IFSO World Congress. Santiago de Chile, Septembre 2025

Gastrointestinal and biliary complications

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IDIBAPS

ciberdem

Declaration of conflicts of interest

Dr. Josep Vidal
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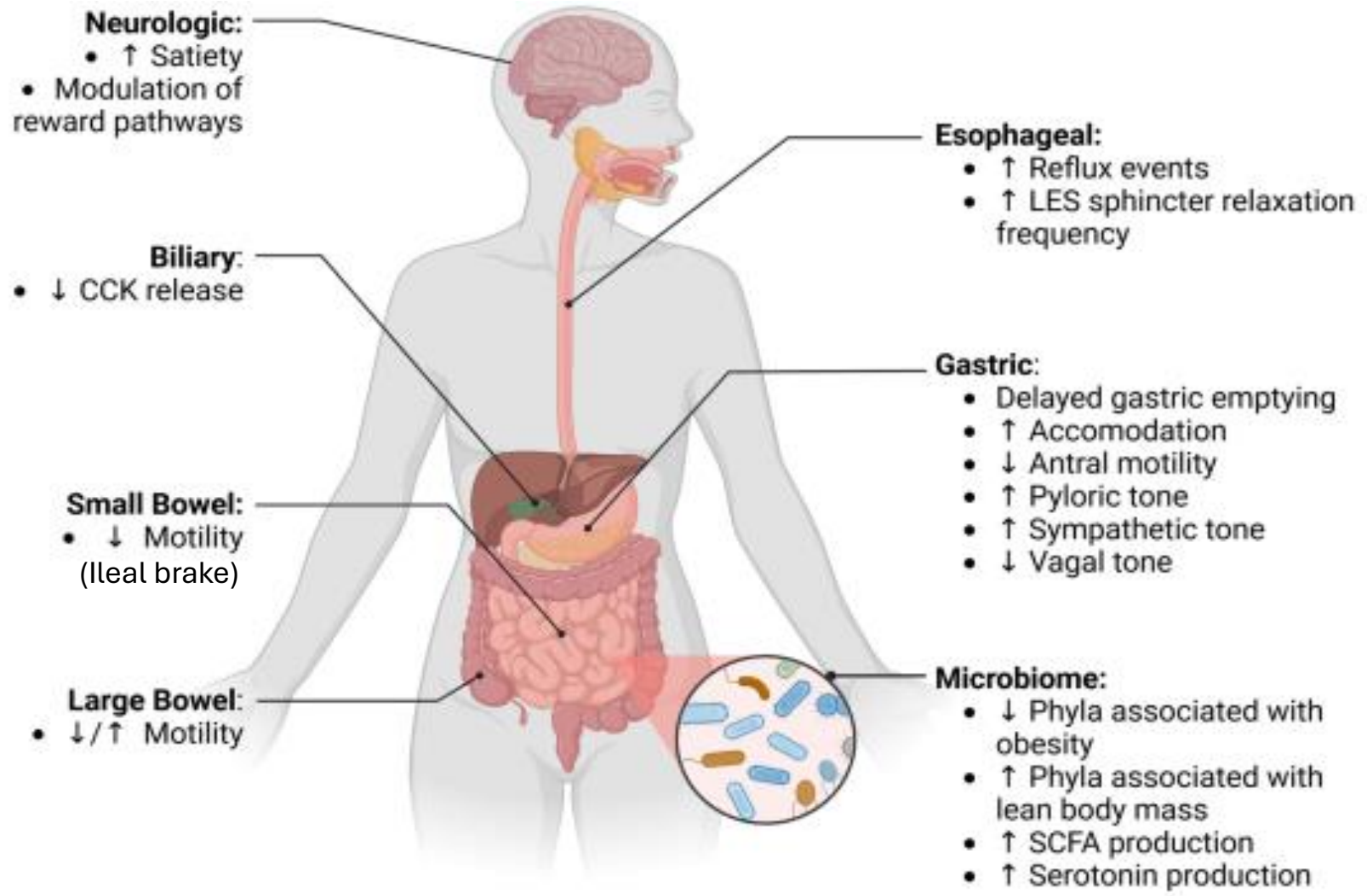
- I have received financial support for research, advice or scientific activities from:Lilly, Novo-Nordisk, Boheringer-Ingelheim, Astra Zeneca, Sanofi, Amgen, Nestlé, Medtronic, Johnson & Johnson.

Effect of GLP-1 and GIP agonism GI physiology

Gastrointestinal Motility Effects of GLP-1 Receptor Agonists [1]

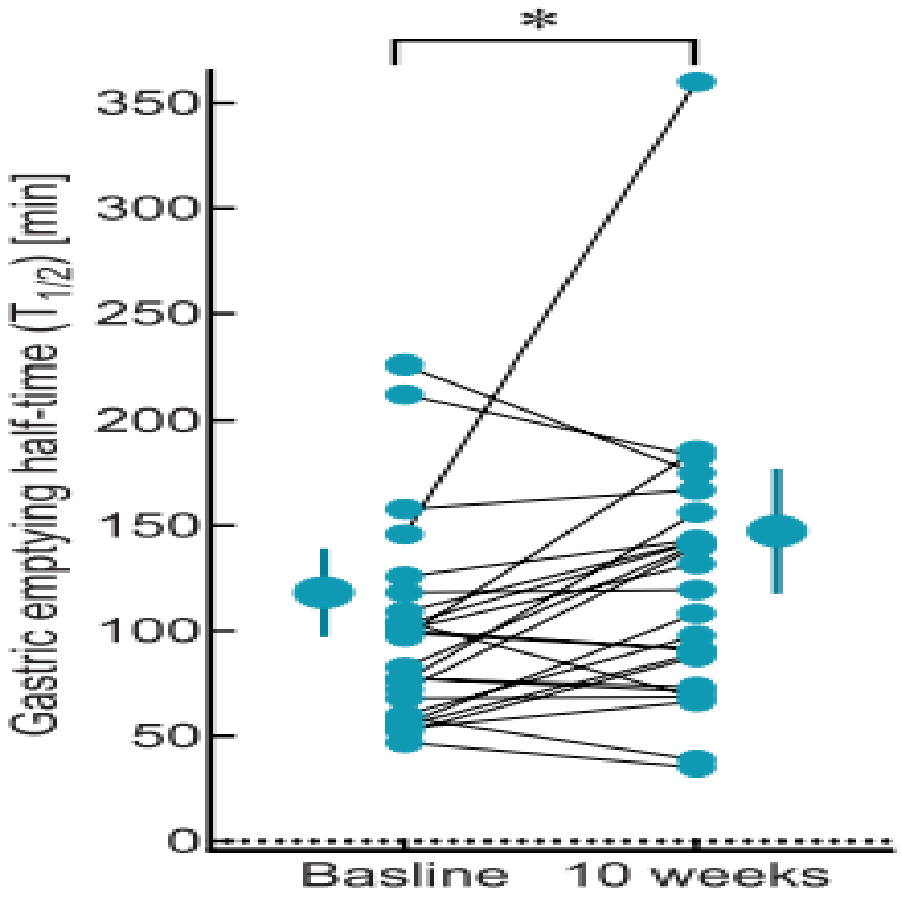


Slowing of gastric emptying (GE) is variable, depends on the baseline rate of GE, and with long-acting GLP-1RAs, may diminish with sustained administration [2].

1. Bellavance D et al. Curr Gastroenterology Reports 2025. 2. Jalleh RJ et al. Endocrinology 2025

Incidence of common GI side effects

Changes in gastric emptying Following Liraglutide * 10 w



Relationship betwen gastric emptying and Gastrointestinal symptoms

In the majority of studies in
health, obesity, or T2D
no or weak correlations have been found

LIMITATIONS

- In most studies, symptoms are self-reported
- In several studies, GE evaluated using methods that are not gold-standard.

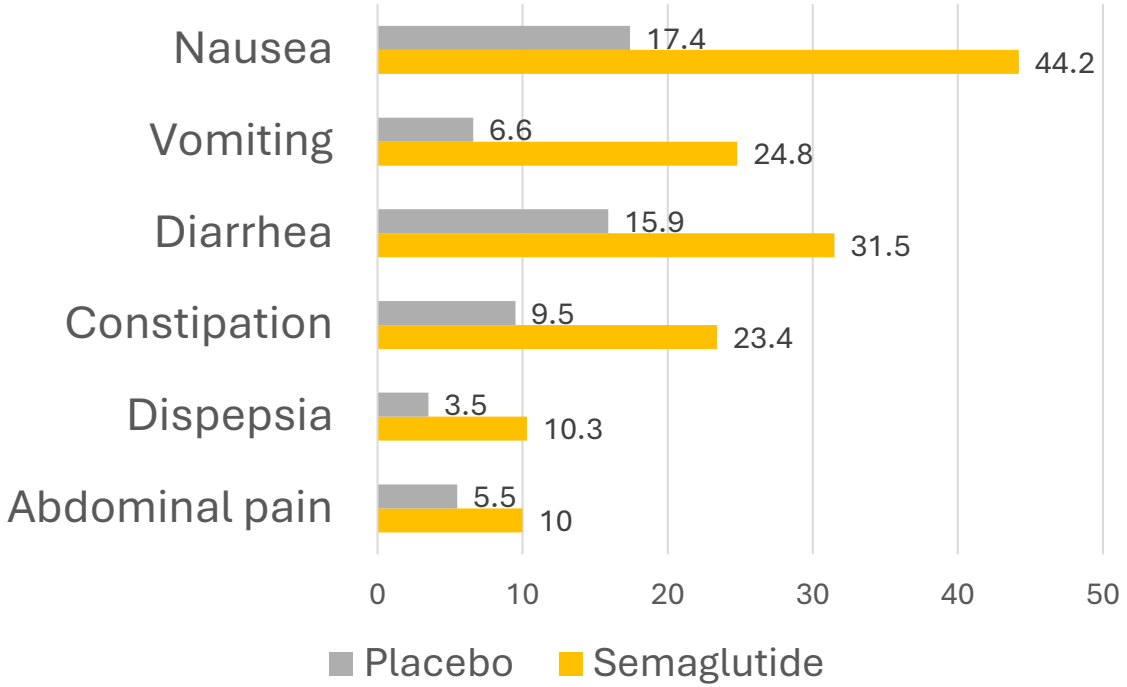
Jalleh RJ et al. J Clin Endocrinol Metab 2025

