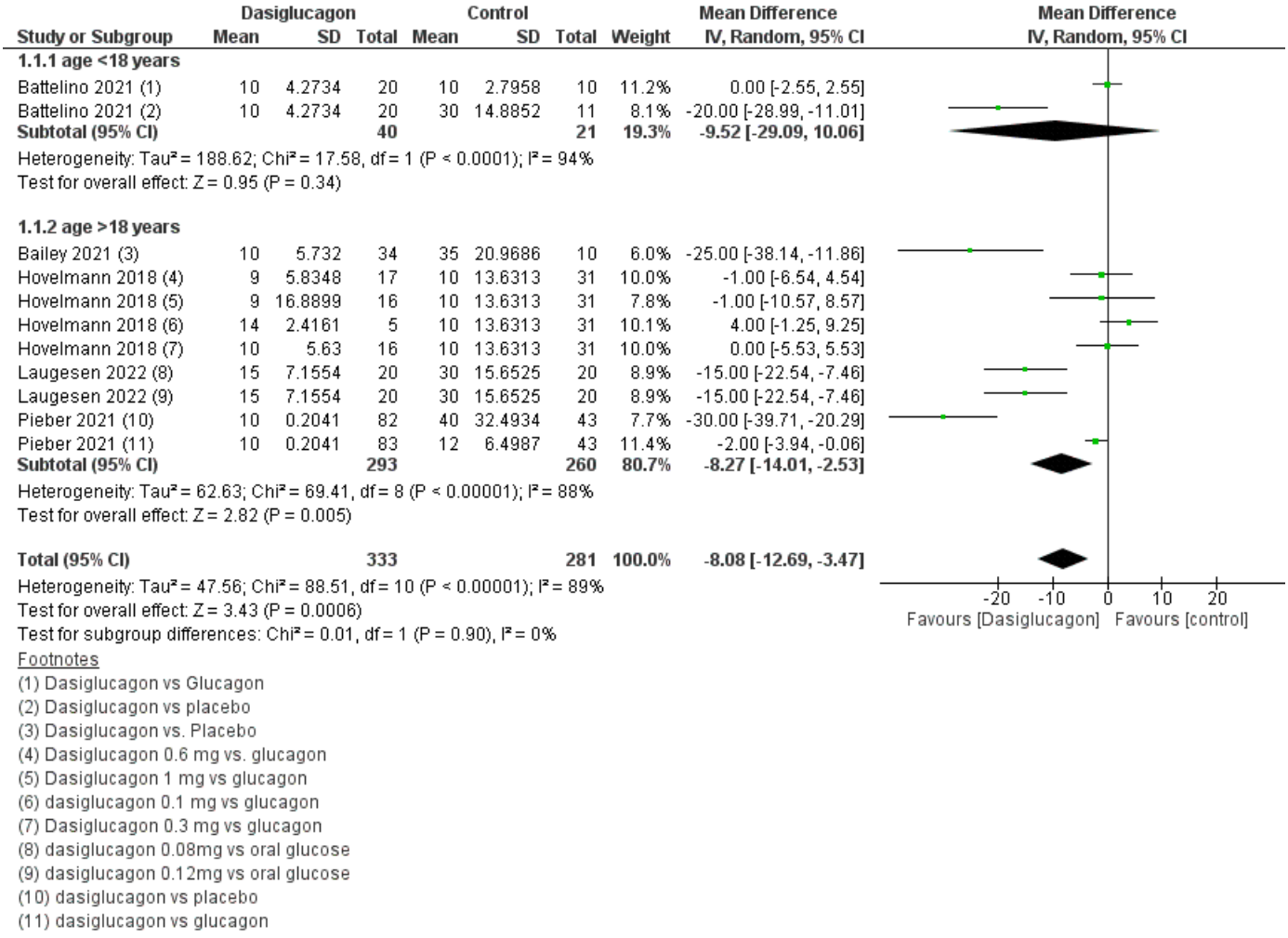
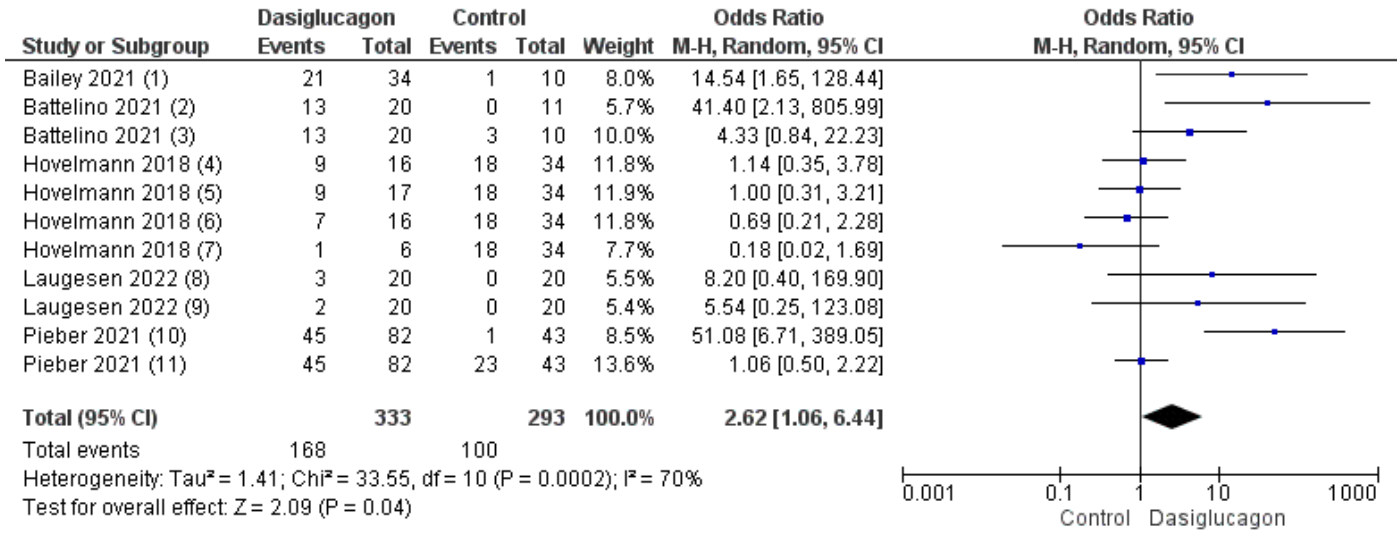


