Navigating the Challenges of Incretin Receptor Agonists in Modern Clinical Practice

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Agenda

- Introduction
- Thyroid-related challenges
- Perioperative Implications
- Take-home messages

Adverse Events of GLP-1 Receptor Agonists

Established Adverse Events

Gastrointestinal Symptoms

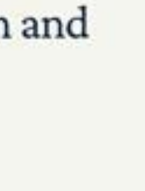
Injection-site reactions

Gallbladder and biliary disorders

Discontinuation due to AEs

Emerging or Potential Adverse Events

Retinopathy progression and NAION



Acute kidney injury

Gastroparesis, GERD, and bowel obstruction

Pancreatitis and pancreatic cancer

Medullary thyroid carcinoma

Lean muscle mass loss

Suicidality

NAION: nonarteritic anterior ischemic optic neuropathy; particularly with semaglutide.

Kunutsor SK, Seidu S. Drugs 2025; https://doi.org/10.1007/s40265-025-02263-0.

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Clinical scenario

- A 35-year-old woman
- BMI: 38 kg/m^2
- She would like to initiate a GLP-1RA to promote weight loss.
- Her mother underwent a total thyroidectomy due to a benign multinodular goiter.
- After viewing a commercials warning on the Instagram that those with thyroid nodule should not take a GLP-1RA, she is concerned about this drug adverse effect.
- She is asking you to order a thyroid ultrasound examination.

Food and Drug Administration warning

- GLP-1 receptor agonists and dual GLP-1/GIP receptor agonists are contraindicated in patients with:
  - Personal history of medullary thyroid carcinoma
  - Family history of medullary thyroid carcinoma
  - Patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)

The first major report to document the phenomenon of liraglutide-associated C-cell hyperplasia in rodent models

Glucagon-Like Peptide-1 Receptor Agonists Activate Rodent Thyroid C-Cells Causing Calcitonin Release and C-Cell Proliferation

Lotte Bjerre Knudsen,* Lars Wichmann Madsen,* Søren Andersen, Kasper Almholt, Anne S. de Boer, Daniel J. Drucker, Carsten Gotfredsen, Frederikke Lihme Egerod, Anne Charlotte Hegelund, Helene Jacobsen, Sóren Dyring Jacobsen, Alan C. Moses, Anne-Marie Mølck, Henriette S. Nielsen, Jette Nowak, Helene Solberg, Tu D. L. Thi, and Milan Zdravkovic

Novo Nordisk A/S (L.B.K., L.W.M., S.A., K.A., A.S.d.B., C.G., F.L.E., A.C.H., H.J., S.D.J., A.C.M., A.M.M., H.S.N., J.N., H.S., T.D.L.T., M.Z.), DK-2760 Maaloev, Denmark; and The Samuel Lunenfeld Research Institute (D.J.D.), Mt. Sinai Hospital, University of Toronto, Ontario, Canada M6B 3G3

Liraglutide is a glucagon-like peptide-1 (GLP-1) analog developed for type 2 diabetes. Long-term liraglutide exposure in rodents was associated with thyroid C-cell hyperplasia and tumors. Here, we report data supporting a GLP-1 receptor-mediated mechanism for these changes in rodents. The GLP-1 receptor was localized to rodent C-cells. GLP-1 receptor agonists stimulated calcitonin release, up-regulation of calcitonin gene expression, and subsequently C-cell hyperplasia in rats and, to a lesser extent, in mice. In contrast, humans and/or cynomolgus monkeys had low GLP-1 receptor expression in thyroid C-cells, and GLP-1 receptor agonists did not activate adenylate cyclase or generate calcitonin release in primates. Moreover, 20 months of liraglutide treatment (at >60 times human exposure levels) did not lead to C-cell hyperplasia in monkeys. Mean calcitonin levels in patients exposed to liraglutide for 2 yr remained at the lower end of the normal range, and there was no difference in the proportion of patients with calcitonin levels increasing above the clinically relevant cutoff level of 20 pg/ml. Our findings delineate important species-specific differences in GLP-1 receptor expression and action in the thyroid. Nevertheless, the long-term consequences of sustained GLP-1 receptor activation in the human thyroid remain unknown and merit further investigation. **(*Endocrinology* 151: 1473–1486, 2010)**

The use of GLP-1 receptor agonists is associated with an increased risk of thyroid cancer

GLP-1 receptor agonists and the risk of thyroid cancer

Bezin J., Gouverneur A., Pénichon M., Mathieu C., Garrel R., Hillaire-Buys D., Pariente A., Faillie J-L.