Prevalence of common GI side effects

Cumulative incidence of reported GI adverse events

STEP 1 Trial: Sema 2.4 mg vs Placebo

(n=1961, age 46 y, female 75%, BMI 38 kg/m2, **follow up: 68 weeks**)



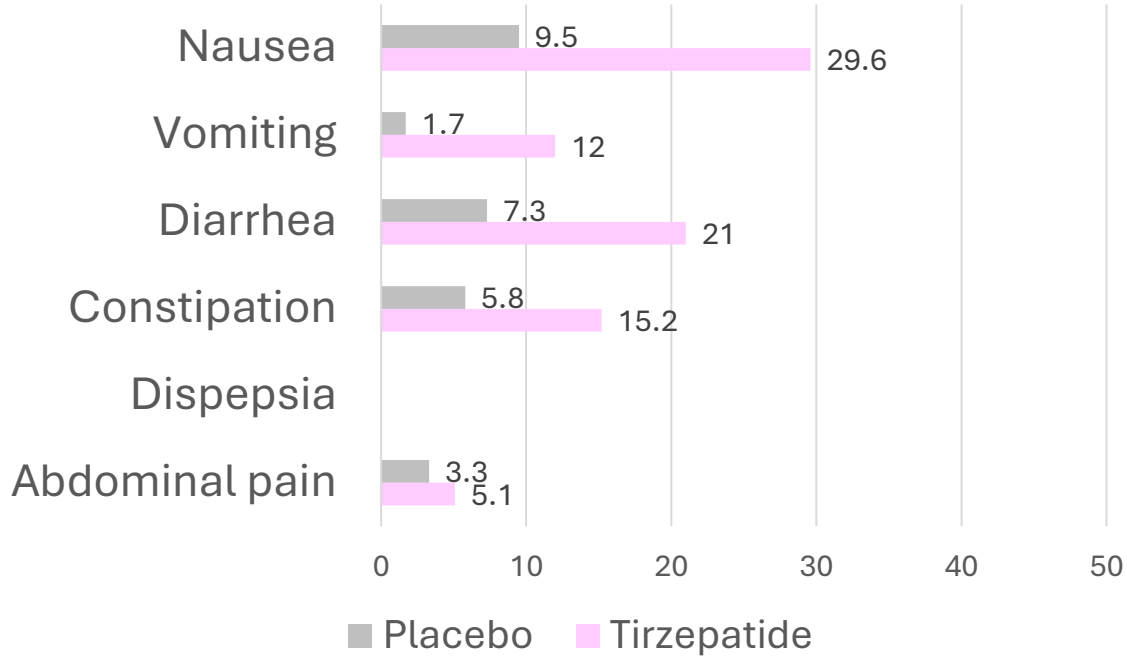
GI AE leading to treatment discontinuation

SEMA: 4.5% PLACEBO: 0.8%

Wilding JPH et al. N Eng J Med 2021

SURMOUNT 1 Trial: Tirze mg vs Placebo

(n=2539, age 45 y, female 68%, BMI 38 kg/m2, **follow up: 72 weeks**)



GI AE leading to treatment discontinuation

TIRZE: 4.3% PLACEBO: 0.3%

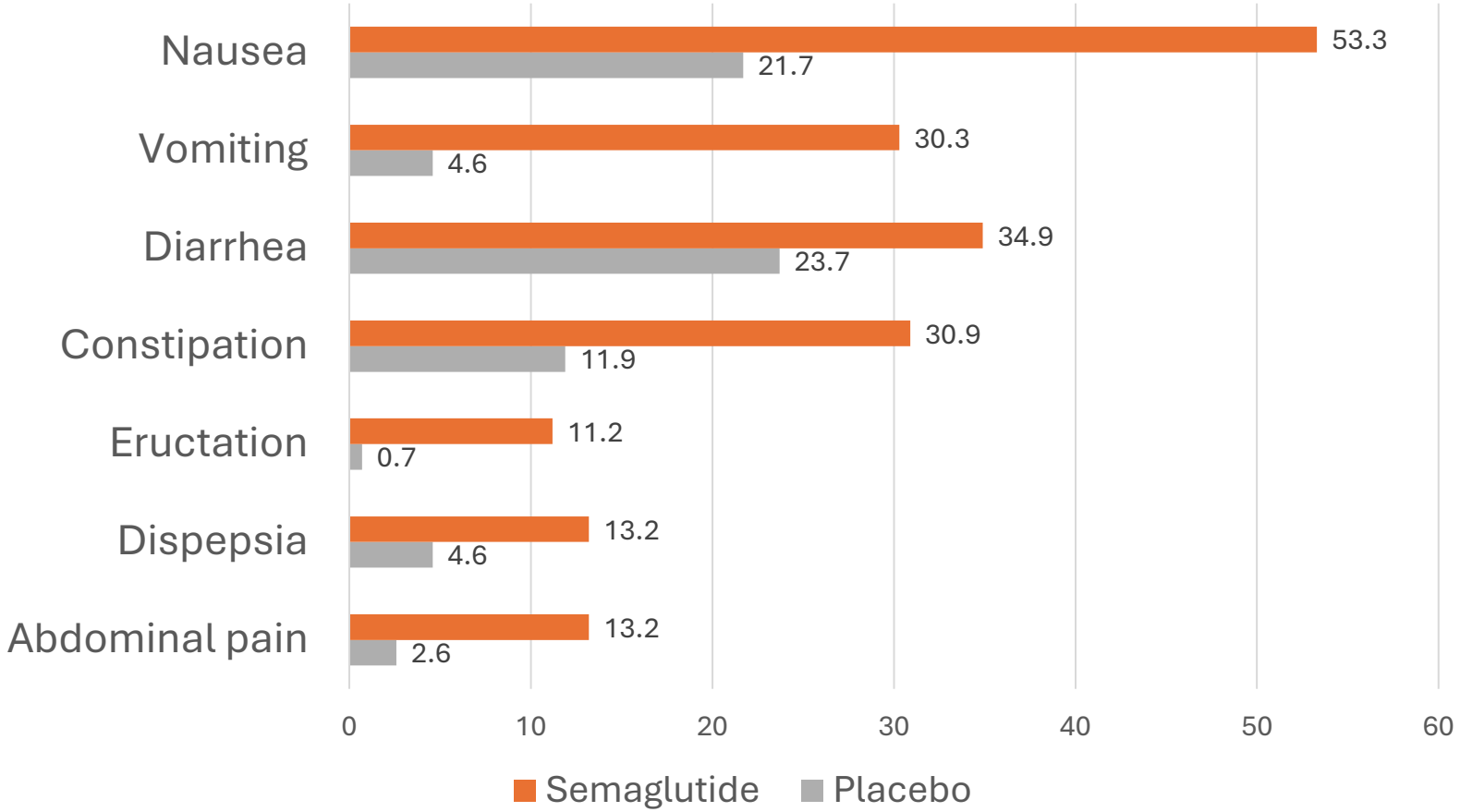
Aronne LJ et al. N Eng J Med 2025

Prevalence of common GI side effects

STEP 5 Trial: RCT Semaglutide 2.4 mg vs Placebo

(n=304, age 47.3 y, female 76%, BMI 38.5 kg/m2, **follow up: 104 weeks**)

Cumulative incidence of GI adverse events reported in at least 10 % of participants



GI side effects leading to treatment discontinuation

SEMA: 3.9%

PLACEBO: 0.7%

Garvey TW al. Nat Med 2022

Prevalence of common GI side effects

SURMOUNT 4 Trial: Tirze vs Placebo

(n=783 tirze lead-in and TZ 335 and Pcb 335 follow up, **follow up: 88 weeks**)

