

Supplementary Materials

Efficacy and Safety of Orforglipron in Obesity with Type 2 Diabetes Mellitus: A GRADE-Assessed Meta-analysis of Randomized Controlled Trials.

The authors have provided this supplementary material to demonstrate additional information about this study.

Supplementary Table I PRISMA 2020 checklist.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title page
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 4,5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 4,5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 6,7, subsection 2.3
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 6, subsection 2.2
Search strategy	7	Present the full search strategies for all databases, registers, and websites, including any filters and limits used.	Page 6, subsection 2.2 Sup. material, table S2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 7,8, subsection 2.4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 7,8, subsection 2.5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 6,7, subsection 2.3
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 6,7, subsection 2.3
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 8, subsection 2.6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 9,10, subsection 2.7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the	Page 7,8, subsection 2.4

Section and Topic	Item #	Checklist item	Location where item is reported
		planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 9,10, subsection 2.7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 9,10, subsection 2.7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 9,10, subsection 2.7
	13e	Describe any methods used to explore plausible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 10 subsection 2.7.3
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 10 subsection 2.7.3
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Not applicable
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 8,9, subsection 2.6
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 12, subsection 3.1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 12, subsection 3.1
Study characteristics	17	Cite each included study and present its characteristics.	Table 1 & 2, Page 12, subsection 3.2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 12,13, subsection 3.3
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimates and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Pages 13-20, subsections 3.4-3.5
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 12,13, subsection 3.3
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Pages 13-20, subsections 3.4-3.5
	20c	Present results of all investigations of plausible causes of heterogeneity among study results.	Pages 13-20, subsections 3.4-3.5
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Pages 13-20, subsections 3.4-3.5

Section and Topic	Item #	Checklist item	Location where item is reported
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Not applicable
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 19, subsection 3.6 Table S4
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 22
	23b	Discuss any limitations of the evidence included in the review.	Page 25-27
	23c	Discuss any limitations of the review processes used.	Page 25-27
	23d	Discuss implications of the results for practice, policy, and future research.	Page 24, 25
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 6, subsection 2.1
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 6, subsection 2.1
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Page 6, subsection 2.1
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 29 Section 5
Competing interests	26	Declare any competing interests of review authors.	Page 29 Section 5
Availability of data, code, and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 29 Section 5

Supplementary Table 2 Search Strategy and Literature Search.

Database	Filters	Access Date	Search Strategy	No of Results
PubMed	All Fields	20/1/2026	(Orforglipron OR orforglipron OR LY3502970 OR "oral GLP-1 receptor agonist") AND ("Type 2 Diabetes Mellitus" OR "type 2 diabetes" OR T2DM) AND (obesity OR overweight OR "body weight" OR "body mass index") AND ("clinical trial" OR "controlled trial" OR randomiz* OR randomis* OR randomly OR random OR RCT OR blind*)	19
Cochrane	All Text	20/1/2026	(Orforglipron OR LY3502970 OR "oral GLP-1 receptor agonist") AND ("Type 2 Diabetes Mellitus" OR "type 2 diabetes" OR T2DM) AND (obesity OR overweight OR "body weight" OR "body mass index") AND ("clinical trial" OR "controlled trial" OR randomiz* OR randomis* OR randomly OR random OR RCT OR blind*)	18
Scopus	All Fields	20/1/2026	(Orforglipron OR LY3502970 OR "oral GLP-1 receptor agonist") AND ("Type 2 Diabetes Mellitus" OR "type 2 diabetes" OR T2DM) AND (obesity OR overweight OR "body weight" OR "body mass index") AND ("clinical trial" OR "controlled trial" OR randomiz* OR randomis* OR randomly OR random OR RCT OR blind*)	552
Web of Science	All Fields	20/1/2026	(Orforglipron OR LY3502970 OR "oral GLP-1 receptor agonist") AND ("Type 2 Diabetes Mellitus" OR "type 2 diabetes" OR T2DM) AND (obesity OR overweight OR "body weight" OR "body mass index") AND ("clinical trial" OR "controlled trial" OR randomiz* OR randomis* OR randomly OR random OR RCT OR blind*)	23
Total				612

Supplemental Table 3 Excluded studies with reasons in the full-text screening.

Study ID	Title	Reason for Exclusion	DOI
Wharton et al., 2023	Daily Oral GLP-I Receptor Agonist Orforglipron for Adults with Obesity	Wrong population: enrolled adults with obesity without T2DM; does not meet population criterion	doi: 10.1056/NEJMoa2302392
Wharton et al., 2025	Orforglipron, an Oral Small-Molecule GLP-I Receptor Agonist for Obesity Treatment	Wrong population: enrolled adults with obesity without T2DM; does not meet population criterion	doi: 10.1056/NEJMoa2511774
Dutta et al., 2024	Orforglipron, a novel non-peptide oral daily glucagon-like peptide-I receptor agonist as an anti-obesity medicine: A systematic review and meta-analysis	Review article: systematic review/meta-analysis, not a primary RCT	doi: 10.1002/osp4.743
Lütkemeyer et al., 2024	Effects of once-daily oral orforglipron on weight and metabolic markers: systematic review and meta-analysis	Review article: systematic review/meta-analysis, not a primary RCT	doi: 10.20945/2359-4292-2023-0469
Kansakar et al. 2026	Orforglipron: A Comprehensive Review of an Oral Small-Molecule GLP-I Receptor Agonist for Obesity and Type 2 Diabetes	Review article: Narrative Review	doi: 10.3390/ijms27031409
Panou et al. 2025	Orforglipron in type 2 diabetes mellitus and obesity: an overview	Review article: Narrative Review	doi:10.1080/17512433.2025.2594493
Seetharaman et al. 2024	Can small molecule GLP-I agonists be the next first-line drugs in type-2 diabetes mellitus?	Editorial	doi: 10.1515/jbcpp-2023-0234

Supplementary Table 4. Minimal Clinically Important Differences (MCID) for Reported Outcomes.

Outcome	Domain	Observed effect (dose range)	MCID threshold	Crosses MCID?	MCID source
Body weight (%)	Efficacy	−2.43% to −7.80% (by dose)	≥5%	✓ At doses ≥24 mg ✗ At doses ≤12 mg	FDA/EMA obesity threshold
BMI (kg/m²)	Efficacy	−0.88 to −2.70 (by dose)	≥1 kg/m ²	✓ At doses ≥12 mg ✗ At 3–6 mg	Clinical consensus
Waist circumference (cm)	Efficacy	−1.53 to −5.90 (by dose)	≥2–3 cm	✓ At doses ≥12 mg ✗ At 3 mg	IDF/WHO cardiometabolic risk
HbA1c (%)	Efficacy	−0.75% to −1.67% (by dose)	≥0.5%	✓ All doses	ADA Standards of Care 2024
Fasting serum glucose (mg/dL)	Efficacy	−20.62 to −44.80 (by dose)	~18–20 mg/dL	✓ All doses	ADA glycemic targets
LDL-C (%)	Efficacy	+3.40% to −13.80% (by dose)	≥10%	✓ At 45 mg only ✗ At doses ≤36 mg	ACC/AHA lipid guidelines
HDL-C (%)	Efficacy	−0.63% to +4.48% (by dose)	≥5%	✗ No dose met threshold	ACC/AHA lipid guidelines
Total cholesterol (%)	Efficacy	−0.70% to −12.60% (by dose)	≥10%	✓ At 45 mg only ✗ At doses ≤36 mg	Clinical consensus
Triglycerides (%)	Efficacy	−4.18% to −20.70% (by dose)	≥15%	✓ At 45 mg only ✗ At doses ≤36 mg	Endocrine Society guidelines
SBP (mmHg)	Efficacy	−1.20 to −4.29 (by dose)	≥5 mmHg	✗ No dose met threshold	ESC/ESH Hypertension Guidelines 2023
DBP (mmHg)	Efficacy	−0.50 to +0.20 (by dose)	≥3–5 mmHg	✗ No dose met threshold	ESC/ESH Hypertension Guidelines 2023
Heart rate (bpm)	Safety	+3.00 to +7.20 (by dose)	<8–10 bpm (clinically neutral zone)	✗ All doses within neutral zone	ACC/AHA; GLP-1RA class data
AEs leading to discontinuation (RR)	Safety	RR 1.32–3.51 (by dose)	RR >1.5 (meaningful excess risk)	✓ At 3, 12, 24, 36 mg ✗ At 6, 45 mg	Clinical judgment threshold
Serious AEs (RR)	Safety	RR 0.29–1.95 (by dose)	RR >1.5 or <0.67	✗ No dose met threshold	Clinical judgment threshold
Hypoglycemia (RR)	Safety	RR 1.93–4.79 (by dose)	RR >2.0 (doubled risk)	✓ At 36 mg (RR 4.38) ✗ Other doses	ADA hypoglycemia risk threshold
Rescue therapy for hyperglycemia (RR)	Safety	RR 0.12–0.50 (by dose)	RR <0.80 (meaningful reduction)	✓ All doses except 24 mg	Clinical glycemic management

Abbreviations: MCID, minimal clinically important difference; ADA, American Diabetes Association; ACC/AHA, American College of Cardiology/American Heart Association; ESC/ESH, European Society of Cardiology/European Society of Hypertension; IDF, International Diabetes Federation; FDA, Food and Drug Administration; EMA, European Medicines Agency; bpm, beats per minute; RR, risk ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HbA1c, glycated hemoglobin; AE: adverse event. For each outcome, the observed pooled effect (dose-subgroup range) is compared against the established or consensus-based MCID threshold. Green shading = effect crosses MCID at all doses; yellow = crosses MCID at higher doses only; red = does not meet MCID at any dose.