Nationwide population-based study on French SNDS database

3,746,672 individuals with type 2 diabetes treated with second-line antidiabetes drugs between 2006-2018

2,562 cases of thyroid cancers

45,184 matched control subjects

	Case subjects *n* = 2,572	Control subjects *n* = 45,184	Adjusted hazard ratio (95%CI)*
GLP-1 receptor agonists			
No use	2,255 (88.0)	40,836 (90.4)	Reference
Cumulative use ≤1 year	117 (4.6)	1,767 (3.9)	1.22 (0.99 to 1.50)
Cumulative use 1-3 years	112 (4.4)	1,419 (3.1)	1.58 (1.27 to 1.95)
Cumulative use >3 years	78 (3.0)	1,162 (2.6)	1.36 (1.05 to 1.74)
DPP-4 inhibitors			
No use	1,522 (59.4)	27,406 (60.7)	Reference
Cumulative use ≤1 year	333 (13.0)	5,209 (11.5)	1.12 (0.99 to 1.28)
Cumulative use 1-3 years	310 (12.1)	5,918 (13.1)	0.96 (0.84 to 1.10)
Cumulative use >3 years	397 (15.5)	6,651 (14.7)	1.19 (1.04 to 1.35)

*Adjusted for social deprivation index, goiter, hypo- and hyperthyroidism in the last year, and use of other antidiabetes drugs in the last 6 years considered in therapeutic class.

Diabetes Care

This study is part of the DRUGS-SAFER research program, funded by the French Medicines Agency. This publication represents the views of the authors and does not necessarily represent the opinion of the French Medicines Agency.

| 1

Bezin J, et al. Diabetes Care 2023;46(2):384-390.

Key findings

- Use of GLP-1RAs for 1-3 years was associated with a significantly increased risk of:
  - All thyroid cancers
    adjusted HR (95 % CI): 1.58 (1.27-1.95)
  - Medullary thyroid cancer
    adjusted HR (95 % CI): 1.78 (1.04-3.05)

Bezin J, et al. Diabetes Care 2023;46(2):384-390.

Glucagon-like peptide 1 receptor agonist use and risk of thyroid cancer: Scandinavian cohort study

Björn Pasternak,[1,2] Viktor Wintzell,[1] Anders Hviid,[2,3] Björn Eliasson,[4,5] Soffia Gudbjörnsdottir,[5,6] Christian Jonasson,[7,8] Kristian Hveem,[7,8] Henrik Svanström,[1,2] Mads Melbye,[7,9,10,11] Peter Ueda[1]

- Design: Scandinavian cohort study.
- Setting: Denmark, Norway, and Sweden, 2007-2021.
- Participants:

Patients who started GLP-1RA treatment were compared with patients who started DPP4 inhibitor treatment, and in an additional analysis, patients who started SGLT2 inhibitor treatment.

- Main outcome measures:

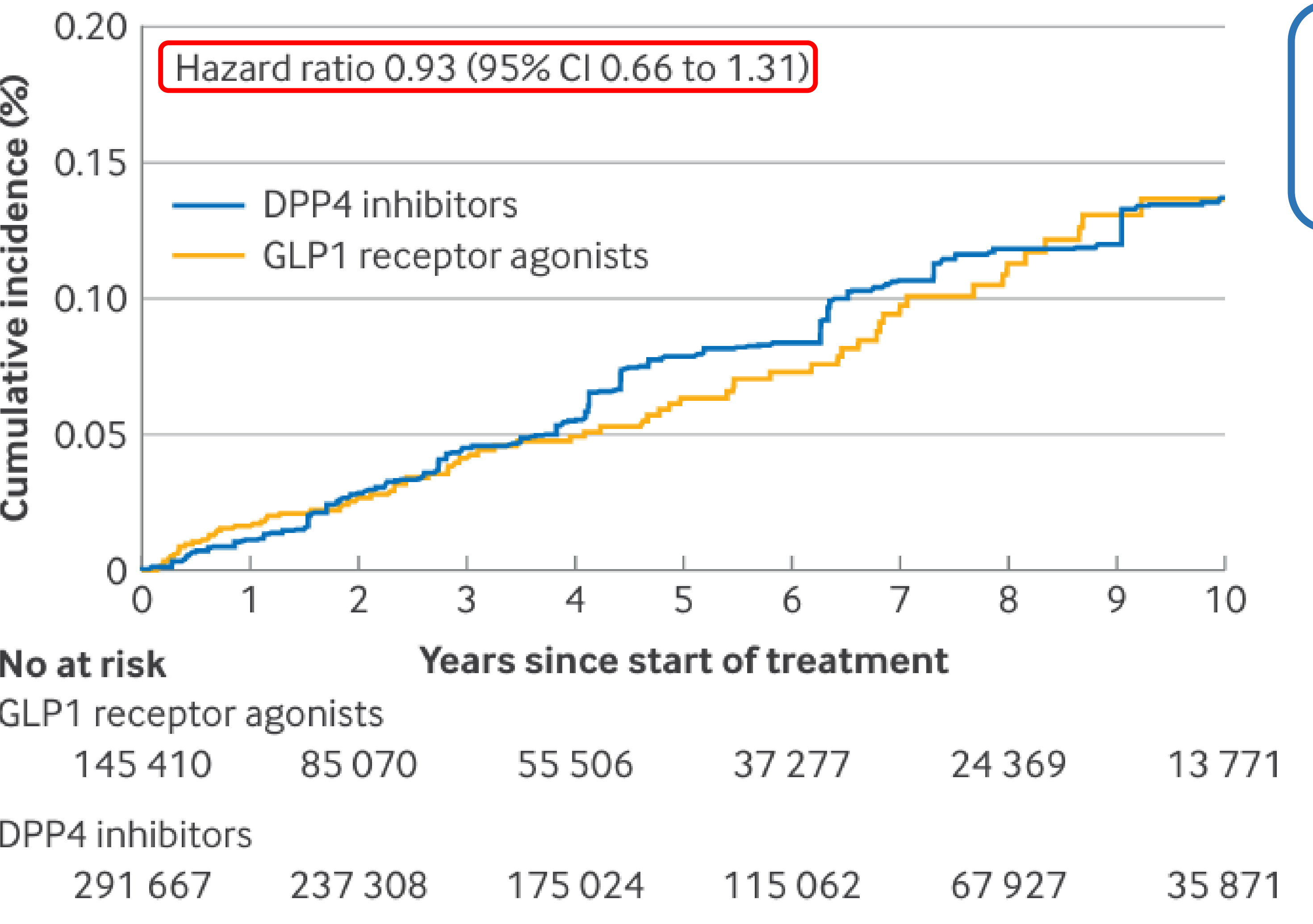
Thyroid cancer identified from nationwide cancer registers. An active-comparator new user study design was used to minimize risks of confounding and time related biases from using real world studies of drug effects.

- Mean F/U (SD) in the GLP-1RA group: 3.9 (3.5) years

Pasternak B, et al. BMJ 2024;385:e078225.

Cumulative incidence of thyroid cancer

Incidence rates: GLP-1RA group 1.33 per 10,000 person years
DPP4 inhibitor group 1.46 per 10,000 person years



The hazard ratio for medullary thyroid cancer:
1.19 (0.37 to 3.86)

Pasternak B, et al. BMJ 2024;385:e078225.