LEAD-IN PERIOD: all on TIRZE

	TIRZE
Nausea	35.0%
Vomiting	16.3%
Diarrhea	21.1%
Constipation	20.7%

GI side effects leading to treatment discontinuation

TIRZE: 4.5%

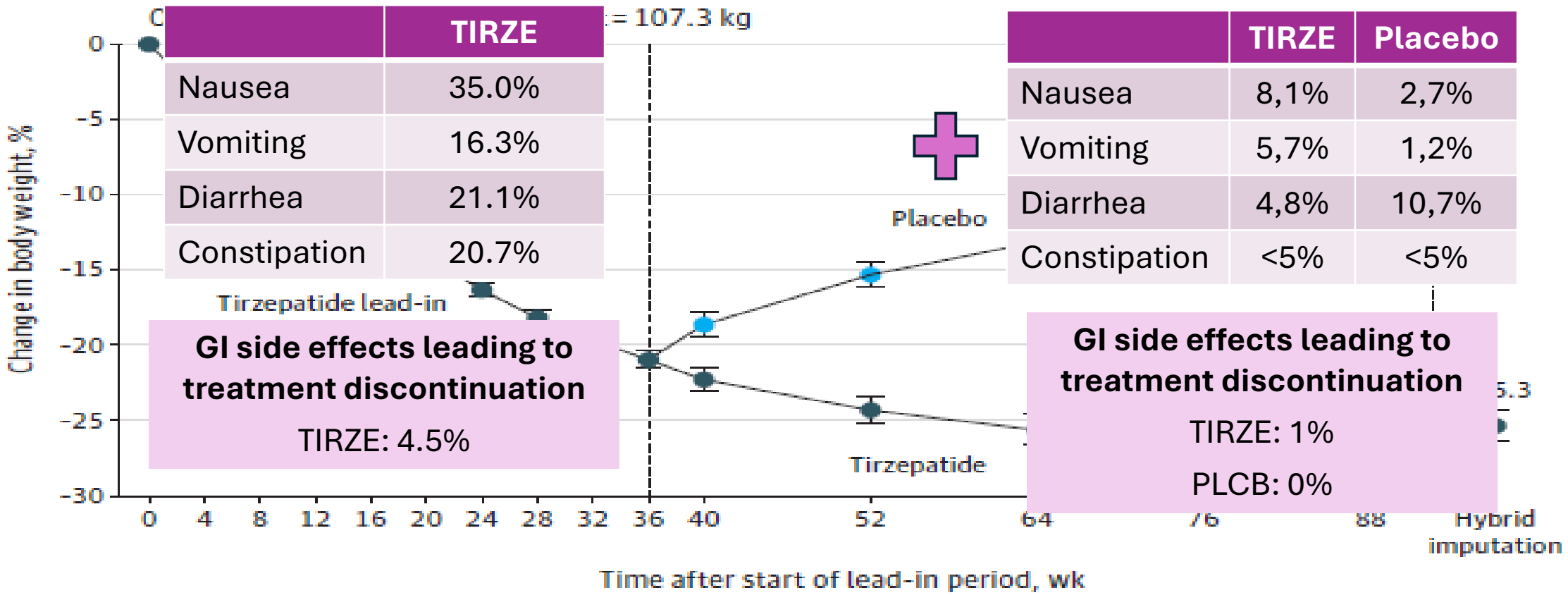
RANDOMIZATION PERIOD: TIRZE vs PCBI

	TIRZE	Placebo
Nausea	8,1%	2,7%
Vomiting	5,7%	1,2%
Diarrhea	4,8%	10,7%
Constipation	<5%	<5%

GI side effects leading to treatment discontinuation

TIRZE: 1%

PLCB: 0%



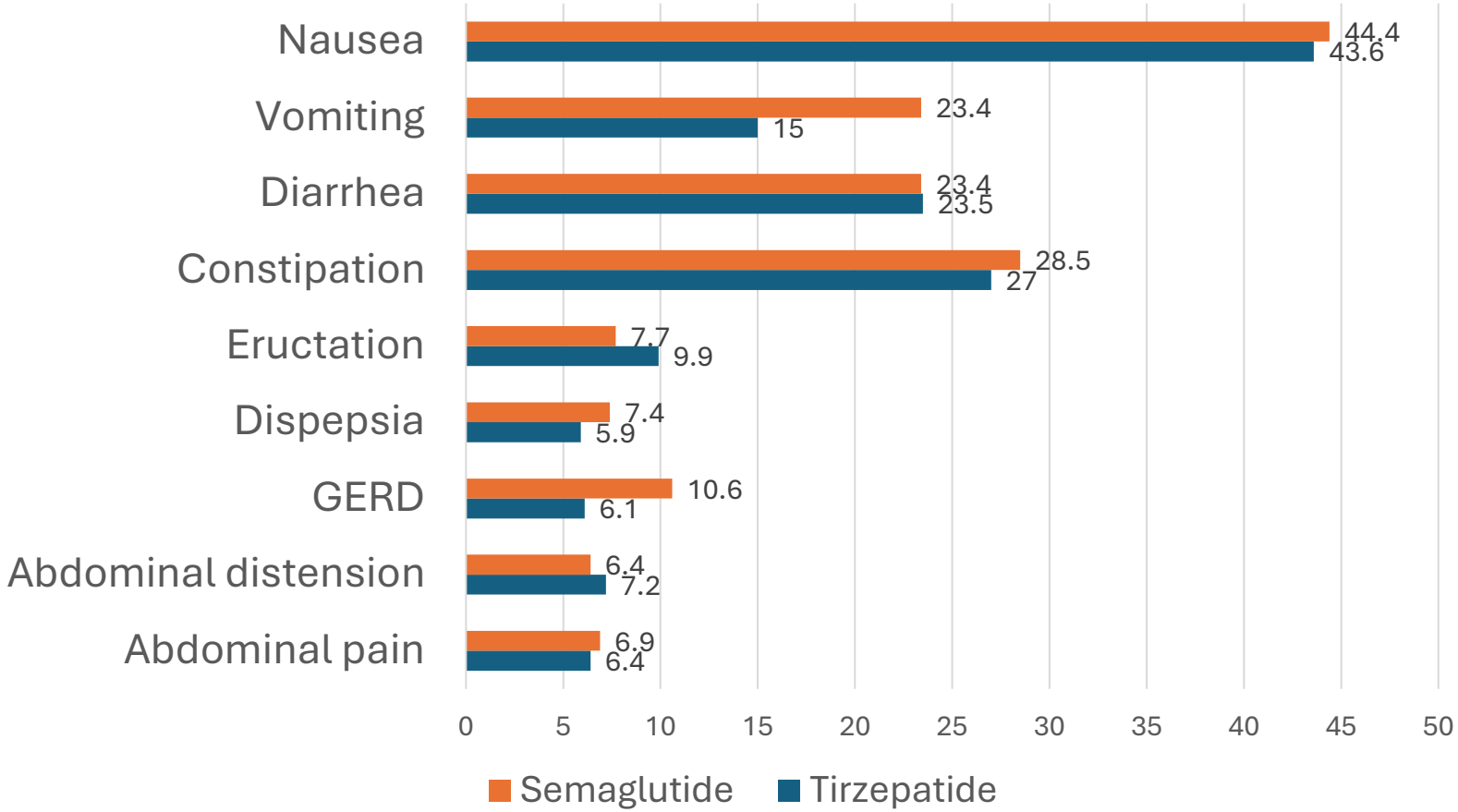
Aronne LJ et al. N Eng J Med 2025

Prevalence of common GI side effects

SURMOUNT 5 Trial: RCT Tirzepatide vs Semaglutide

(n=751, age 44.7 y, female 64.7%, BMI 39.4 kg/m2, **follow up: 72 weeks**)

Cumulative incidence of GI adverse events reported in at least 5% of participants



GI side effects leading to treatment discontinuation

SEMA: 5.6%

TIRZE: 2.7%

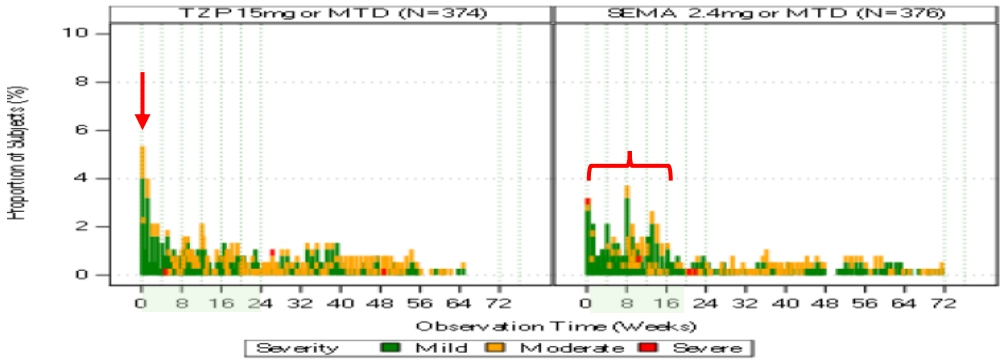
Aronne LJ et al. N Eng J Med 2025

Incidence of common GI side effects

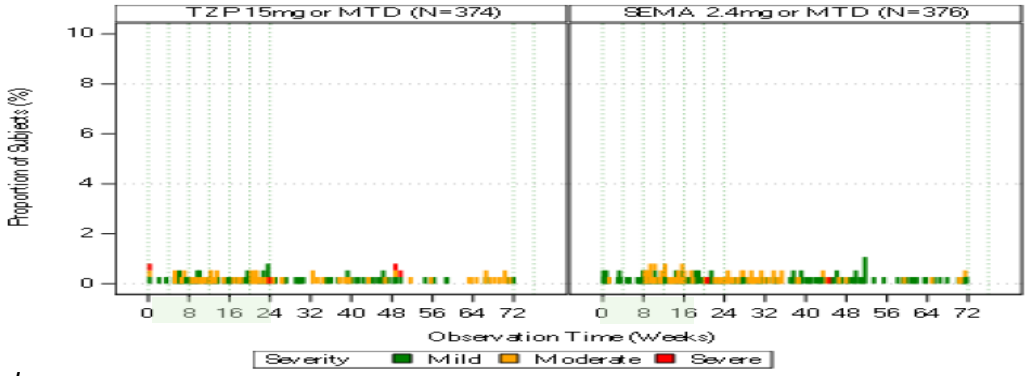
Tirzepatide vs Semaglutide (SURMOUNT 5 Trial- RCT)

(n=751, age 44.7 y, female 64.7%, BMI 39.4 kg/m2, follow up: 72 weeks)