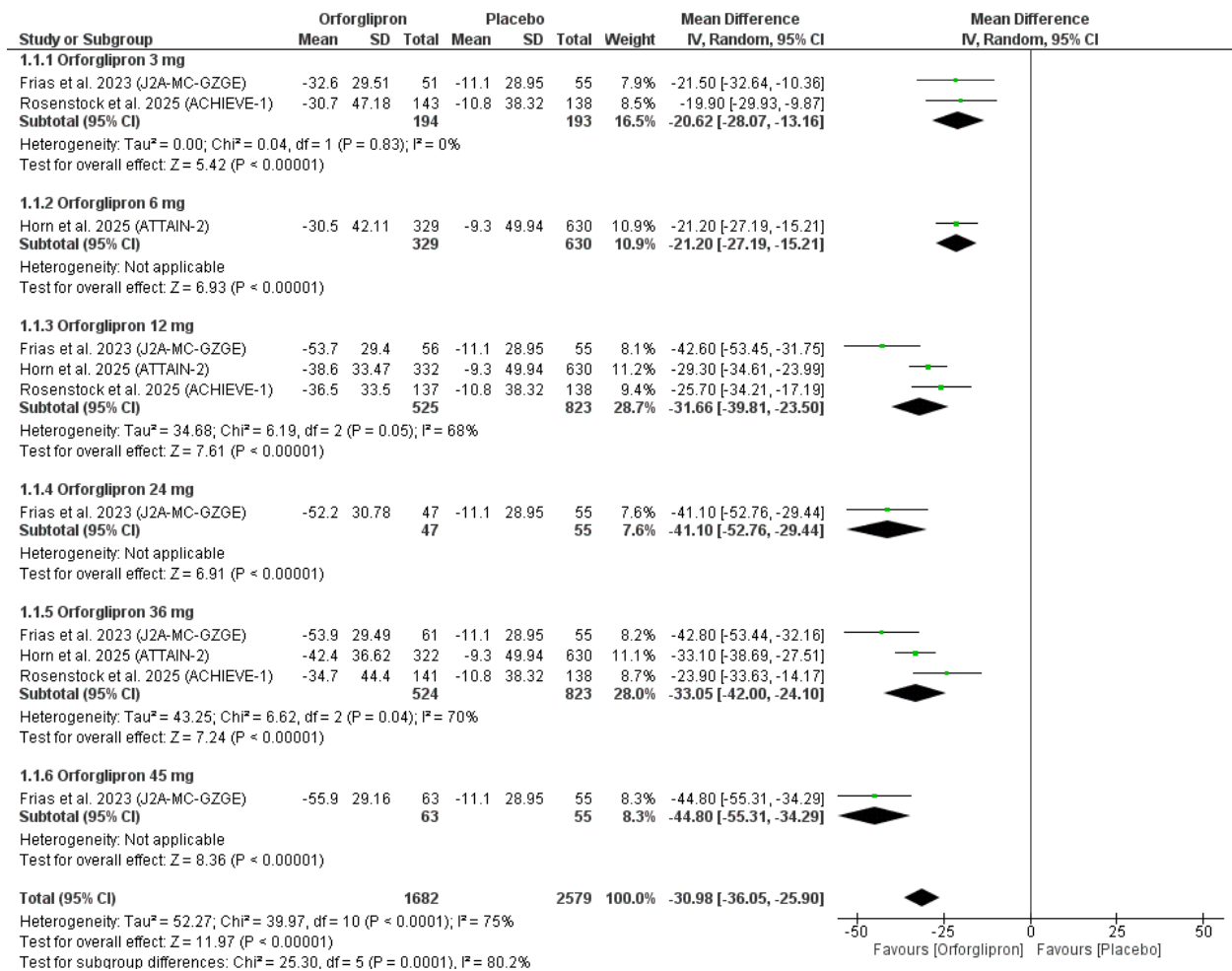
Supplementary Table 5. Grading of recommendations assessment, development, and evaluation.

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Orforglipron	Placebo	Relative (95% CI)	Absolute (95% CI)	
Change in BMI ^a (3)	randomised trials	serious ^b	serious ^c	not serious	not serious	none	1610	2453	-	MD 1.75 lower (2.16 lower to 1.35 lower)	⊕⊕○○ Low ^{b,c}
Percentage change in body weight ^a (3)	randomised trials	serious ^b	serious ^c	not serious	not serious	none	1682	2579	-	MD 5 lower (6.21 lower to 3.78 lower)	⊕⊕○○ Low ^{b,c}
Change in waist circumference ^a (3)	randomised trials	serious ^b	serious ^c	not serious	not serious	none	1610	2453	-	MD 3.68 lower (4.76 lower to 2.61 lower)	⊕⊕○○ Low ^{b,c}
Change in HbA1c ^a (3)	randomised trials	serious ^b	serious ^c	not serious	not serious	none	1682	2579	-	MD 1.14 lower (1.32 lower to 0.97 lower)	⊕⊕○○ Low ^{b,c}
Serious adverse events ^a (3)	randomised trials	serious ^b	not serious	not serious	serious ^d	none	124/1679 (7.4%)	195/2573 (7.6%)	RR 1.09 (0.87 to 1.35)	7 more per 1,000 (from 10 fewer to 27 more)	⊕⊕○○ Low ^{b,d}
Adverse events leading to discontinuation ^a (3)	randomised trials	serious ^b	not serious	not serious	not serious	none	0/0	0/0	RR 2.20 (1.72 to 2.82)	2 fewer per 1,000 (from 3 fewer to 2 fewer)	⊕⊕⊕○ Moderate ^b
Incidence of hypoglycaemia ^a (3)	randomised trials	serious ^b	not serious	not serious	not serious	none	26/1679 (1.5%)	9/2573 (0.3%)	RR 3.81 (1.84 to 7.86)	10 more per 1,000 (from 3 more to 24 more)	⊕⊕⊕○ Moderate ^b

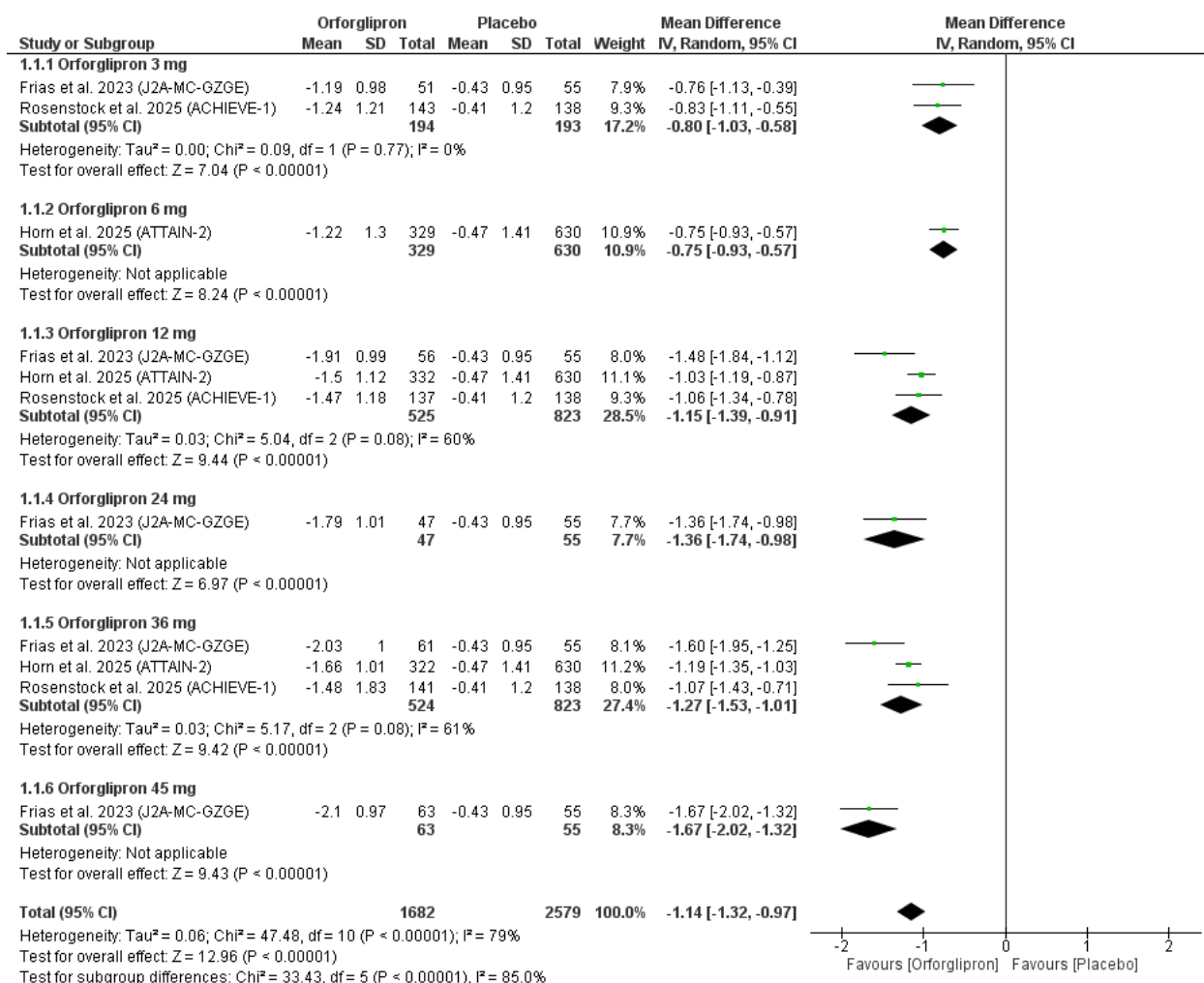
CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