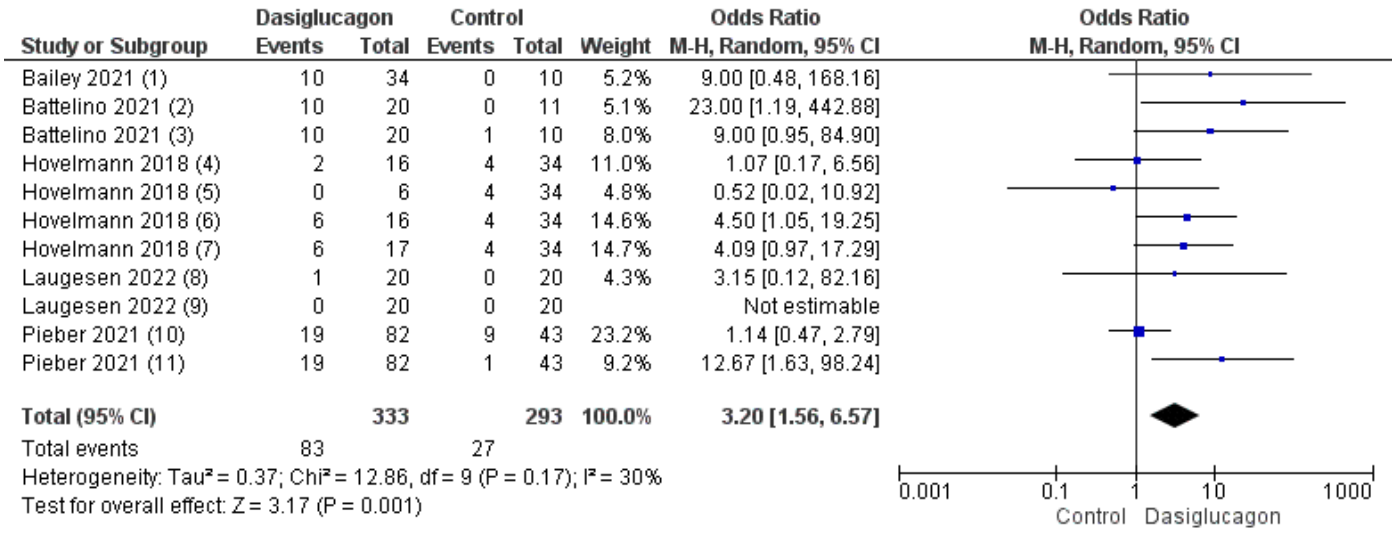
Figure S1: The forest plot for included studies pooled together using random-effects model for Time to recovery subgroup analysis according to age (<18 years and ≥18 years)