Nausea

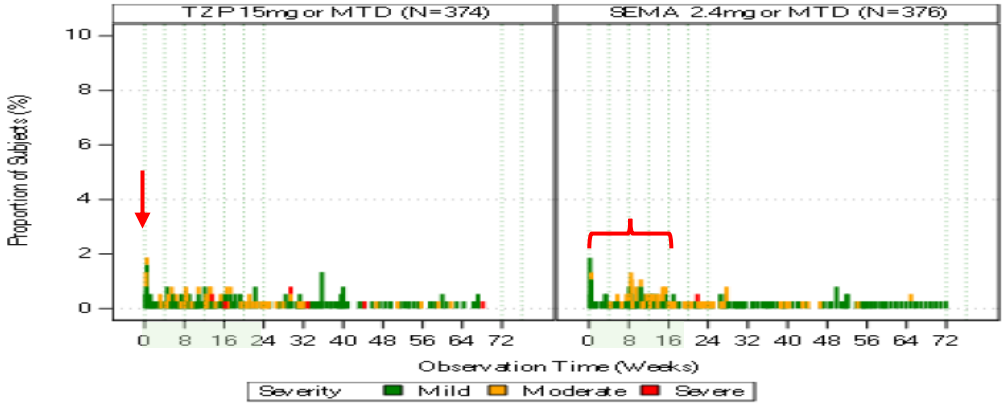


Vomiting

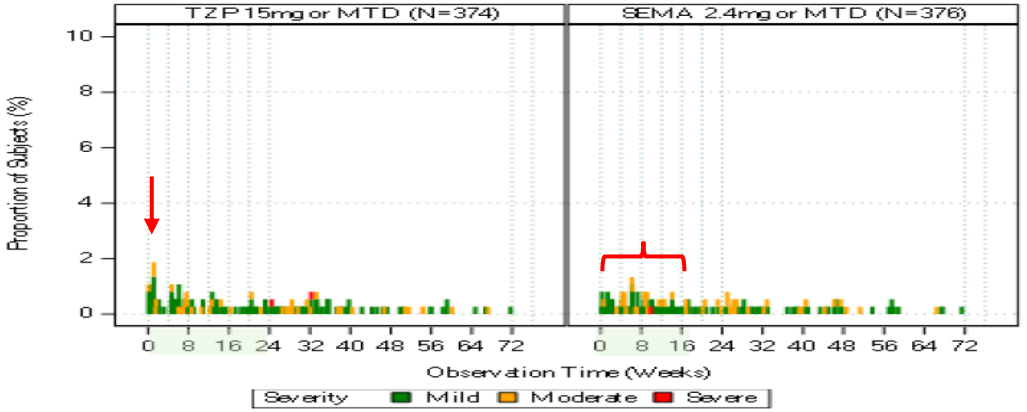


Titration period

Diarrhea



Constipation



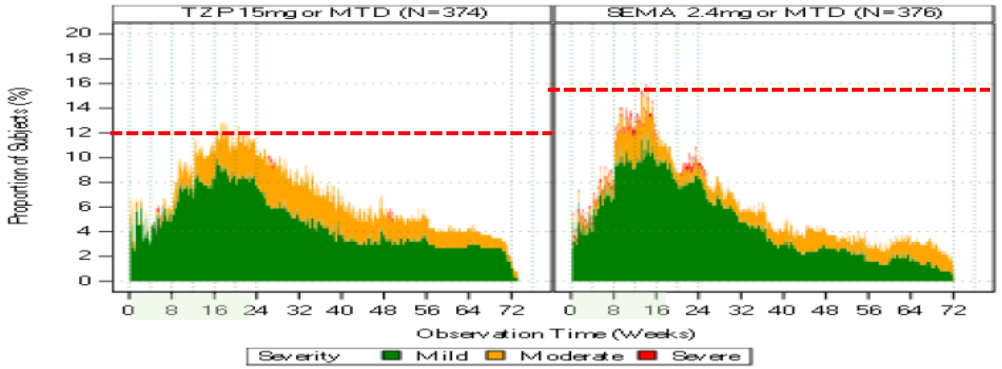
Aronne LJ et al. N Eng J Med 2025

Prevalence of common GI side effects

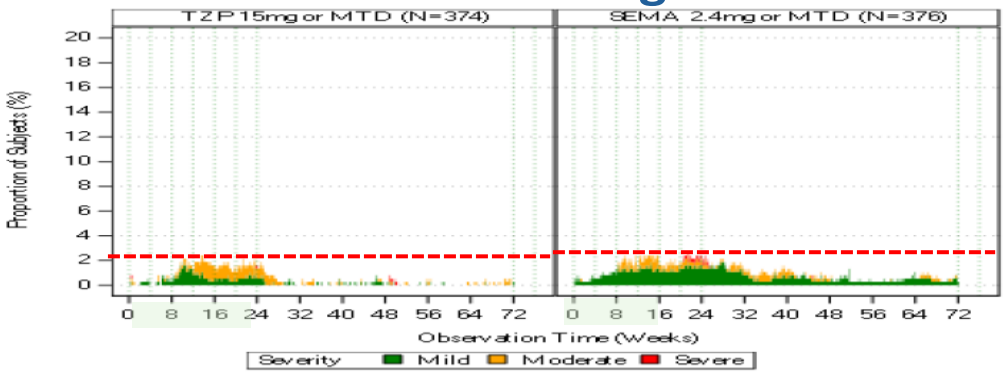
Tirzepatide vs Semaglutide (SURMOUNT 5 Trial- RCT)

(n=751, age 44.7 y, female 64.7%, BMI 39.4 kg/m2, follow up: 72 weeks)

Nausea

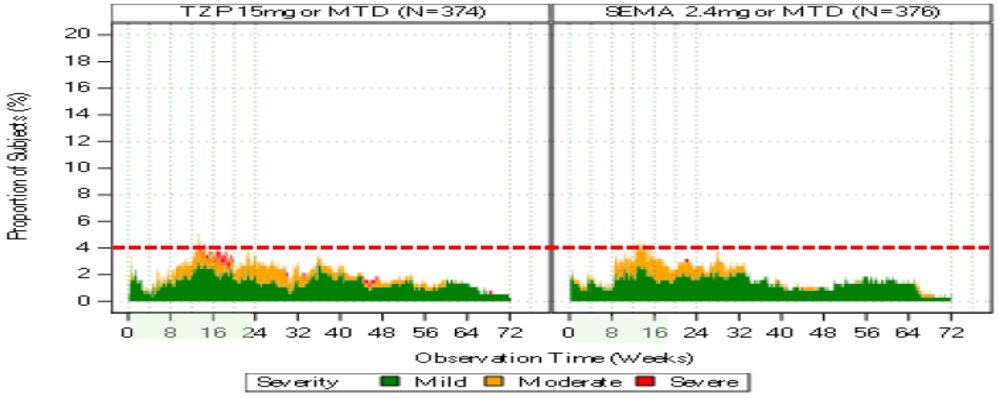


Vomiting

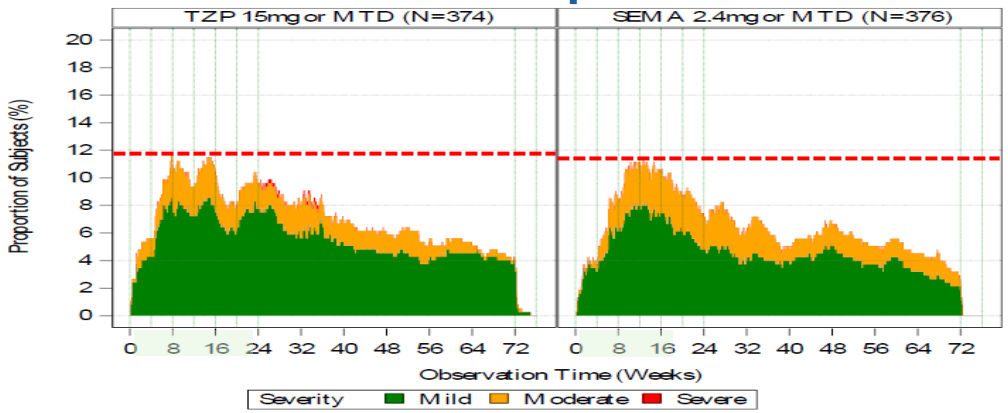


Titration period

Diarrhea



Constipation



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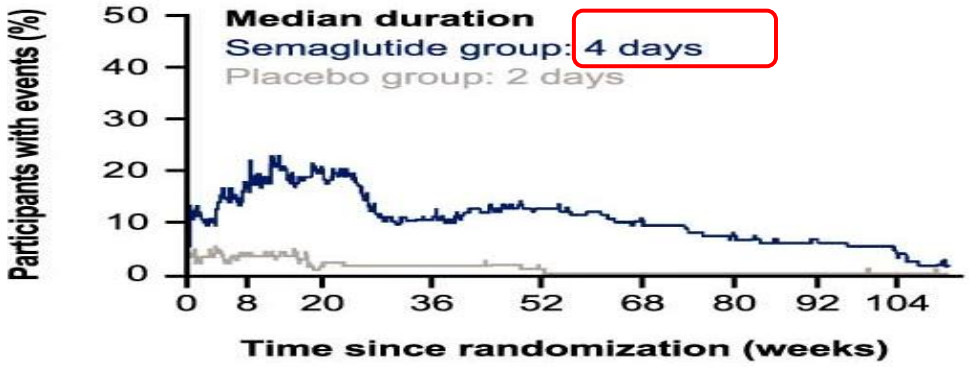
Duration of common GI side effects