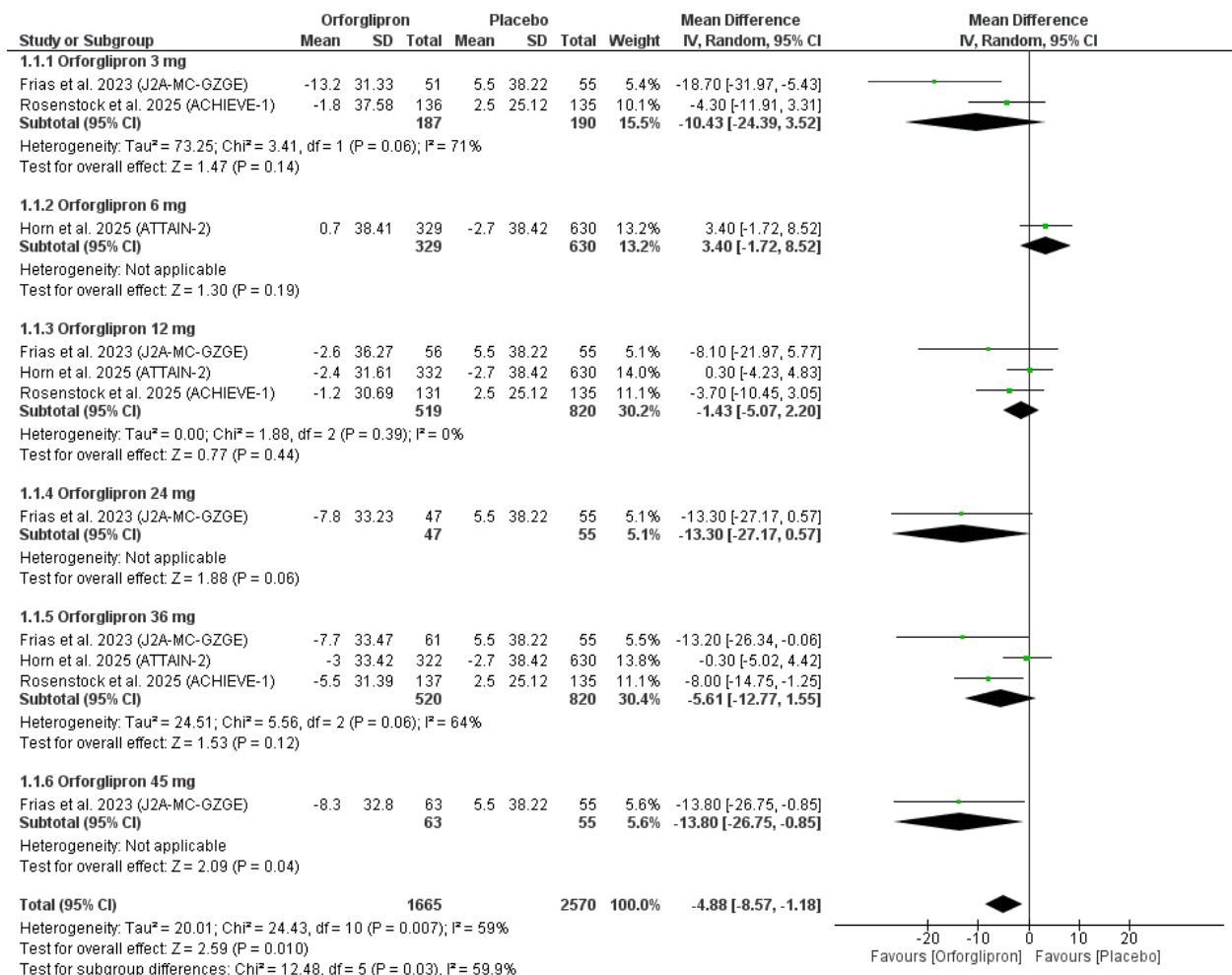
- a. Pooled across all orforglipron doses (3–45 mg) vs placebo at the main follow-up time.
- b. One of the three contributing trials was judged at high risk of bias
- c. $I^2 \geq 50\%$
- d. The 95% confidence interval around the pooled RR (0.87 to 1.35) includes both a possible important reduction and a possible important increase in serious adverse events, so we downgraded one level for imprecision.



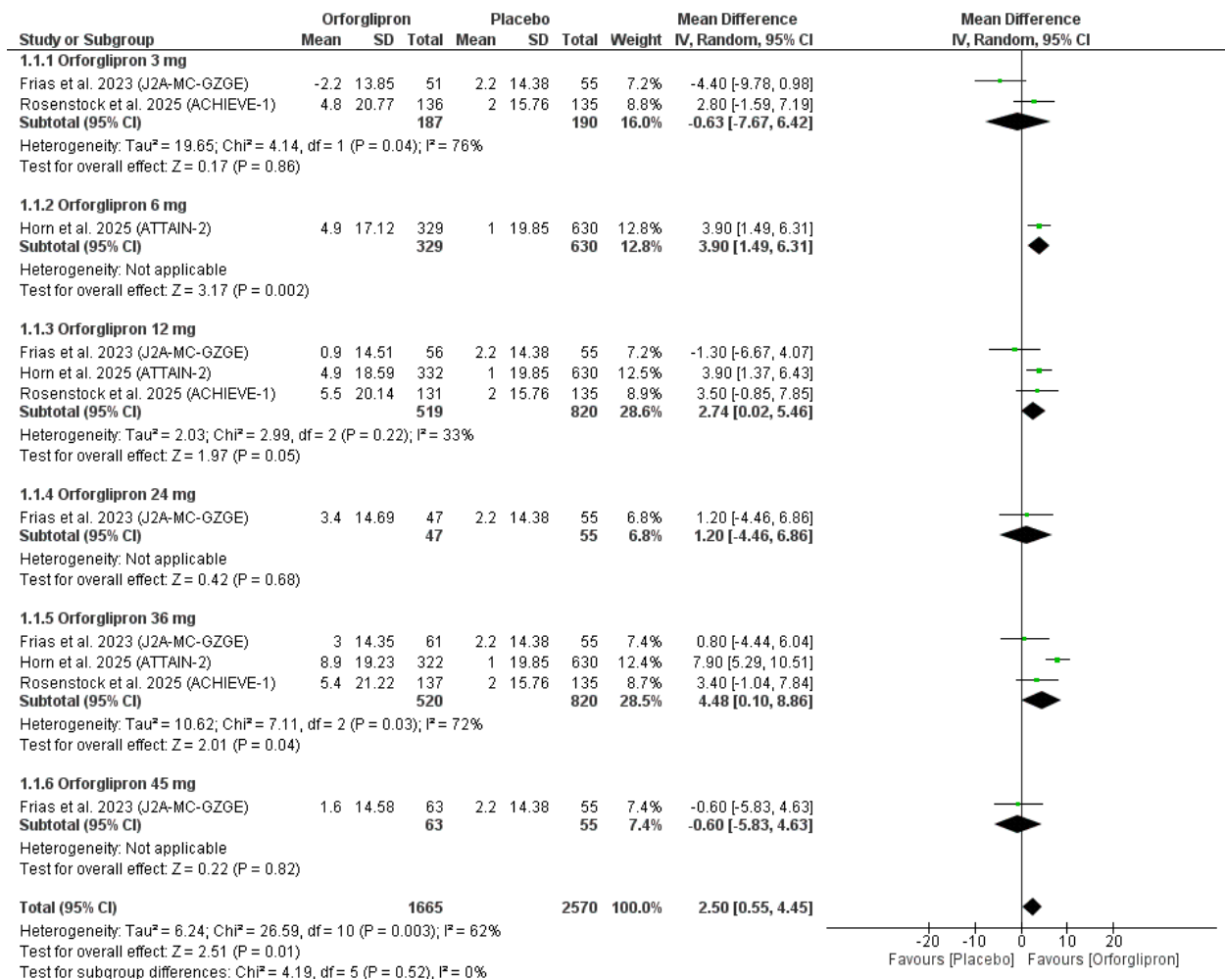
Supplementary Figure I. Forest plot of Change in Fasting Serum Glucose in Mg/dL.



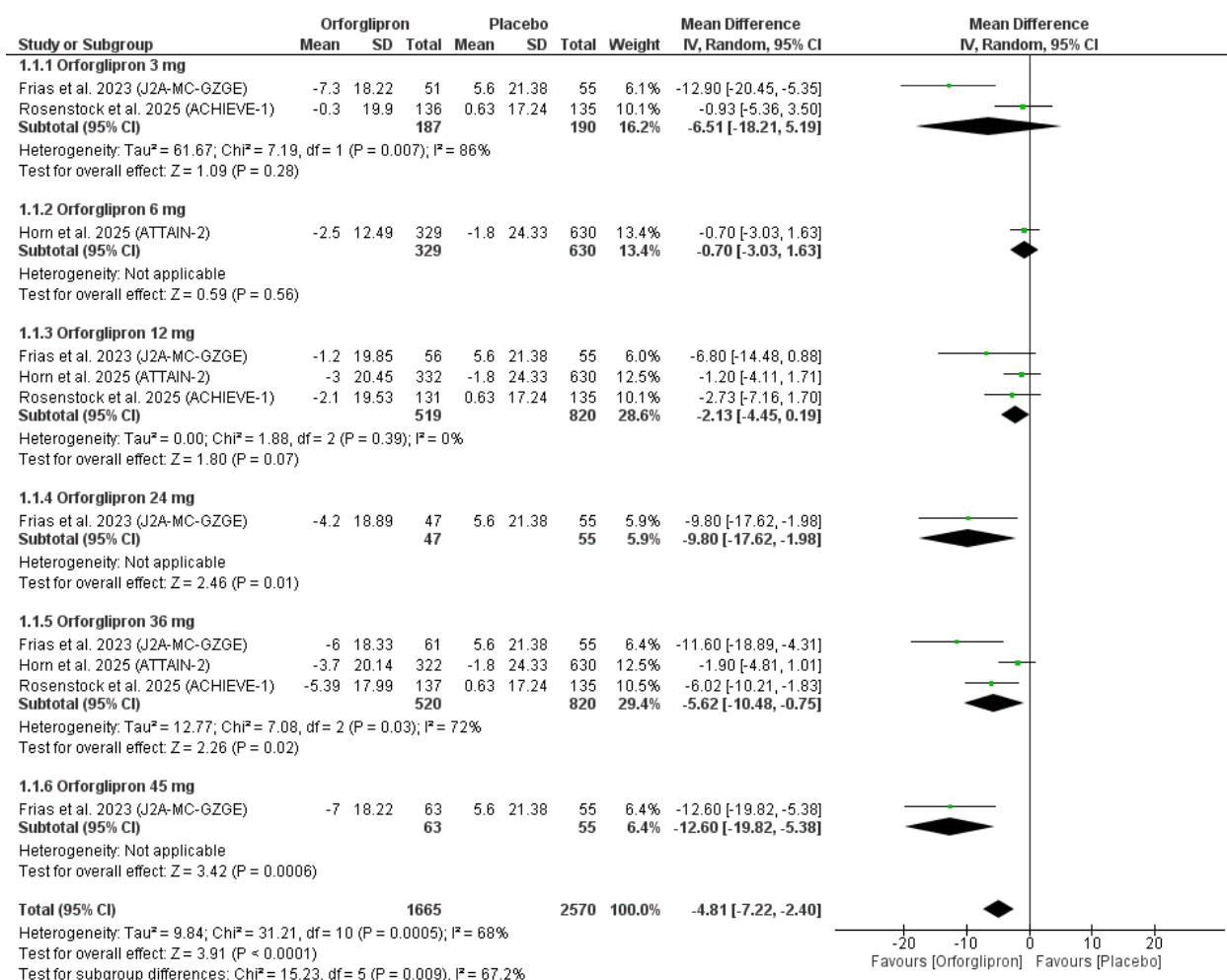
Supplementary Figure 2. Forest plot of Change in HbA1C.