Footnotes

(1) Dasiglucagon vs placebo
(2) dasiglucagon vs placebo
(3) dasiglucagon vs glucagon
(4) Dasiglucagon 0.3 mg vs glucagon
(5) Dasiglucagon 0.6 mg vs glucagon
(6) Dasiglucagon 1.0 mg vs glucagon
(7) Dasiglucagon 0.1 mg vs glucagon
(8) Dasiglucagon 0.08mg vs oral glucose
(9) dasiglucagon 0.12 mg vs oral glucose
(10) dasiglucagon vs placebo
(11) dasiglucagon vs glucagon

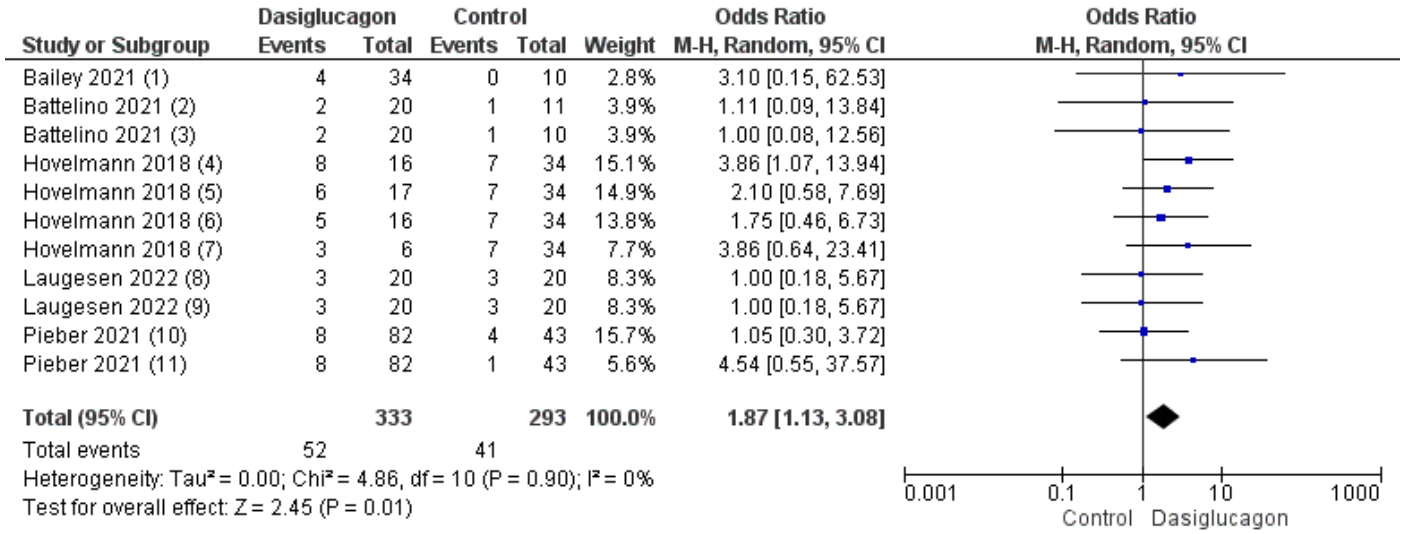
Figure S2: The forest plot for included studies pooled together using random-effects model for assessing the incidence of nausea among the treatment arm and comparator arm.



Footnotes

(1) Dasiglucagon vs placebo
(2) Dasiglucagon vs placebo
(3) Dasiglucagon vs glucagon
(4) Dasiglucagon 1.0 mg vs glucagon
(5) Dasiglucagon 0.1 mg vs glucagon
(6) Dasiglucagon 0.3 mg vs glucagon
(7) Dasiglucagon 0.6 mg vs glucagon
(8) Dasiglucagon 0.08mg vs oral glucose
(9) Dasiglucagon 0.12mg vs oral glucose
(10) Dasiglucagon vs glucagon
(11) Dasiglucagon vs placebo

Figure S3: The forest plot for included studies pooled together using random-effects model for assessing the incidence of vomiting among the treatment arm and comparator arm.



Footnotes

(1) Dasiglucagon vs placebo
(2) Dasiglucagon vs placebo
(3) Dasiglucagon vs glucagon
(4) Dasiglucagon 0.3 mg vs glucagon
(5) Dasiglucagon 0.6 mg vs glucagon
(6) Dasiglucagon 1.0 mg vs glucagon
(7) Dasiglucagon 0.1 mg vs glucagon
(8) Dasiglucagon 0.08mg vs oral glucose
(9) Dasiglucagon 0.12mg vs oral glucose
(10) Dasiglucagon vs glucagon
(11) Dasiglucagon vs placebo

Figure S4: The forest plot for included studies pooled together using random-effects model for assessing the incidence of headache among the treatment arm and comparator arm.