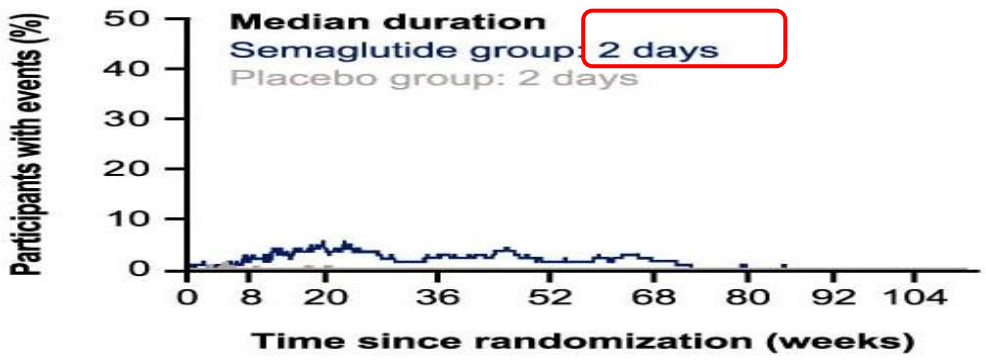
STEP 5 Trial: RCT Semaglutide 2.4 mg vs Placebo

(n=304, age 47.3 y, female 76%, BMI 38.5 kg/m2, **follow up: 104 weeks**)

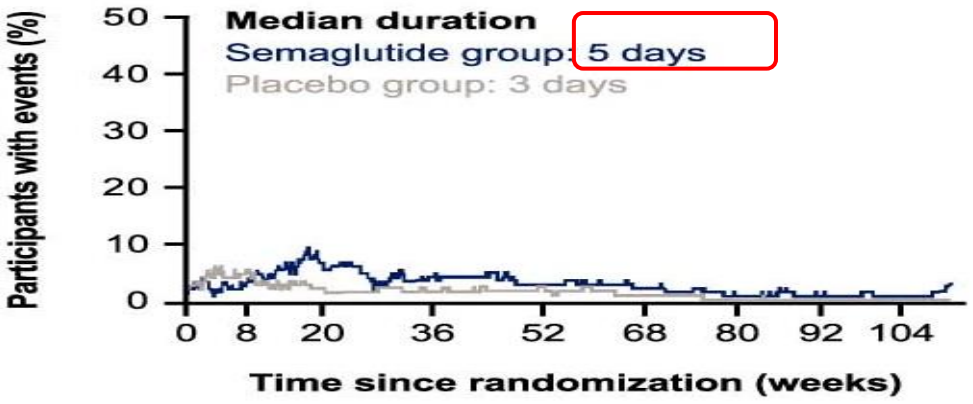
Nausea



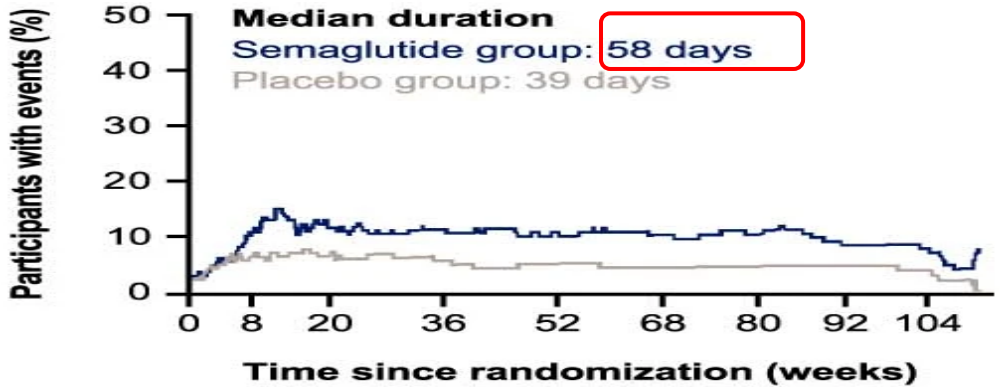
Vomiting



Diarrhea



Constipation



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Uncommon gastrointestinal side effects

Gastroparesis and food retention

No specific recommendation on witholding GLP1RA

1. **Subjects with clinically significant GE abnormality (for example, severe gastroparesis or gastric outlet obstruction) were excluded from clinical trials.**
2. **Gastoparesis (defined as use of code oral promotility agent) [1]**
   - Sema 9,1/1000 person-yeras (Lira 7,3; Nalt-Bup 3,1)
3. **Food retention**

American Society for Gastrointestinal Endoscopy position statement on peri-endoscopic management of patients on glucagon-like peptide-1 receptor agonists

Statement 1. The ASGE recommends immediate preprocedure evaluation for GI symptoms (severe nausea, vomiting, regurgitation when lying supine, abdominal bloating, abdominal distention, and abdominal pain) suggestive of possible delayed gastric emptying for all patients on GLP-1RAs.

Statement 2. The ASGE recommends a detailed discussion regarding possible risk of aspiration with all patients on GLP-1RAs undergoing endoscopic evaluation.

Statement 3. The ASGE suggests a liquid diet 24 hours before endoscopic procedure for all patients on GLP-1RAs.

1. Sodhi M et al; JAMA 2023. 2.Sharaiha RZ et al. Gastrointest Endosc 2025

Uncommon gastrointestinal side effects

Bowel obstruction or Ileus

Described in the prescribing information of Wegovy and Mounjaro, as adverse reactions recognized from the post-marketing experience

Setting	Association	Comments
UK	+	Incidence 1,9/1000 persons-year
US-FDA	-	Lira +, Sema -
Sweden, Denmark, Norway	-	

Jalleh RJ et al. J Clin Endocrinol Metab 2025

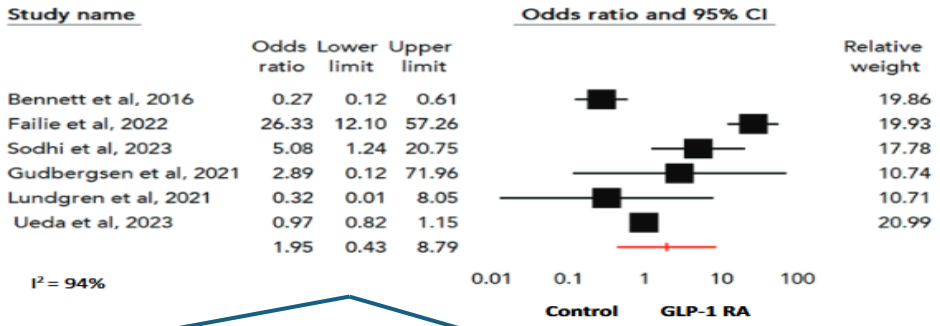
Uncommon gastrointestinal side effects

Bowel obstruction or Ileus

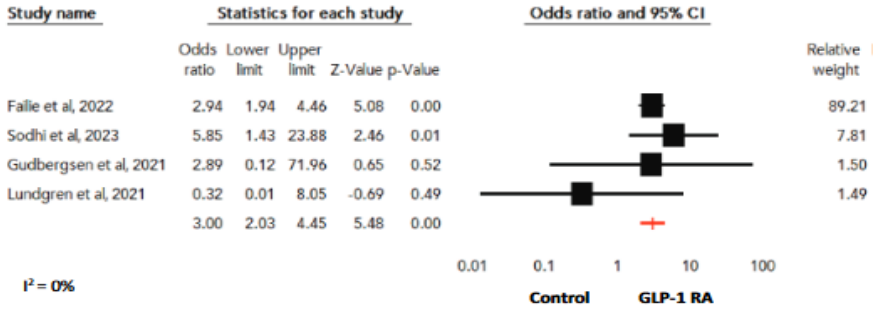
Described in the prescribing information of Wegovy and Mounjaro, as adverse reactions recognized from the post-marketing experience

Bowel obstruction and ileus events in patients on GLP-1 receptor agonists: A systematic review and meta-analysis

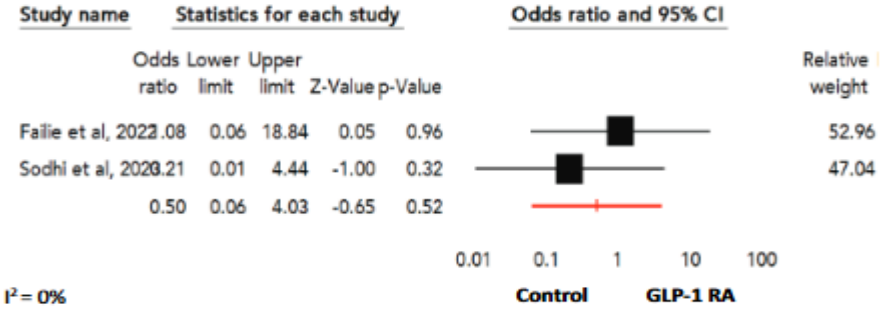
Overall



Liraglutide



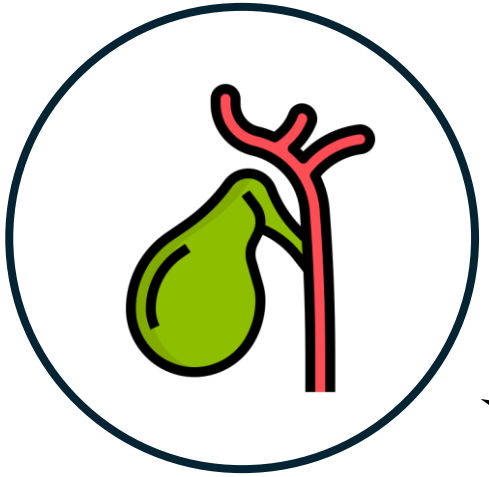
Semaglutide



Alfehaid L et al. Exp Op Drug Safety 2025

Effect of GLP-1 and GIP agonism on gallbladder physiology

GLP-1 RA



↓ Meal induced release of CCK

↓ Gallbladder myocite responsiveness to CCK

↓ Gallbladder emptying

Adapted from: Jalleh RJ et al. Endocrinology 2025

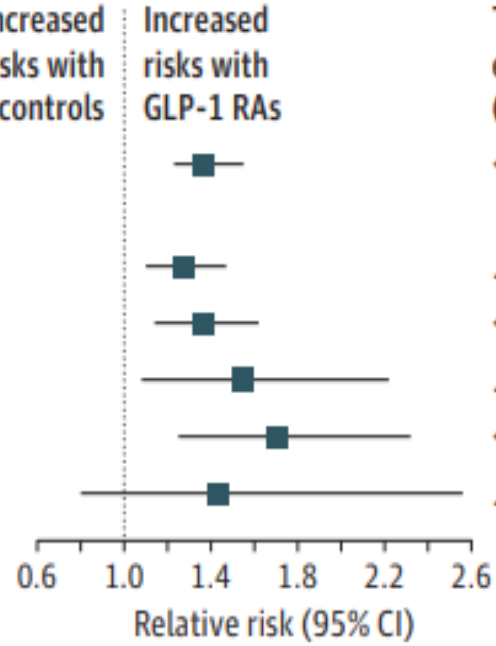
Incidence of common GI side effects

Association of GLP-1 RA Use With Risk of Gallbladder and Biliary Diseases
A Systematic Review and Meta-analysis of Randomized Clinical Trials