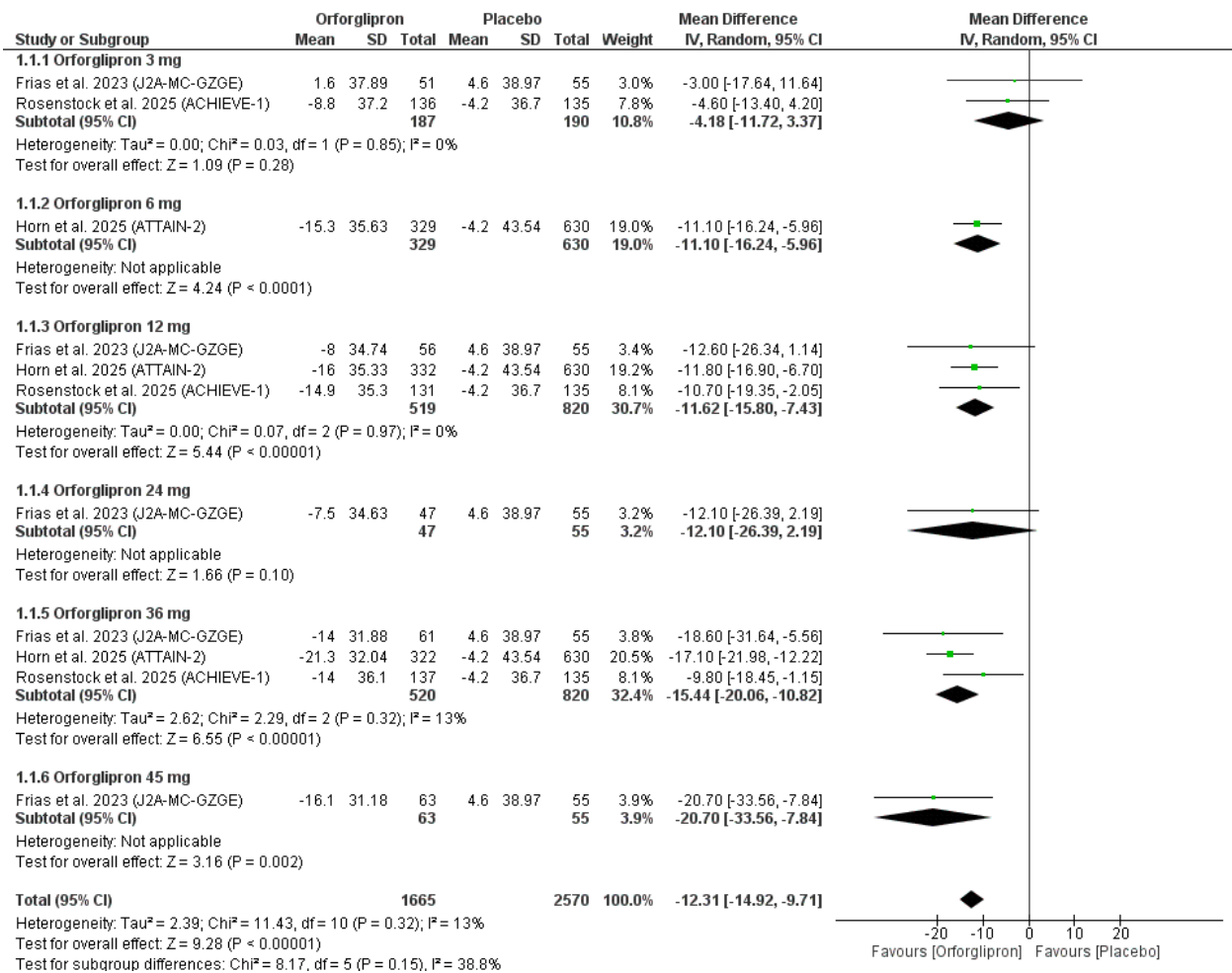
Supplementary Figure 3. Forest plot of Change in LDL-C levels.



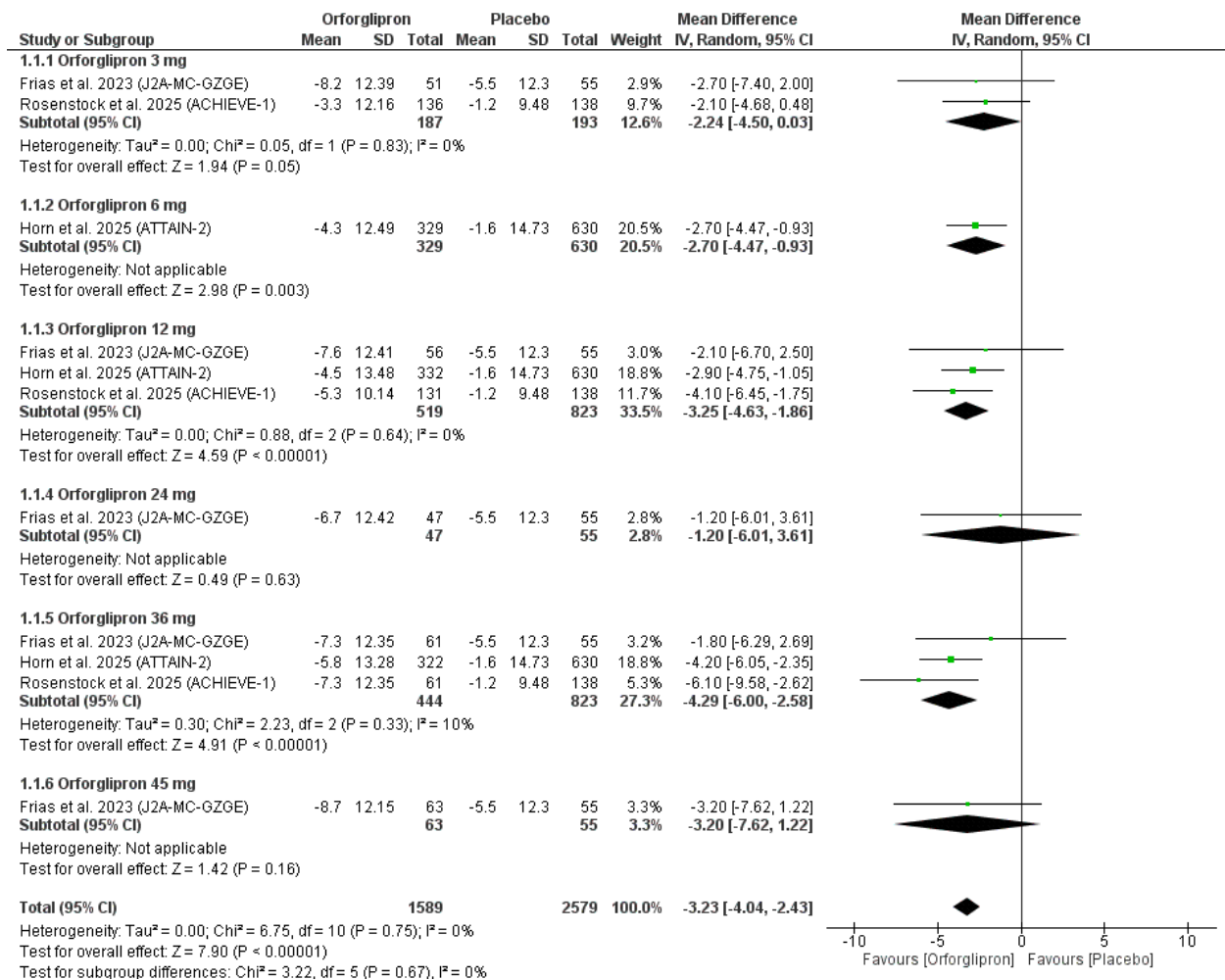
Supplementary Figure 4. Forest plot of Change in HDL-C levels.