Glucagon-like peptide-1 receptor agonists and risk of thyroid cancer: A systematic review and meta-analysis of randomized controlled trials

Giovanni Antonio Silverii MD[1] | Matteo Monami PhD[1] | Marco Gallo MD[2] | Alberto Ragni MD[2] | Francesco Prattichizzo PhD[3] | Valerio Renzelli MD[4] | Antonio Ceriello MD[3] | Edoardo Mannucci MD[1]

- **Inclusion criteria:**

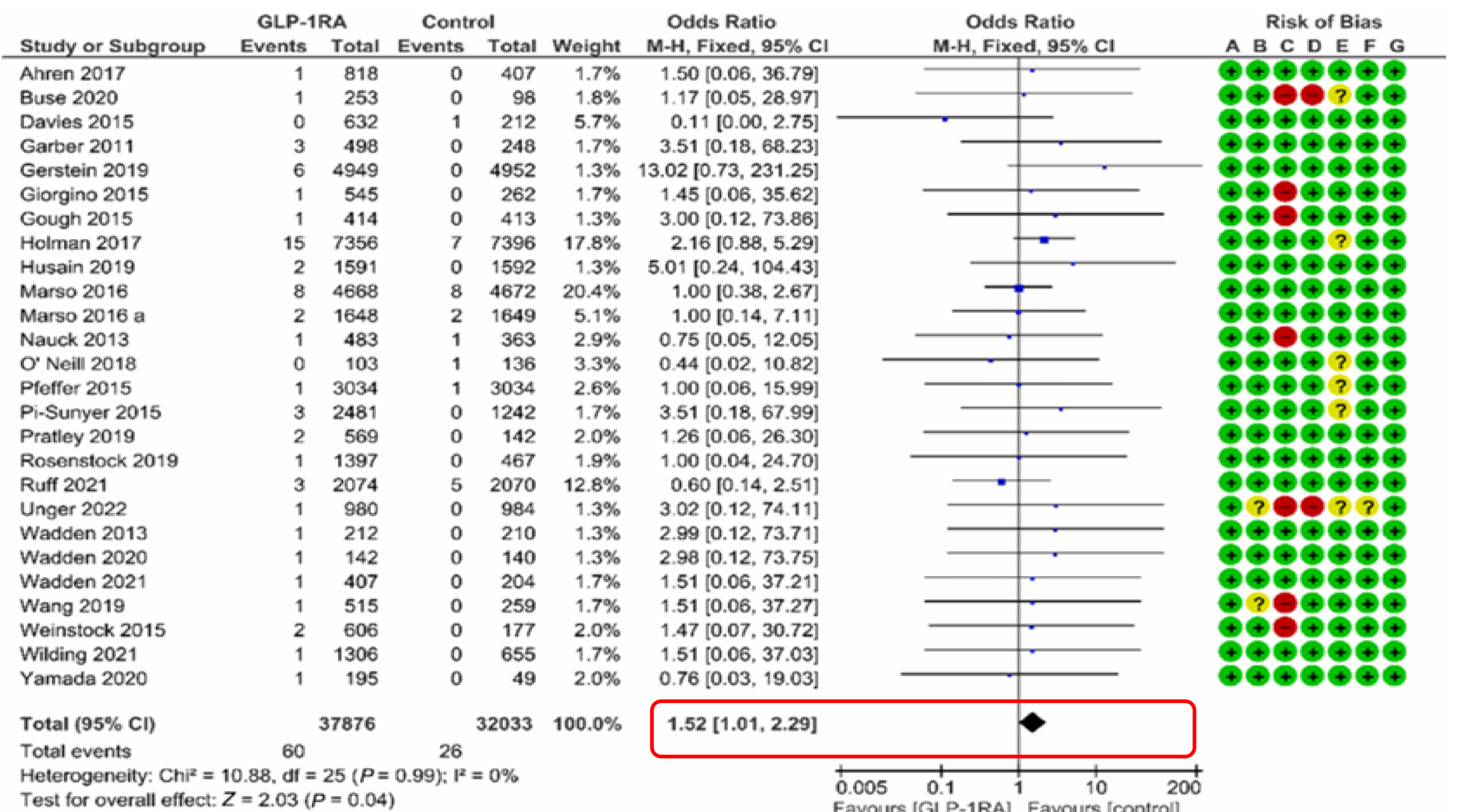
RCTs in which any GLP-1RA approved by European Medical Agency for any indication (i.e., type 2 diabetes or obesity) was compared with either placebo or active comparators lasting at least 52 weeks.

