Controlled Trials

Bibliography: Lüttemeyer et al.

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 [Placebo]	With Orforglipron		Risk with [Placebo]	Risk difference with Orforglipron
Weight Reduction (kg)											
733 (4 RCTs)	serious ^a	serious ^{b,c}	not serious	not serious	none	⊕⊕⊕⊕ Low	137	596	-		MD 6.14 lower (9.62 lower to 2.66 lower)
BMI (kg/m ²)											
605 (2 RCTs)	serious ^a	serious ^{b,c}	not serious	serious ^d	none	⊕⊕⊕⊕ Very low	105	500	-		MD 2.87 lower (4.56 lower to 1.1 lower)
Waist Circumference (cm)											
605 (2 RCTs)	serious ^a	serious ^{b,c}	not serious	serious ^d	none	⊕⊕⊕⊕ Very low	105	500	-		MD 5.32 lower (9.13 lower to 1.51 lower)
Weight Reduction ≥ 5%											
438 (2 RCTs)	serious ^a	serious ^b	not serious	serious ^d	none	⊕⊕⊕⊕ Very low	19/81 (23.5%)	276/357 (77.3%)	RR 3.31 (2.23 to 4.93)	235 per 1,000	542 more per 1,000 (from 289 more to 922 more)
Weight Reduction ≥ 10%											
438 (2 RCTs)	serious ^a	serious ^b	not serious	serious ^d	none	⊕⊕⊕⊕ Very low	7/81 (8.6%)	168/357 (47.1%)	RR 5.24 (2.07 to 13.31)	86 per 1,000	366 more per 1,000 (from 92 more to 1,000 more)
Weight Reduction ≥ 15%											
438 (2 RCTs)	serious ^a	serious ^b	not serious	serious ^d	none	⊕⊕⊕⊕ Very low	1/81 (1.2%)	80/357 (22.4%)	RR 9.53 (1.26 to 71.89)	12 per 1,000	105 more per 1,000 (from 3 more to 875 more)
HbA1c (%)											
673 (3 RCTs)	serious ^a	serious ^{b,c}	not serious	serious ^e	none	⊕⊕⊕⊕ Very low	122	551	-		MD 0.84 lower (1.54 lower to 0.14 lower)

CI: confidence interval; MD: mean difference; RR: risk ratio

Explanations

- a. All studies had some concerns about risk of bias.
- b. Heterogeneity between studies due to differences in baseline patient characteristics.
- c. High heterogeneity.
- d. Only 2 studies reported the outcome.
- e. Only 3 studies reported the outcome.