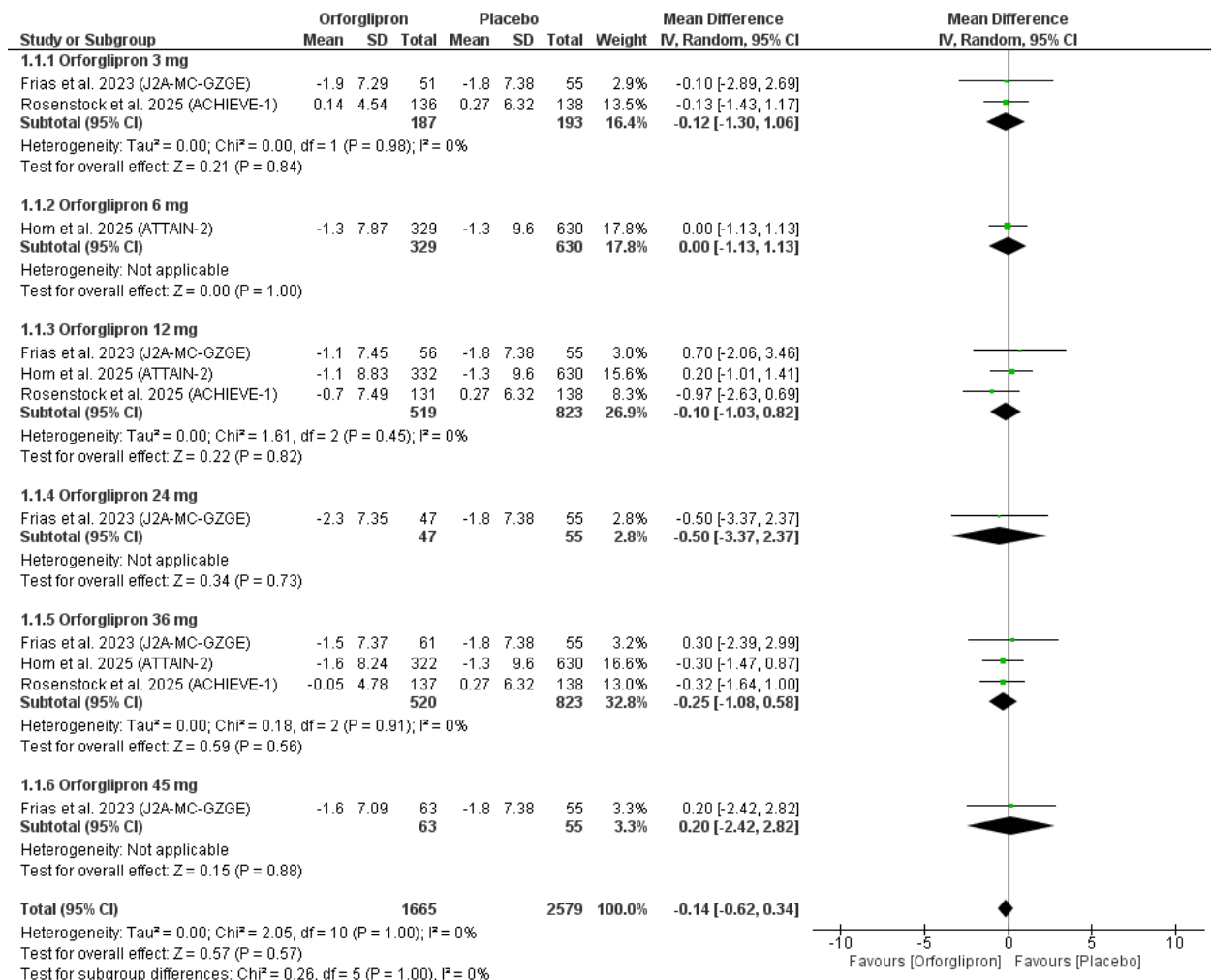
Supplementary Figure 5. Forest plot of Change in Total serum cholesterol.



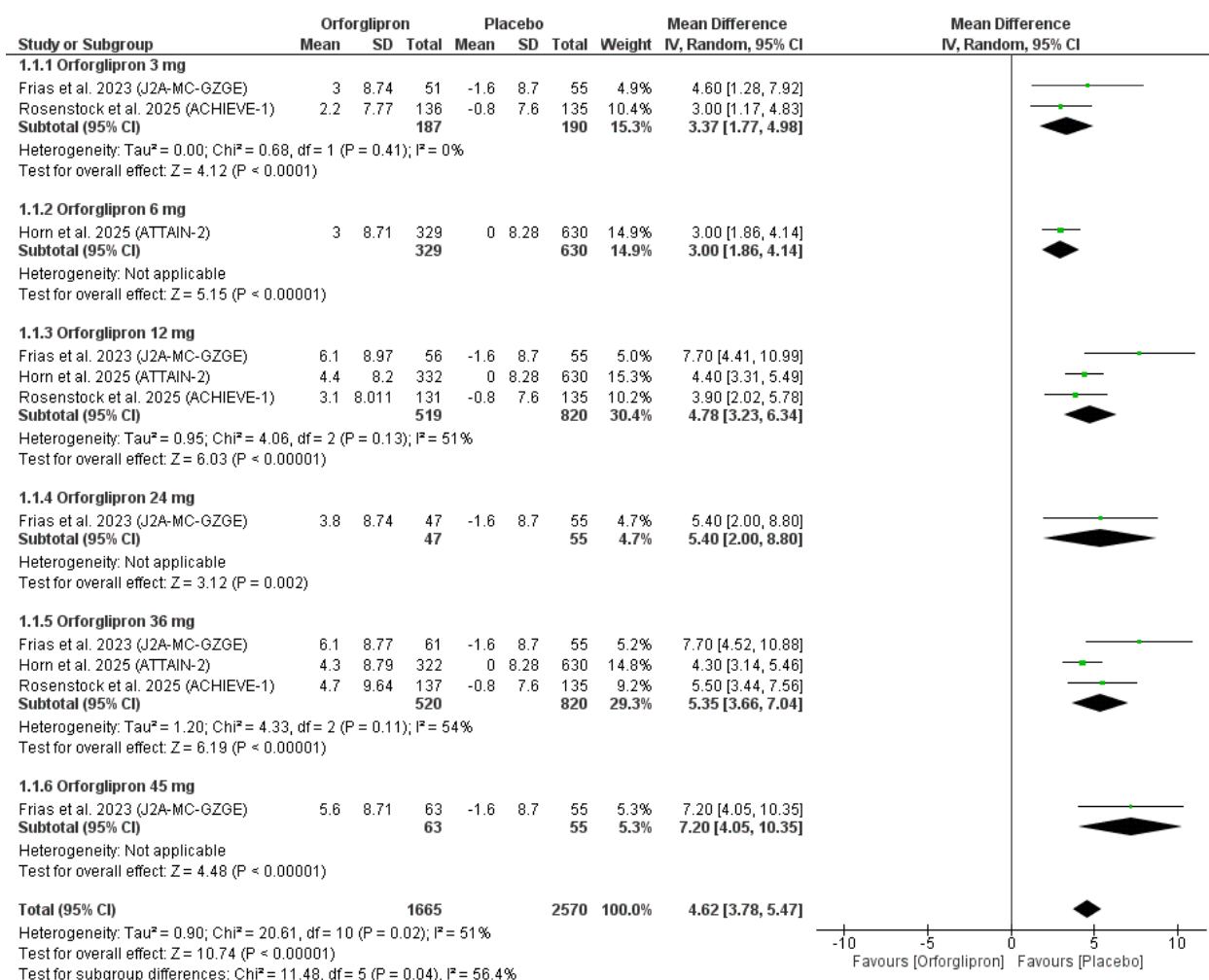
Supplementary Figure 6. Forest plot of Change in Triglycerides level.



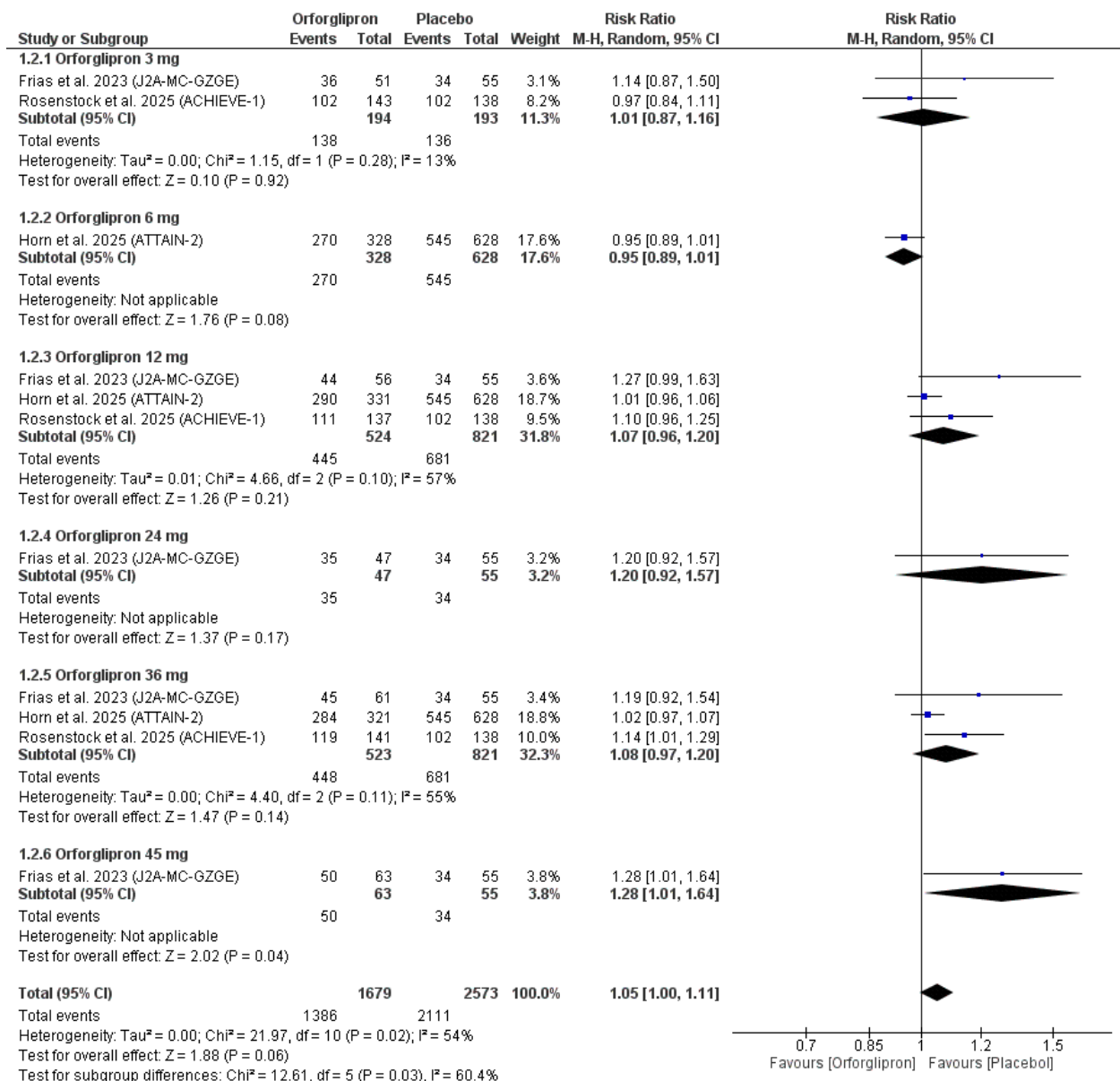
Supplementary Figure 7. Forest plot of Change in SBP.