- **Number of studies:**

64 RCTs, of which 26 reported at least one case of thyroid cancer

Silverii GA, et al. Diabetes Obes Metab. 2024;26:891-900.

Risk of overall thyroid cancers

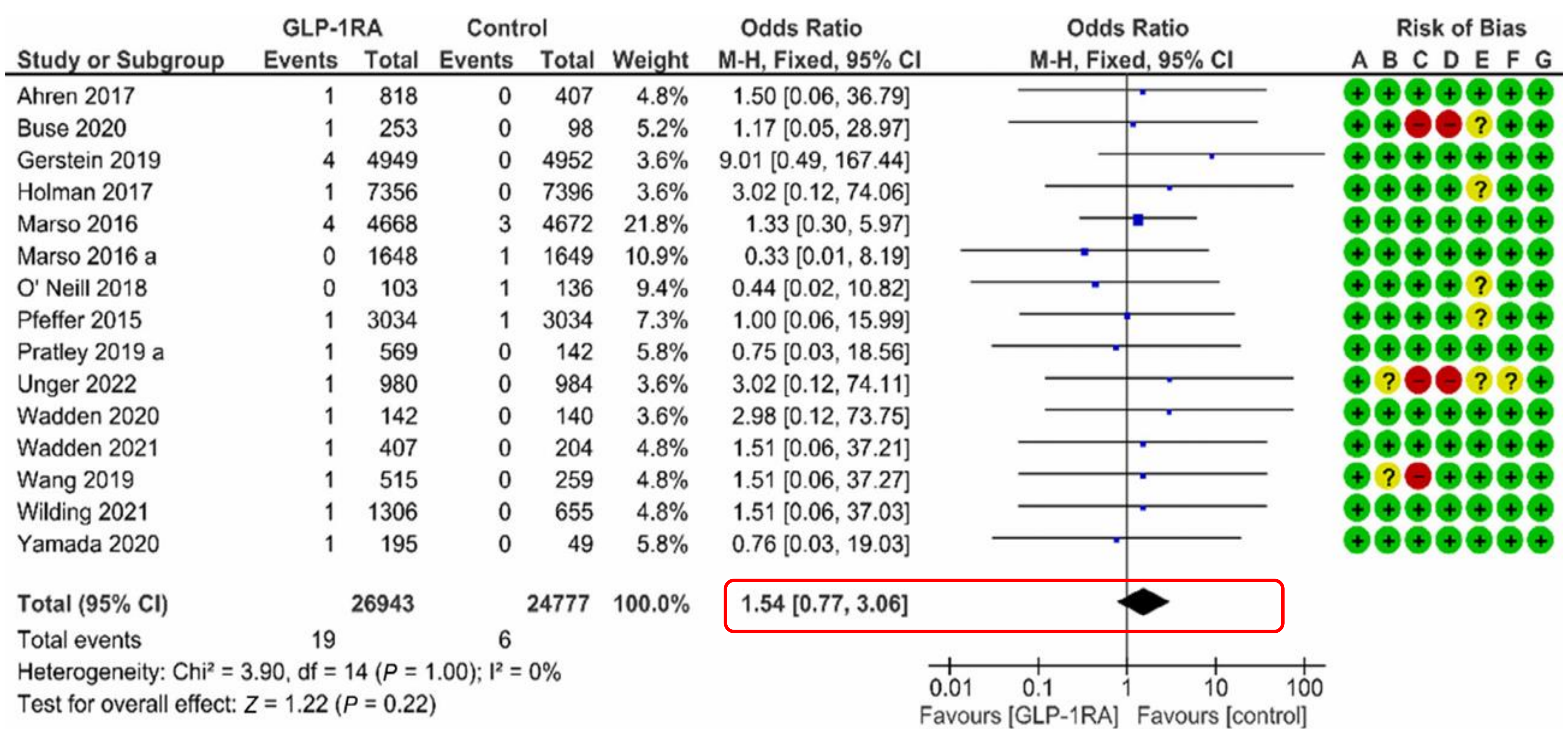


Study or Subgroup	GLP-1RA Events	GLP-1RA Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F	G
Ahren 2017	1	818	0	407	1.7%	1.50 [0.06, 36.79]	+	+	+	+	+	+	+
Buse 2020	1	253	0	98	1.8%	1.17 [0.05, 28.97]	+	+	−	−	?	+	+
Davies 2015	0	632	1	212	5.7%	0.11 [0.00, 2.75]	+	+	+	+	+	+	+
Garber 2011	3	498	0	248	1.7%	3.51 [0.18, 68.23]	+	+	+	+	+	+	+
Gerstein 2019	6	4949	0	4952	1.3%	13.02 [0.73, 231.25]	+	+	+	+	+	+	+
Giorgino 2015	1	545	0	262	1.7%	1.45 [0.06, 35.62]	+	+	−	+	+	+	+
Gough 2015	1	414	0	413	1.3%	3.00 [0.12, 73.86]	+	+	−	+	+	+	+
Holman 2017	15	7356	7	7396	17.8%	2.16 [0.88, 5.29]	+	+	+	+	?	+	+
Husain 2019	2	1591	0	1592	1.3%	5.01 [0.24, 104.43]	+	+	+	+	+	+	+
Marso 2016	8	4668	8	4672	20.4%	1.00 [0.38, 2.67]	+	+	+	+	+	+	+
Marso 2016 a	2	1648	2	1649	5.1%	1.00 [0.14, 7.11]	+	+	+	+	+	+	+
Nauck 2013	1	483	1	363	2.9%	0.75 [0.05, 12.05]	+	+	−	+	+	+	+
O' Neill 2018	0	103	1	136	3.3%	0.44 [0.02, 10.82]	+	+	+	+	?	+	+