(76 studies, >100.000 subjects)

Figure 2. Risks of Cholelithiasis, Cholecystitis, and Biliary Diseases in Patients Randomized to GLP-1 RA Treatment Compared With Controls in All Trials

Outcomes	No. of studies	No. of events/total: GLP-1 RAs groups	No. of events/total: Control groups	ARD (95% CI) per 10 000 persons/year	I^2, % (95% CI)	Relative risk (95% CI)	Test of effect (*P* value)	Q test (*P* value)
Gallbladder or biliary disease	76	916/57 856	544/45 515	27 (17 to 38)	0 (0-27)	1.37 (1.23-1.55)	<.001	.86
Cholelithiasis	61	454/53 674	287/42 212	14 (5 to 24)	0 (0 to 30)	1.27 (1.10 to 1.47)	.001	.99
Cholecystitis	53	302/49 491	187/40 574	10 (4 to 18)	0 (0 to 32)	1.36 (1.14 to 1.62)	<.001	.99
Biliary disease	21	77/36 225	41/32 741	2 (0 to 5)	0 (0 to 48)	1.55 (1.08 to 2.22)	.02	.99
Cholecystectomy	7	125/13 690	61/11 479	9 (3 to 17)	0 (0 to 71)	1.70 (1.25 to 2.32)	<.001	.49
Biliary cancer	12	25/31 010	15/30 026	5 (-3 to 20)	0 (0 to 58)	1.43 (0.80 to 2.56)	.22	.86



He L et al. JAMA 2022

Incidence of common GI side effects

Association of GLP-1 RA Use With Risk of Gallbladder and Biliary Diseases
A Systematic Review and Meta-analysis of Randomized Clinical Trials

(76 studies, >100.000 subjects)

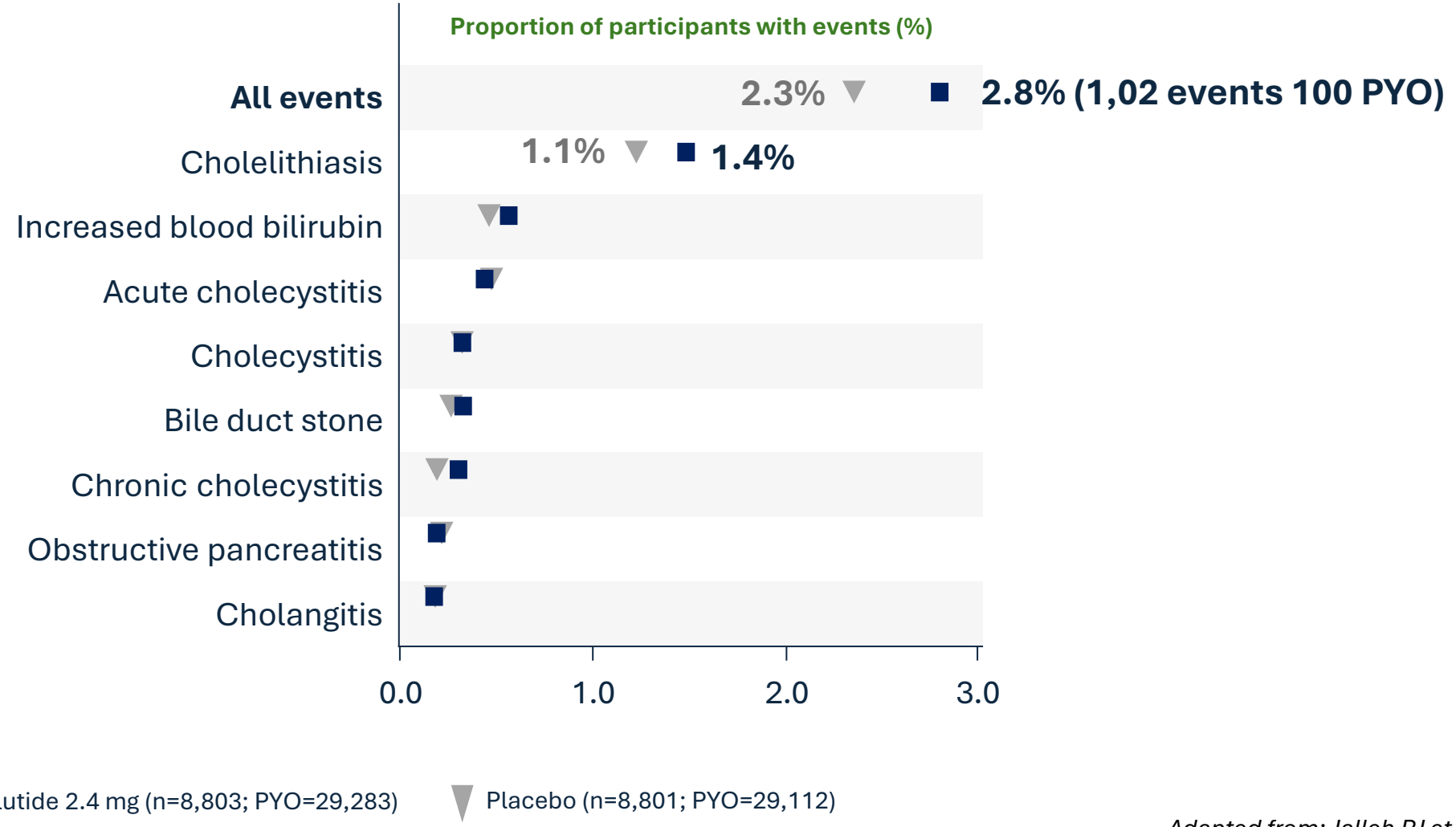
Table. Factors and Risks of Gallbladder or Biliary Diseases in 76 Randomized Clinical Trials of GLP-1 RA Drug Use

Factor	No. of patients	No. of trials	Relative risks (95% CI)	Heterogeneity I^2 %	Heterogeneity *P* value	*P* value for interaction[a]
Treatment						
Dose[b]						
High	61 962	54	1.56 (1.36-1.78)	0	.99	.006
Low	16 952	33	0.99 (0.74-1.33)	0	.67	
Duration, wk						
≤26	13 401	24	0.79 (0.48-1.31)	0	.97	.03
>26	90 417	53	1.40 (1.26-1.56)	0	.64	
Indication[c]						
Weight loss	11 282	13	2.29 (1.64-3.18)	0	.85	<.001
T2D/other	92 090	63	1.27 (1.14-1.43)	0	.94	
Baseline BMI[d]						
High	25 275	33	1.49 (1.20-1.84)	0	.50	.36
Low	77 530	42	1.33 (1.18-1.50)	0	.89	

He L et al. JAMA 2022

Effect of GLP-1 and GIP agonism on gallbladder physiology

Gallbladder disorders in the SELECT TRIAL



Adapted from: Jalleh RJ et al. Endocrinology 2025

Incidence of common GI side effects

SURMOUNT 5 Trial: RCT Tirzepatide vs Semaglutide

(n=751, age 44.7 y, female 64.7%, BMI 39.4 kg/m2, follow up: 72 weeks)

Table S9. Adverse Events of Special Interest

Variable*	Tirzepatide MTD (N=374)	Semaglutide MTD (N=376)	Total (N=750)
	number (percent)		
Pancreatitis, adjudication-confirmed	0 (0.0)	1 (0.3)	1 (0.1)
Major adverse cardiovascular events	0 (0.0)	0 (0.0)	0 (0.0)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)
Severe or serious GI AEs	17 (4.5)	14 (3.7)	31 (4.1)
Severe or serious Gallbladder Diseases	4 (1.1)	5 (1.3)	9 (1.2)
Severe or serious hepatic disorders	1 (0.3)	0 (0.0)	1 (0.1)
Severe or serious arrhythmias and cardiac conductive disorders	3 (0.8)	1 (0.3)	4 (0.5)
Hypoglycemia with a blood glucose level <54 mg/dl	0 (0.0)	1 (0.3)	1 (0.1)
Hypoglycemia level 3	0 (0.0)	0 (0.0)	0 (0.0)
Thyroid malignancies and C-cell hyperplasia	0 (0.0)	0 (0.0)	0 (0.0)
Severe or serious hypersensitivity events	0 (0.0)	0 (0.0)	0 (0.0)
Severe or serious injection site reactions	0 (0.0)	0 (0.0)	0 (0.0)
Severe or serious acute renal events	1 (0.3)	0 (0.0)	1 (0.1)
Severe or serious major depressive disorder, suicidal ideation, or suicidal behaviors	0 (0.0)	0 (0.0)	0 (0.0)

*Safety end points were analyzed with data from participants regardless of adherence to treatment and regardless of initiation of other anti-obesity medication or bariatric surgery.