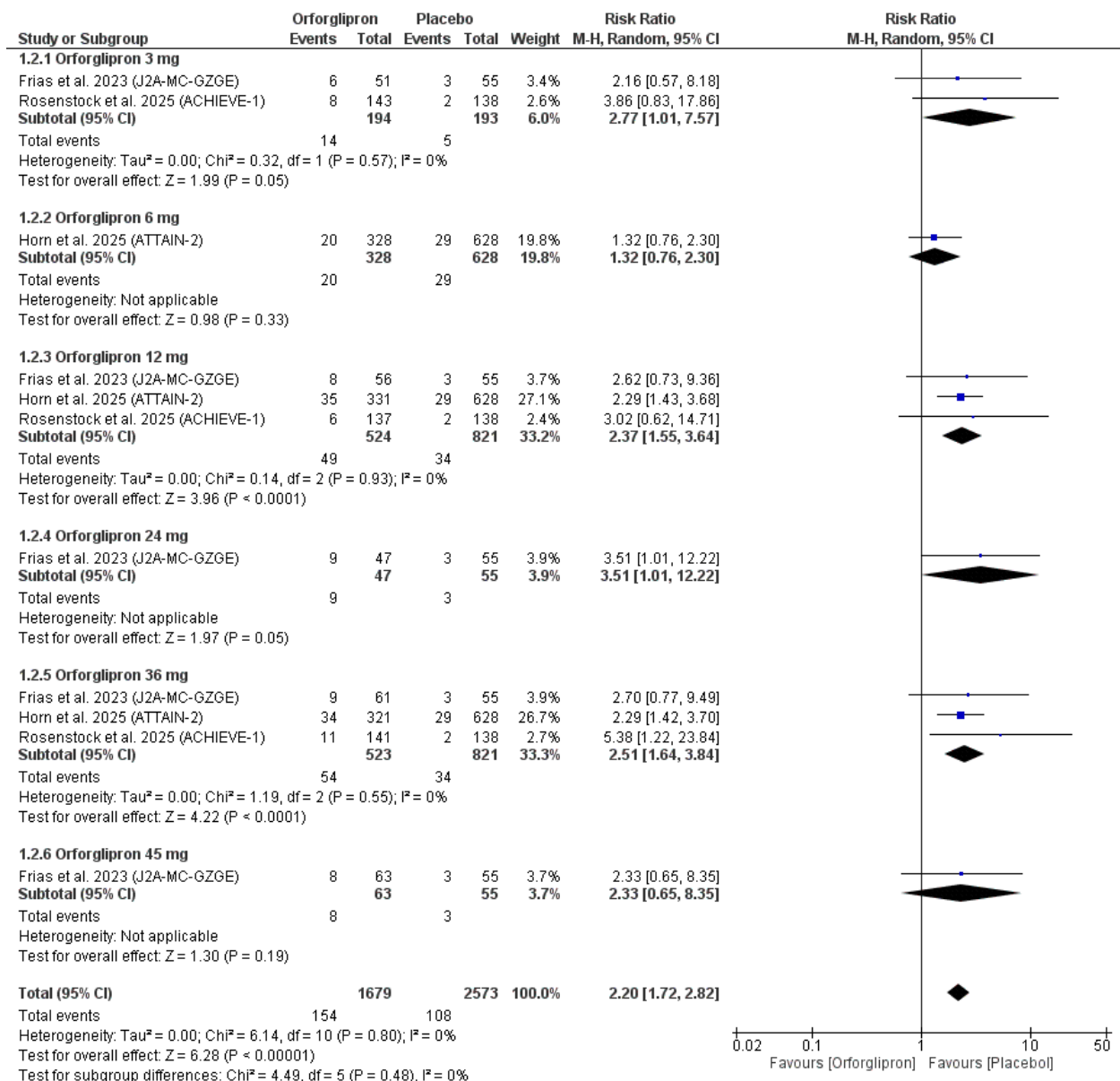
Supplementary Figure 8. Forest plot of Change in DBP.



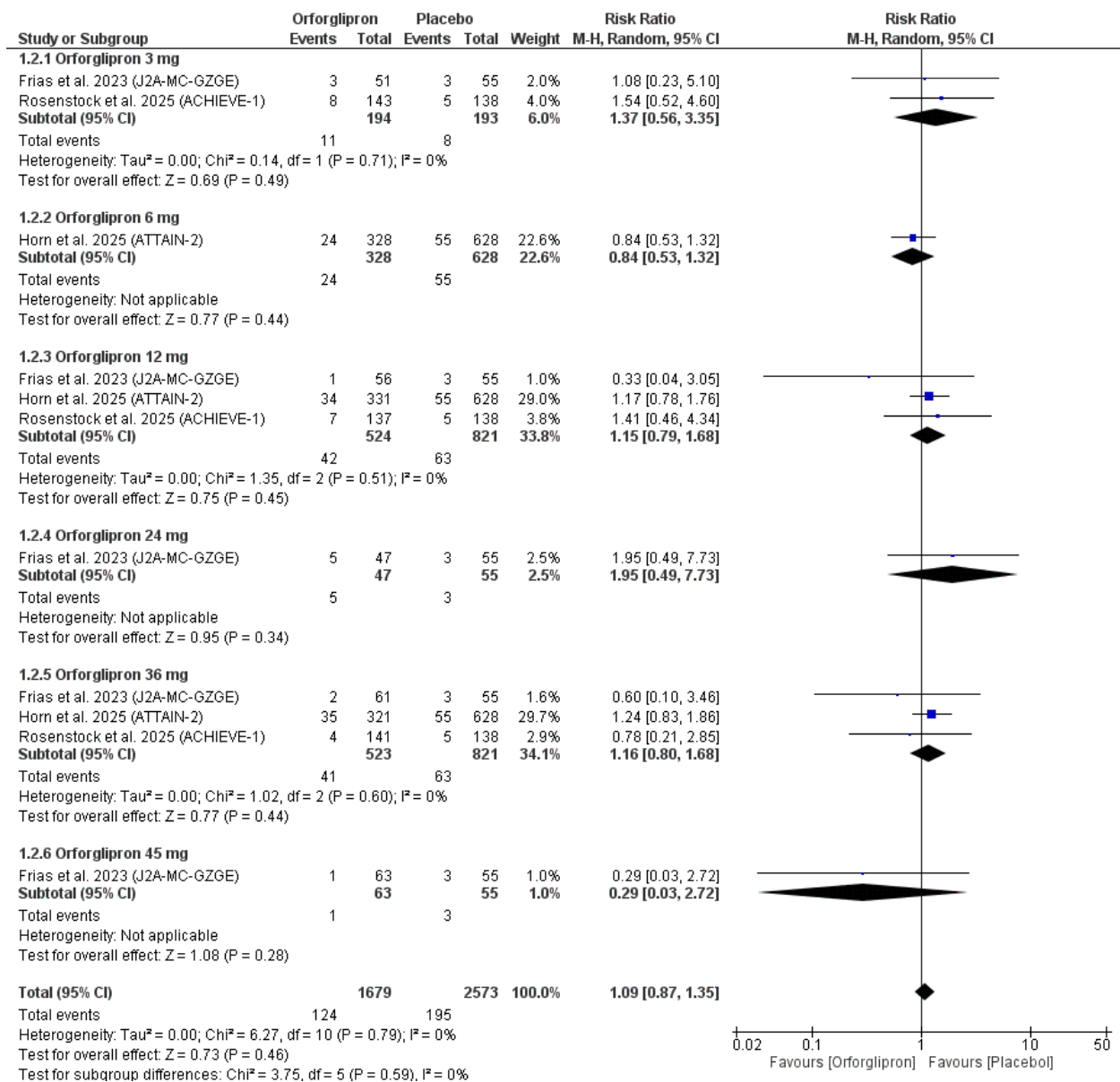
Supplementary Figure 9. Forest plot of Change in Heart Rate.