Pfeffer 2015	1	3034	1	3034	2.6%	1.00 [0.06, 15.99]	+	+	+	+	?	+	+
Pi-Sunyer 2015	3	2481	0	1242	1.7%	3.51 [0.18, 67.99]	+	+	+	+	?	+	+
Pratley 2019	2	569	0	142	2.0%	1.26 [0.06, 26.30]	+	+	+	+	+	+	+
Rosenstock 2019	1	1397	0	467	1.9%	1.00 [0.04, 24.70]	+	+	+	+	+	+	+
Ruff 2021	3	2074	5	2070	12.8%	0.60 [0.14, 2.51]	+	+	+	+	+	+	+
Unger 2022	1	980	0	984	1.3%	3.02 [0.12, 74.11]	+	?	−	−	?	?	+
Wadden 2013	1	212	0	210	1.3%	2.99 [0.12, 73.71]	+	+	+	+	+	+	+
Wadden 2020	1	142	0	140	1.3%	2.98 [0.12, 73.75]	+	+	+	+	+	+	+
Wadden 2021	1	407	0	204	1.7%	1.51 [0.06, 37.21]	+	+	+	+	+	+	+
Wang 2019	1	515	0	259	1.7%	1.51 [0.06, 37.27]	+	?	−	+	+	+	+
Weinstock 2015	2	606	0	177	2.0%	1.47 [0.07, 30.72]	+	+	−	+	+	+	+
Wilding 2021	1	1306	0	655	1.7%	1.51 [0.06, 37.03]	+	+	+	+	+	+	+
Yamada 2020	1	195	0	49	2.0%	0.76 [0.03, 19.03]	+	+	+	+	+	+	+
Total (95% CI)		**37876**		**32033**	**100.0%**	**1.52 [1.01, 2.29]**							
Total events	60		26										

Heterogeneity: Chi² = 10.88, df = 25 (P = 0.99); I² = 0%
Test for overall effect: Z = 2.03 (P = 0.04)

Silverii GA, et al. Diabetes Obes Metab. 2024;26:891-900.