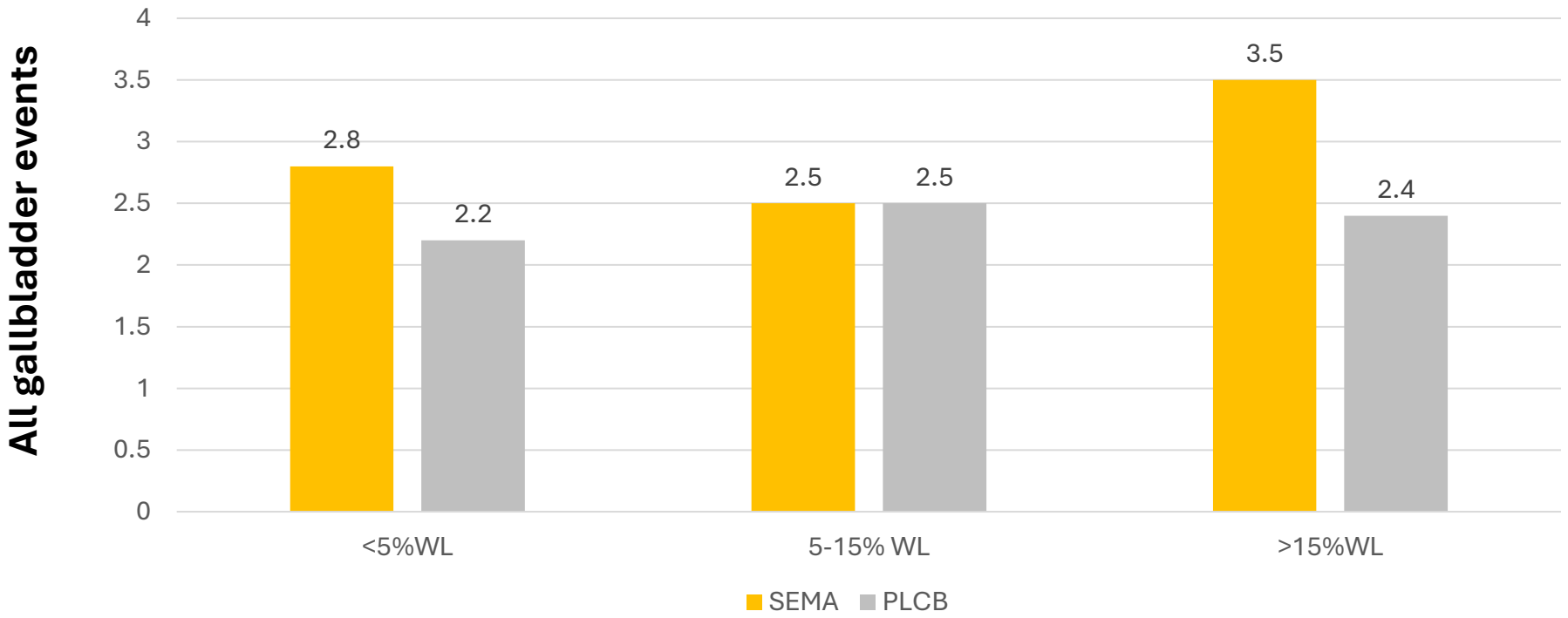
Hypersensitivity includes immediate (≤24 hours after administration of tirzepatide or semaglutide) and nonimmediate (>24 hours after administration of tirzepatide or semaglutide) severe or serious hypersensitivity events

Aronne LJ et al. N Eng J Med 2025

Effect of GLP-1 and GIP agonism on gallbladder physiology

Gallbladder disorders in the SELECT TRIAL

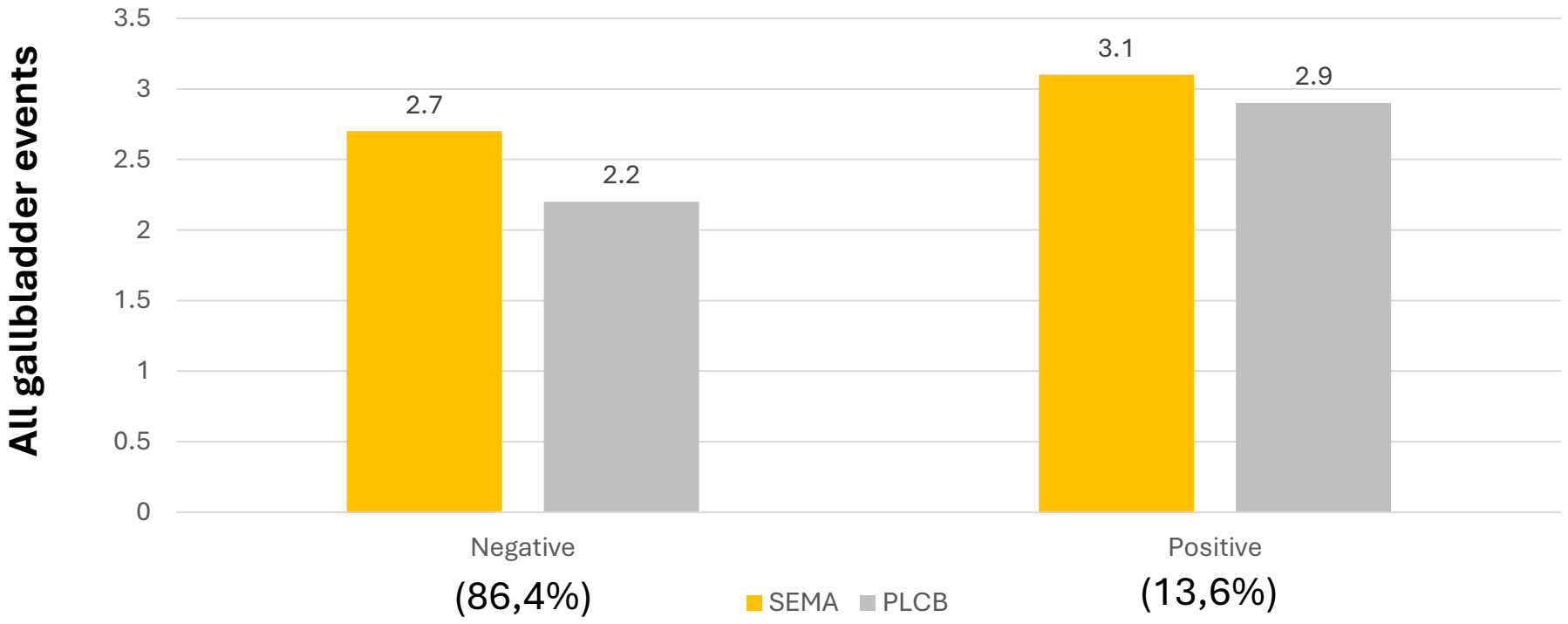
Incidence by weight loss category



Effect of GLP-1 and GIP agonism on gallbladder physiology

Gallbladder disorders in the SELECT TRIAL

Incidence in subjects according the presence of gallbladder disease @ screening (13.6%)



GLP-1 RA in MBS patients

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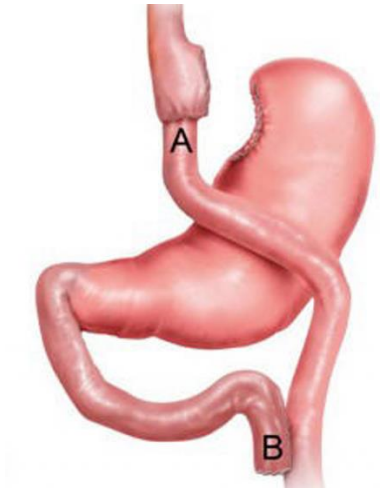

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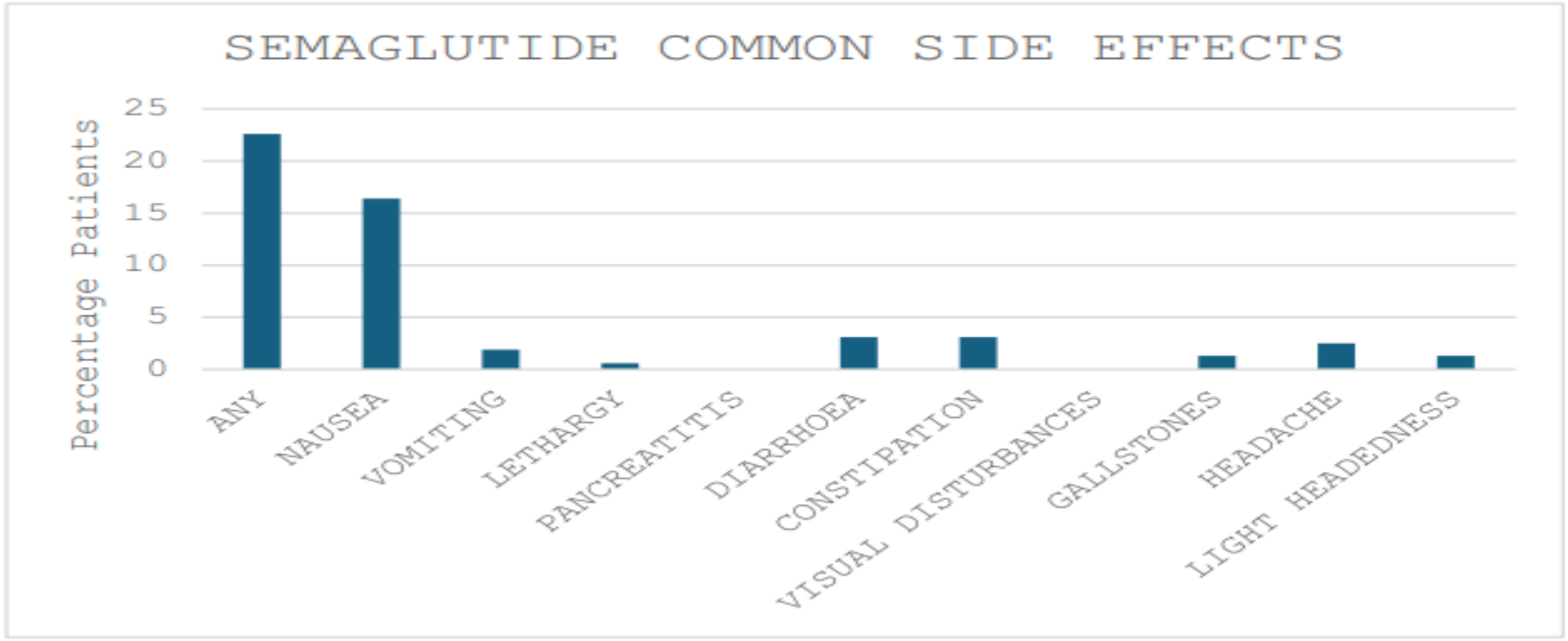
>AE??