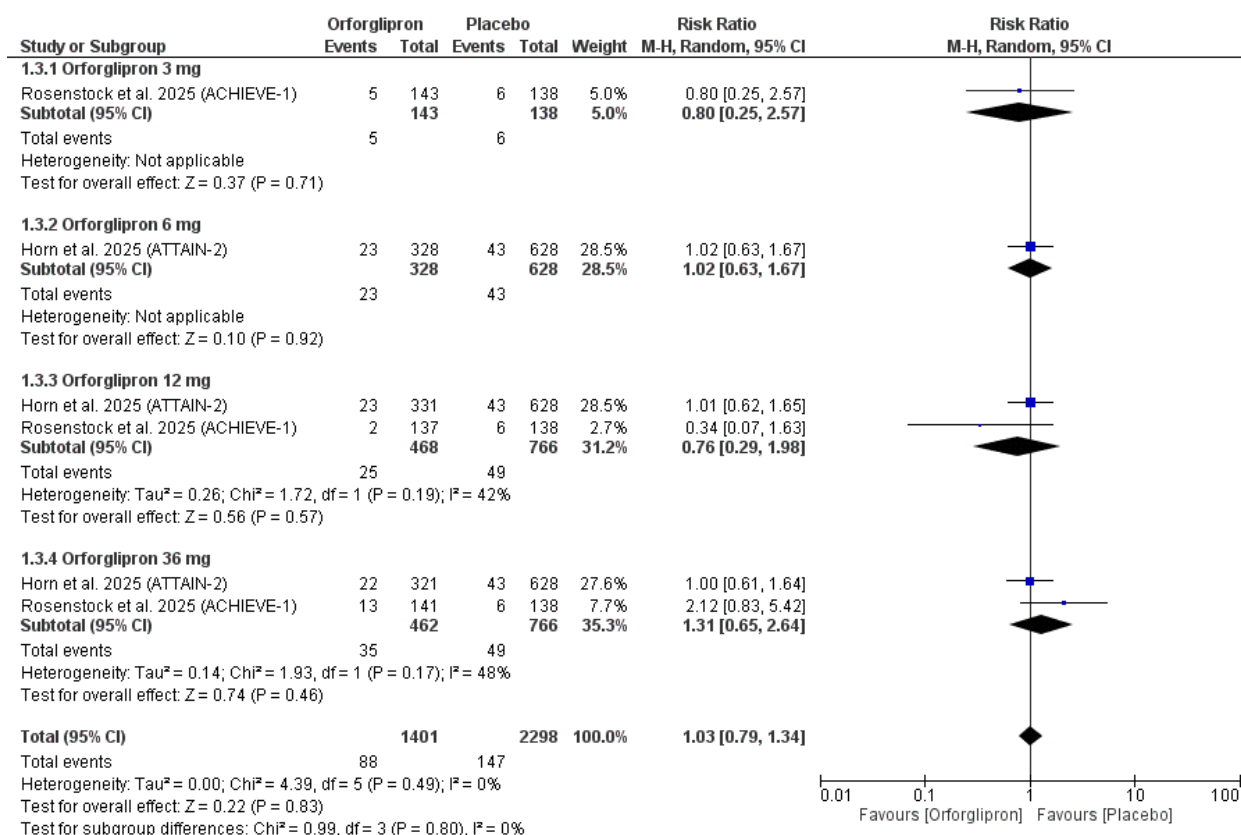
Supplementary Figure 10. Forest plot of Any Adverse Events.



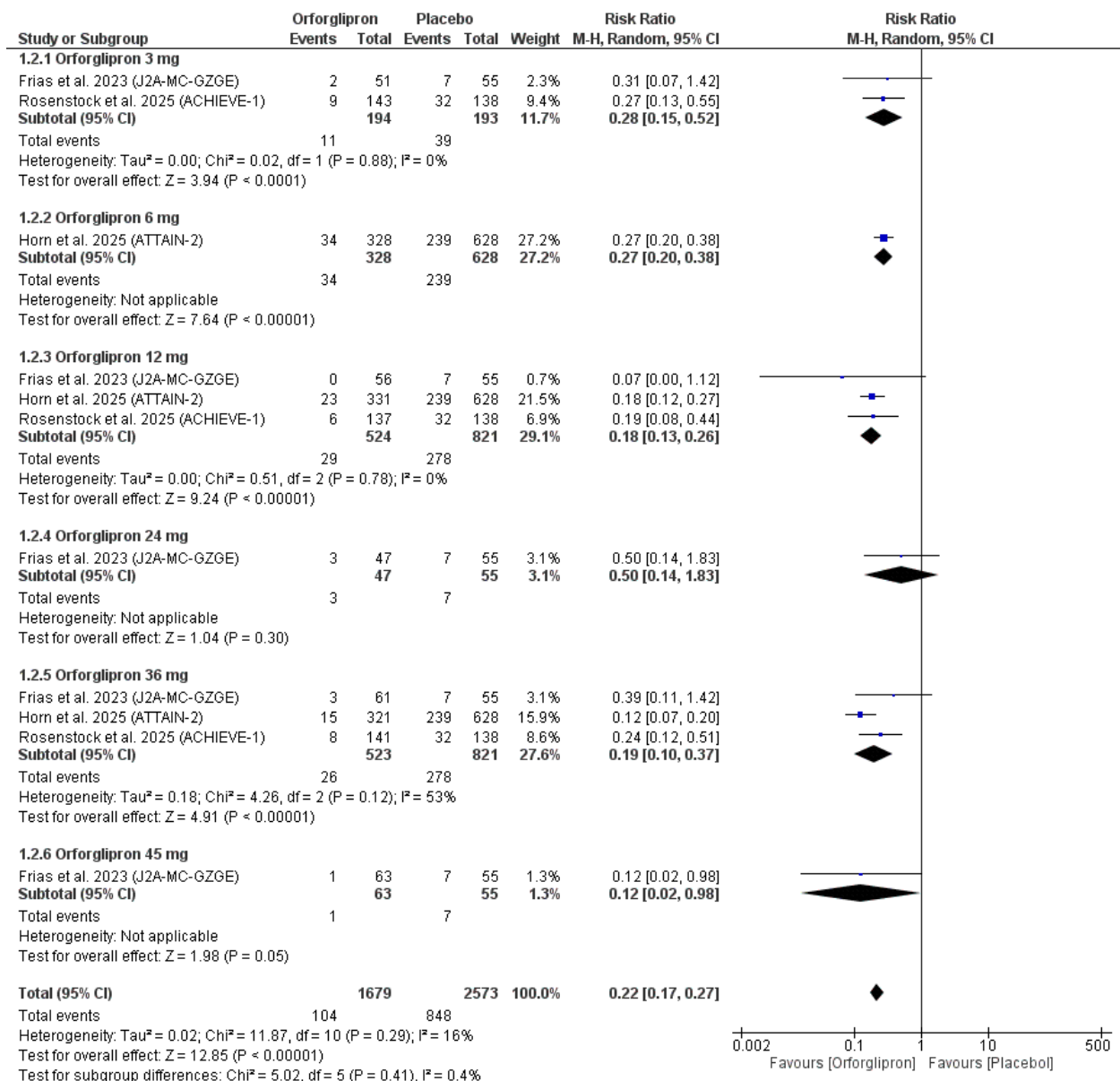
Supplementary Figure I I. Forest plot of Adverse Events Leading to discontinuations.



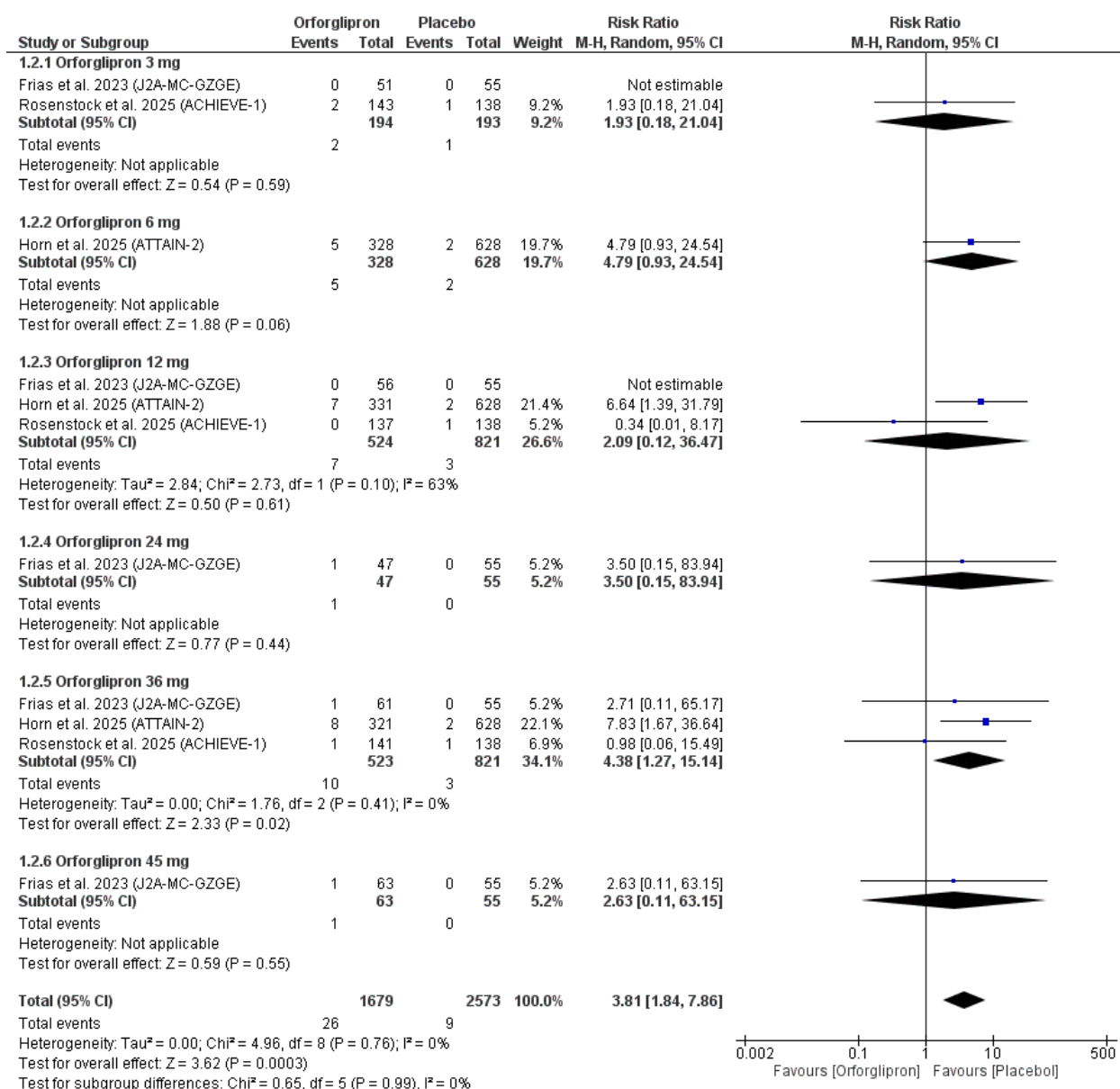
Supplementary Figure I2. Forest plot of Serious Adverse Events