Risk of papillary thyroid cancer



Study or Subgroup	GLP-1RA Events	GLP-1RA Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	A	B	C	D	E	F	G
Ahren 2017	1	818	0	407	4.8%	1.50 [0.06, 36.79]	+	+	+	+	+	+	+
Buse 2020	1	253	0	98	5.2%	1.17 [0.05, 28.97]	+	+	−	−	?	+	+
Gerstein 2019	4	4949	0	4952	3.6%	9.01 [0.49, 167.44]	+	+	+	+	+	+	+
Holman 2017	1	7356	0	7396	3.6%	3.02 [0.12, 74.06]	+	+	+	+	?	+	+
Marso 2016	4	4668	3	4672	21.8%	1.33 [0.30, 5.97]	+	+	+	+	+	+	+
Marso 2016 a	0	1648	1	1649	10.9%	0.33 [0.01, 8.19]	+	+	+	+	+	+	+
O' Neill 2018	0	103	1	136	9.4%	0.44 [0.02, 10.82]	+	+	+	+	?	+	+
Pfeffer 2015	1	3034	1	3034	7.3%	1.00 [0.06, 15.99]	+	+	+	+	?	+	+
Pratley 2019 a	1	569	0	142	5.8%	0.75 [0.03, 18.56]	+	+	+	+	+	+	+
Unger 2022	1	980	0	984	3.6%	3.02 [0.12, 74.11]	+	?	−	−	?	?	+
Wadden 2020	1	142	0	140	3.6%	2.98 [0.12, 73.75]	+	+	+	+	+	+	+
Wadden 2021	1	407	0	204	4.8%	1.51 [0.06, 37.21]	+	+	+	+	+	+	+
Wang 2019	1	515	0	259	4.8%	1.51 [0.06, 37.27]	+	?	−	+	+	+	+
Wilding 2021	1	1306	0	655	4.8%	1.51 [0.06, 37.03]	+	+	+	+	+	+	+
Yamada 2020	1	195	0	49	5.8%	0.76 [0.03, 19.03]	+	+	+	+	+	+	+
Total (95% CI)		**26943**		**24777**	**100.0%**	**1.54 [0.77, 3.06]**							
Total events	19		6										

Heterogeneity: Chi² = 3.90, df = 14 (P = 1.00); I² = 0%

Test for overall effect: Z = 1.22 (P = 0.22)

Silverii GA, et al. Diabetes Obes Metab. 2024;26:891-900.