GI and biliary side effects in MBS subjects

SEMAGLUTIDE: single-center analysis in Australia

(poor WL or significant WR. N=265, female 81%, age 40.9 y, Surgery: SG 52% - AGB 25%, GBP 23%, BW@GLP-1R 96,5 kg)



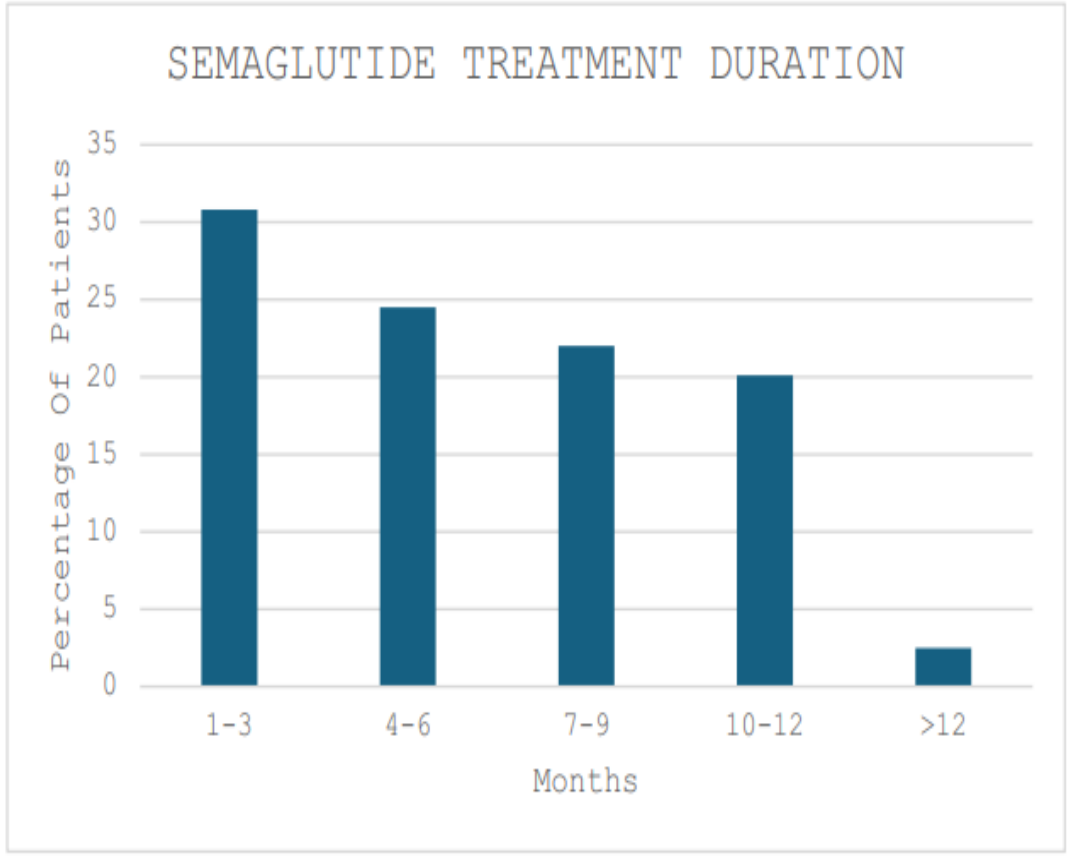
Proportion of subjects reporting one or more side effects: 22.6%

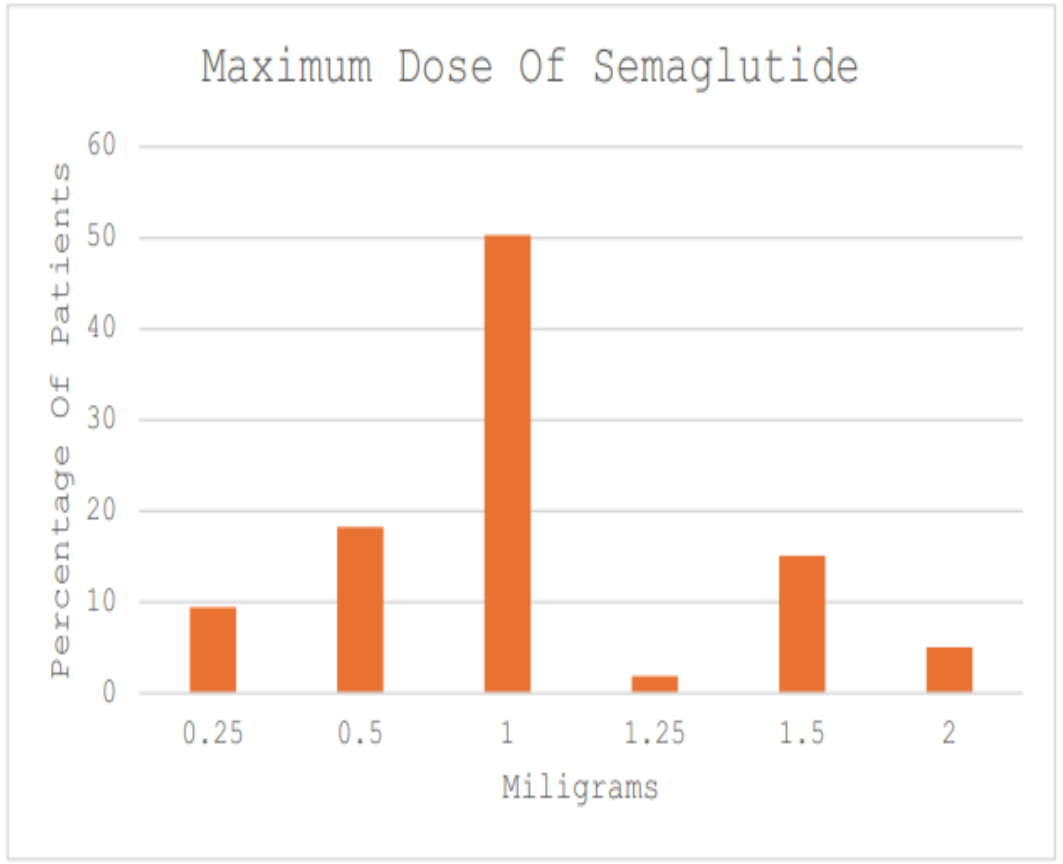
Ferguson J et al. Obesity Surgery 2025

GI and biliary side effects in MBS subjects

SEMAGLUTIDE: single-center analysis in Australia

(poor WL or significant WR. N=265, female 81%, age 40.9 y, Surgery: SG 52% - AGB 25%, GBP 23%, BW@GLP-1R 96,5 kg)





Ferguson J et al. Obesity Surgery 2025

GI and biliary side effects in MBS subjects

LIRA 3.0 mg or SEMA 1.0 mg: single-center analysis in Switzerland

Excessive WR. N=40, female 80%, age 50 y, GLP1RA initiated at 75 mo after surgery

Adverse events were reported in 32.5% (*n* = 13) of the patients, all of which were mild and transien

Supplemental Table 2. Registered adverse events in connection to GLP1-RA therapy (N=40).

Adverse events	All n=40	Liraglutide n=22	Semaglutide n=18
Any adverse events	13 (32.5)	5 (22.7)	8 (44.4)
Nausea	6 (15.0)	3 (13.6)	3 (16.7)
Constipation	5 (12.5)	1 (4.5)	4 (22.2)
Vomiting	1 (2.5)	0	1 (5.6)
Diarrhea	1 (2.5)	0	1 (5.6)
Injection site reaction	2 (5.0)	1 (4.5)	1 (5.6)
Headache	1 (2.5)	0	1 (5.6)

Data are presented as frequency (%). Three patients in the semaglutide group reported two adverse events, in the liraglutide group only singular adverse events were reported. GLP1-RA, glucagon-like peptide-1 receptor agonist.

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Take home messages

1. The physiology of GLP-1RA accounts for the GI and biliary AE associated with family of drugs.
2. Mild and transient side GI side effects are common and should be treated symptomatically. However, GI AE are the most common reason for the discontinuation of GLP-1RA therapy.
3. Attention should be paid to clinical symptoms of biliary AE, specially when GLP-1RA are used at higher doses and for prolonged periods of time.
4. Data on the safety of the GLP-1RA+MBS combination is scarce. However, data suggest the use of this combination is safe.

Thank you for your attention