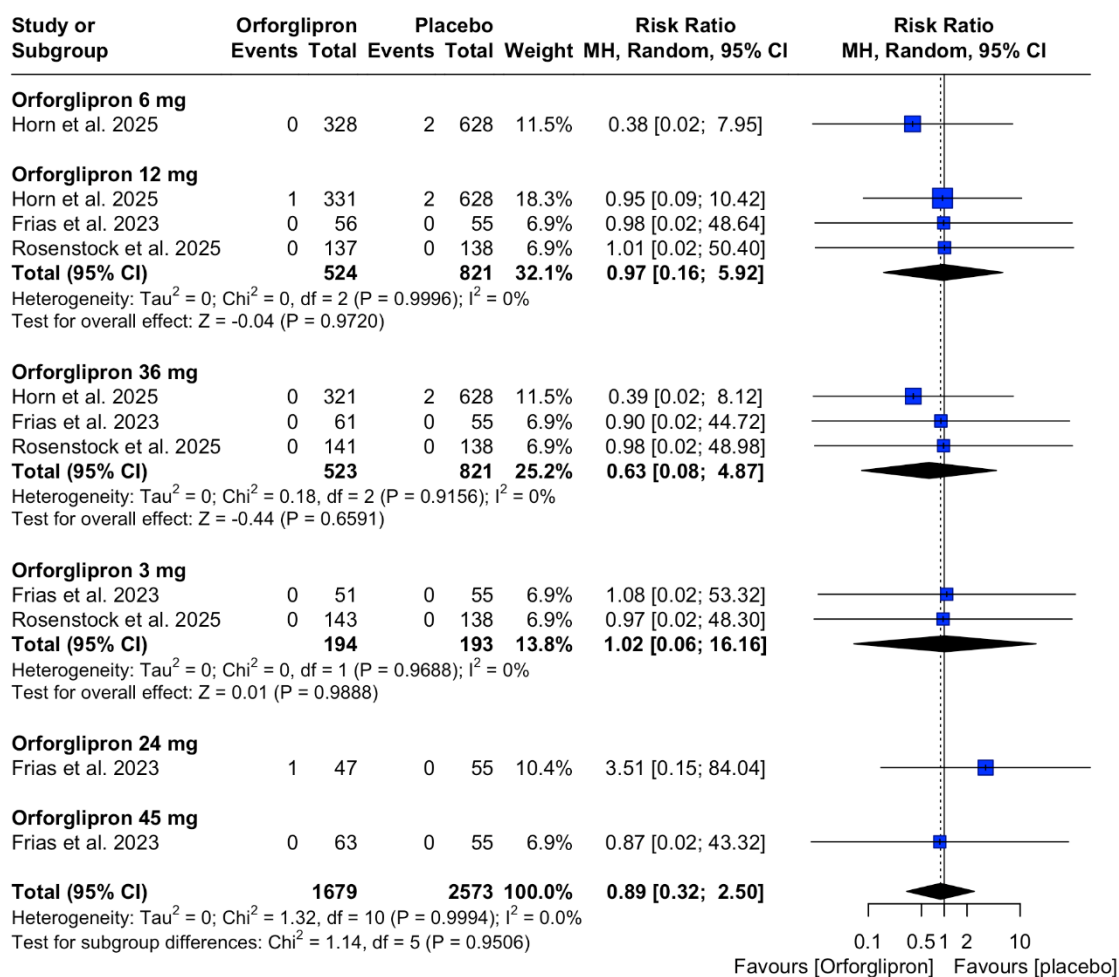
Supplementary Figure 13. Forest plot of Incidence of Diabetes Retinopathy.



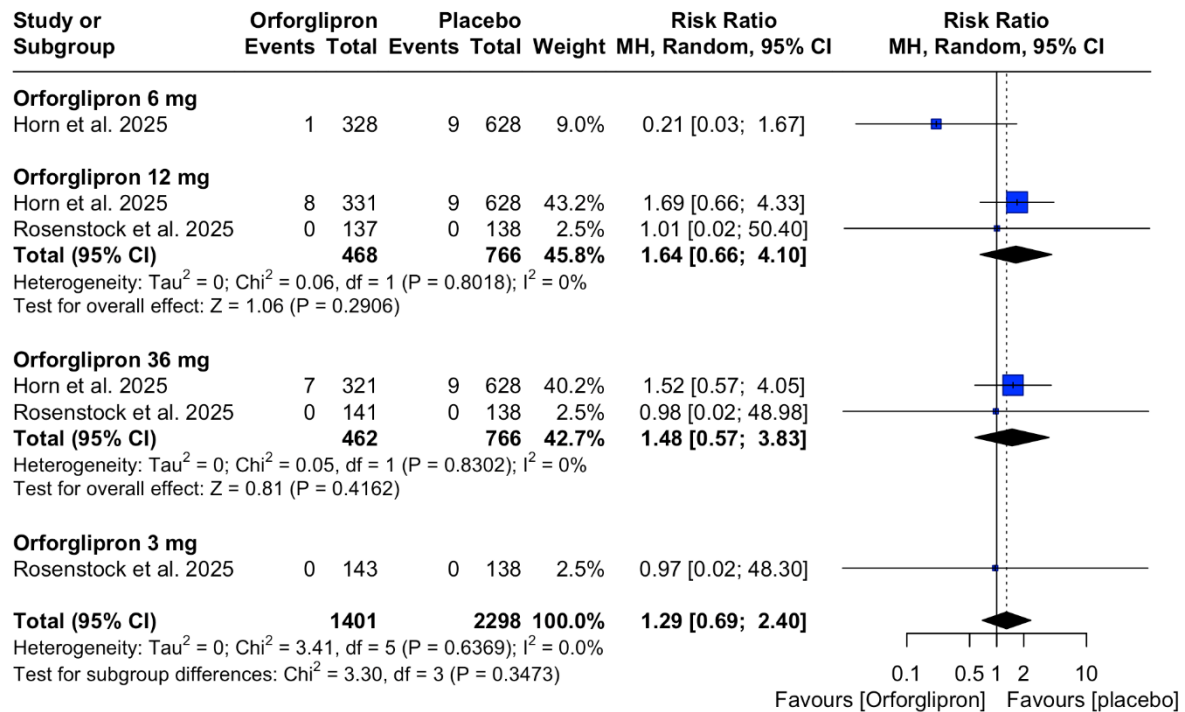
Supplementary Figure I4. Forest plot of Rescue therapy for severe persistent hyperglycaemia.



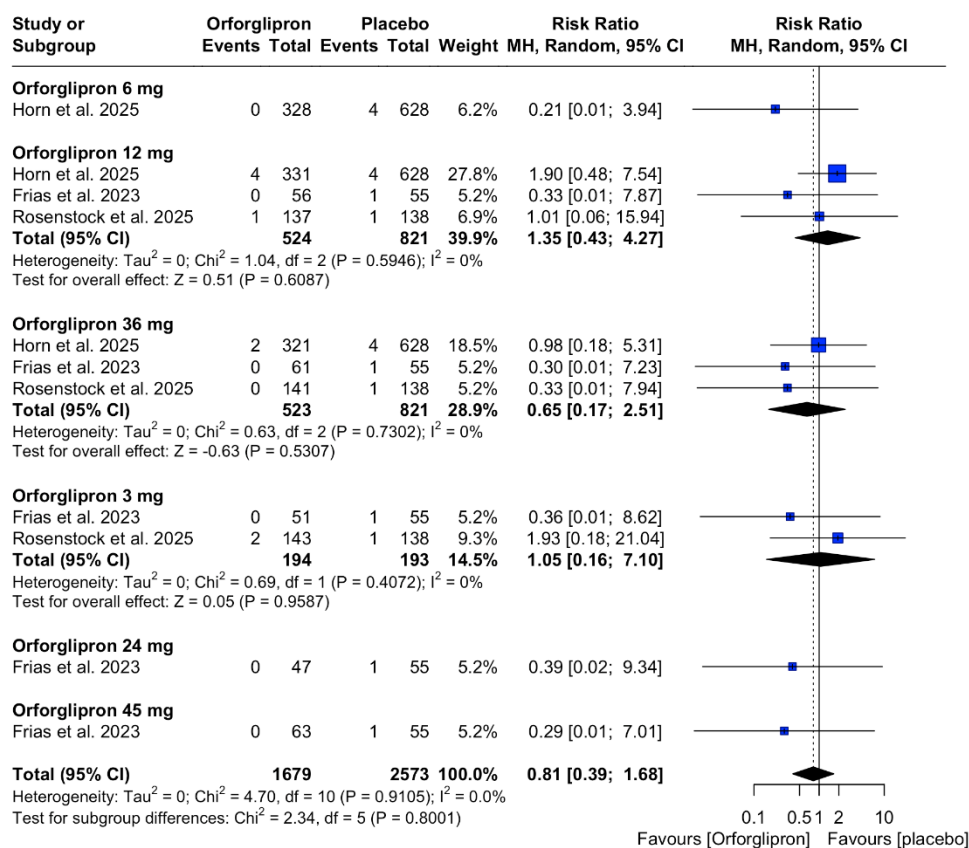
Supplementary Figure 15. Forest plot of Incidence of Hypoglycemia.



Supplementary Figure I6. Forest plot of Incidence of Acute pancreatitis.



Supplementary Figure I7. Forest plot of MACE.



Supplementary Figure I8. Forest plot of Death.