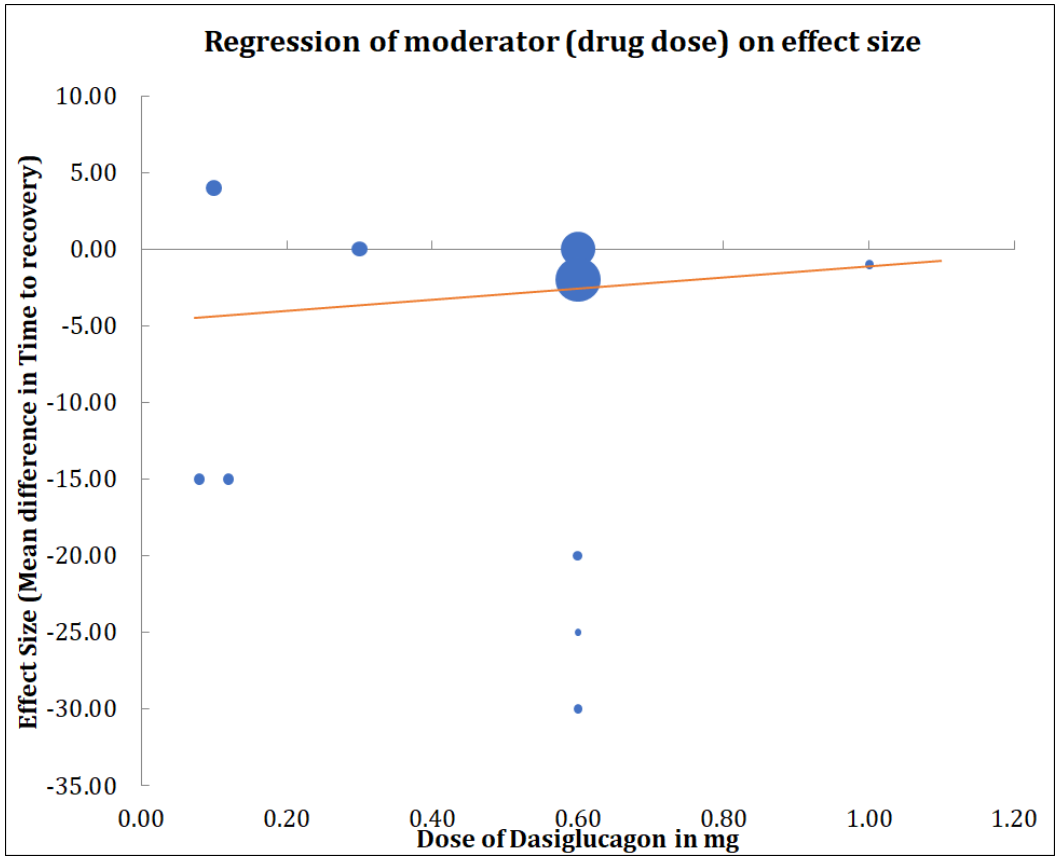


Figure S5: The bubble plot showing the effect of dose of dasiglucagon on time to recovery. The studies are depicted by circles along the line of meta-regression.

Table S1: Characteristics of studies included in the meta-analysis

Trial and Location	Methods	Participants	Number of Participants	Interventions	Outcomes	Remarks
Hövelmann et al. (2018) Germany	Single-center, Randomized Double-blind, 0.5mg and 1mg glucagon -controlled trial	Primary diagnosis of type 1 diabetes (Aged 18-50 years)	Dasiglucagon 0.1mg: 5, Dasiglucagon 0.3mg: 16, Dasiglucagon 0.6mg: 17, Dasiglucagon 1mg: 16, Glucagon 0.5mg: 17, Glucagon 1mg: 33	Dasiglucagon 0.1 mg/ 0.3mg/0.6mg/ 1.0mg single sub cutaneous injection Glucagon 0.5mg/1.0mg single sub cutaneous injection	Time to increase plasma glucose of ≥20mg/dl (1.1mmol/L)	Dasiglucagon was well tolerated and showed an early PD response similar to that of glucagon at corresponding doses, suggesting comparable clinical effect of the two.
Battelino et al. (2021) Germany, Slovenia, USA	Randomized Double-blind, Placebo/glucagon - controlled, Fixed-dose multi-centric trial	Primary diagnosis of type 1 diabetes (Aged 6-17 years)	Dasiglucagon 0.6mg: 20, 1 mg glucagon: 10, Placebo: 11	Single subcutaneous injection of Dasiglucagon 0.6mg, Placebo injection, Glucagon 1 mg single subcutaneous injection	time to increase plasma glucose of ≥20mg/dl (1.1mmol/L) No. of patients recovered at the end of 10,15,20,30 minutes post-intervention	Dasiglucagon rapidly and effectively restored plasma glucose levels following insulin-induced hypoglycemia in children and adolescents
Pieber et al. (2021) Germany, Austria, USA, Canada	Randomized Double-blind, Parallel group, Placebo and glucagon-controlled, Fixed-dose multi-centric study	Primary diagnosis of type 1 diabetes (Aged 18-75 years)	Dasiglucagon 0.6mg: 82, 1 mg glucagon: 43, Placebo: 43	Single subcutaneous injection of Dasiglucagon 0.6mg, Placebo injection, Glucagon 1 mg single subcutaneous injection	time to increase plasma glucose of ≥20mg/dl (1.1mmol/L) No. of patients recovered at the end of 10,15,20,30 minutes post-intervention	Dasiglucagon provided rapid and effective reversal of hypoglycemia in adults with T1D with safety and tolerability similar to that of reconstituted glucagon injection
Bailey et al. (2021) USA	Randomized Double-blind, Placebo-controlled, Fixed-dose multi-centric trial	Primary diagnosis of type 1 diabetes (Aged 18-75 years)	Dasiglucagon 0.6 mg: 34, Placebo: 10	Single subcutaneous injection of Dasiglucagon 0.6mg, Placebo injection	time to increase plasma glucose of ≥20mg/dl (1.1mmol/L) No. of patients recovered at the end of 10,15,20,30 minutes post-intervention	Dasiglucagon provided rapid reversal of hypoglycemia in adults with type 1 diabetes and was well tolerated.
Laugesen et al. (2022) Denmark	Randomized, single-blind, Three-arm crossover, Oral glucose-controlled, Fixed-dose multi-centric laboratory classroom study	Primary diagnosis of type 1 diabetes (Aged 18-64 years)	Dasiglucagon 80 µg: 20, Dasiglucagon 120 µg:20, 15 g oral glucose: 20	Dasiglucagon single subcutaneous injection of 80 microgram, 120 microgram, 15g oral glucose from dextrose tablet	time to increase plasma glucose of ≥20mg/dl (1.1mmol/L)	Low dose dasiglucagon safely and effectively prevented insulin-induced hypoglycemia with a faster glucose-elevating profile than oral glucose

Table S2: Risk of bias table for included studies

Included studies	Domain 1: Randomization process	Domain 2: Deviations from the intended interventions	Domain 3: Missing outcome data	Domain 4: Measurement of the outcome	Domain 5: Selection of the reported result	Overall risk-of-bias judgement
Hovelmann 2018	L	S	L	L	L	S
Pieber 2021	L	L	L	L	L	L
Battelino 2021	L	S	L	L	L	S
Bailey 2021	L	L	L	L	L	L
Laugesen 2022	L	L	L	L	L	L

L, Low risk of bias; S, Some concerns; H, High risk of bias.

Table S3: Summary of findings

Outcomes	Number of participants (studies/unit)	Relative effect (95% CI)	Anticipated absolute effects		Certainty of the evidence (GRADE)
			Risk with Control	Risk difference with Dasiglucagon	
Time to recovery	614 (5 RCTs/ 11 units)	-		MD 8.08 minute lower (12.69 lower to 3.47 lower)	⊕⊕⊕◯ Moderate
Number of patients recovered at 10 minutes	355 3 RCTs/ 5 units)	OR 7.98 (1.56 to 40.82)	231 per 1,000	475 more per 1,000 (88 more to 694 more)	⊕⊕⊕⊕ High
Number of patients recovered at 20 minutes	355 3 RCTs/ 5 units)	OR 73.25 (6.72 to 798.35)	521 per 1,000	466 more per 1,000 (358 more to 477 more)	⊕⊕⊕⊕ High
Number of patients recovered at 30 minutes	355 3 RCTs/ 5 units)	OR 15.46 (2.72 to 87.80)	726 per 1,000	250 more per 1,000 (152 more to 269 more)	⊕⊕⊕⊕ High
Number of patients with TEAE	435 (4 RCTs/ 7 units)	OR 2.42 (0.90 to 6.55)	363 per 1,000	217 more per 1,000 (24 fewer to 426 more)	⊕⊕⊕⊕ High

CI, confidence interval; MD, mean difference; OR, odds ratio; TEAE, Treatment-Emergent Adverse Event

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect; Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.