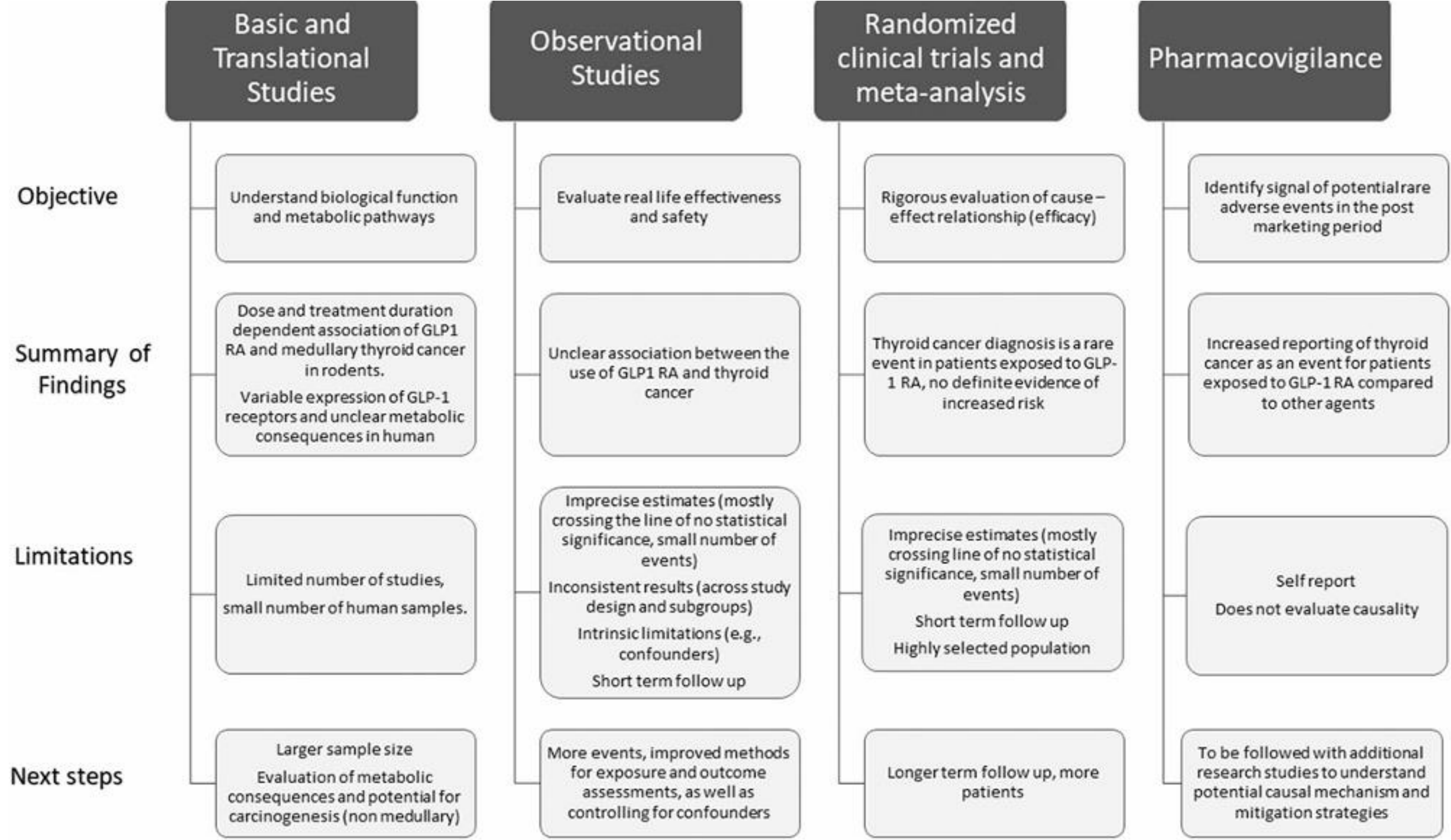
Conclusions of meta-analysis

- GLP-1RA treatment was associated with a significant increase in the risk of overall thyroid cancer with a 5-year number needed to harm of 1349.

- No significant association was found for papillary thyroid cancer (OR 1.54 [95%CI 0.77,3.06]; P=0.22) or medullary thyroid cancer (OR 1.44 [95%CI 0.23,9.16]; P=0.55).

Silverii GA, et al. Diabetes Obes Metab. 2024;26:891-900.

GLP-1RA and thyroid cancer across different research methodologies



De Ycaza AEE, et al. Thyroid 2024;34(4):403-418.

Take-home messages

- While theoretical and preclinical concerns remain-particularly regarding MTC-the totality of human evidence from clinical trials, observational studies, and population registries provides reassurance regarding the thyroid safety of GLP-1RAs.

- Prior to initiating a GLP-1RA, screening for thyroid nodules with a US of the neck or measurement of a serum calcitonin is not necessary based on the existing data. Similarly, the evaluation of a patient with known thyroid nodules should follow the current clinical guidelines independent of the use of a GLP-1RA.

- Use of GLP-1RA should be limited to those lacking a personal or family history of MTC and MEN2.

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Anaesthesia 2025, 80, 846–858 doi:10.1111/anae.16601

Review Article

Association between glucagon-like peptide-1 receptor agonist use and peri-operative pulmonary aspiration: a systematic review and meta-analysis

Jasmin Elkin, Siddharth Rele, Priya Sumithran, Michael Hii, Sharmala Thuraisingam, Tim Spelman, Tuong Phan, Peter Choong, Michelle Dowsey and Cade Shadbolt

- **Inclusion criteria:**

RCTs and observational studies on the association between pre-operative GLP-1 RA use and the risk of pulmonary aspiration or residual gastric contents in fasted patients undergoing anaesthesia or procedural sedation, or in healthy volunteers who had fasted for at least 6 h from solid foods and at least 2 h from clear liquids

- **Number of studies:**

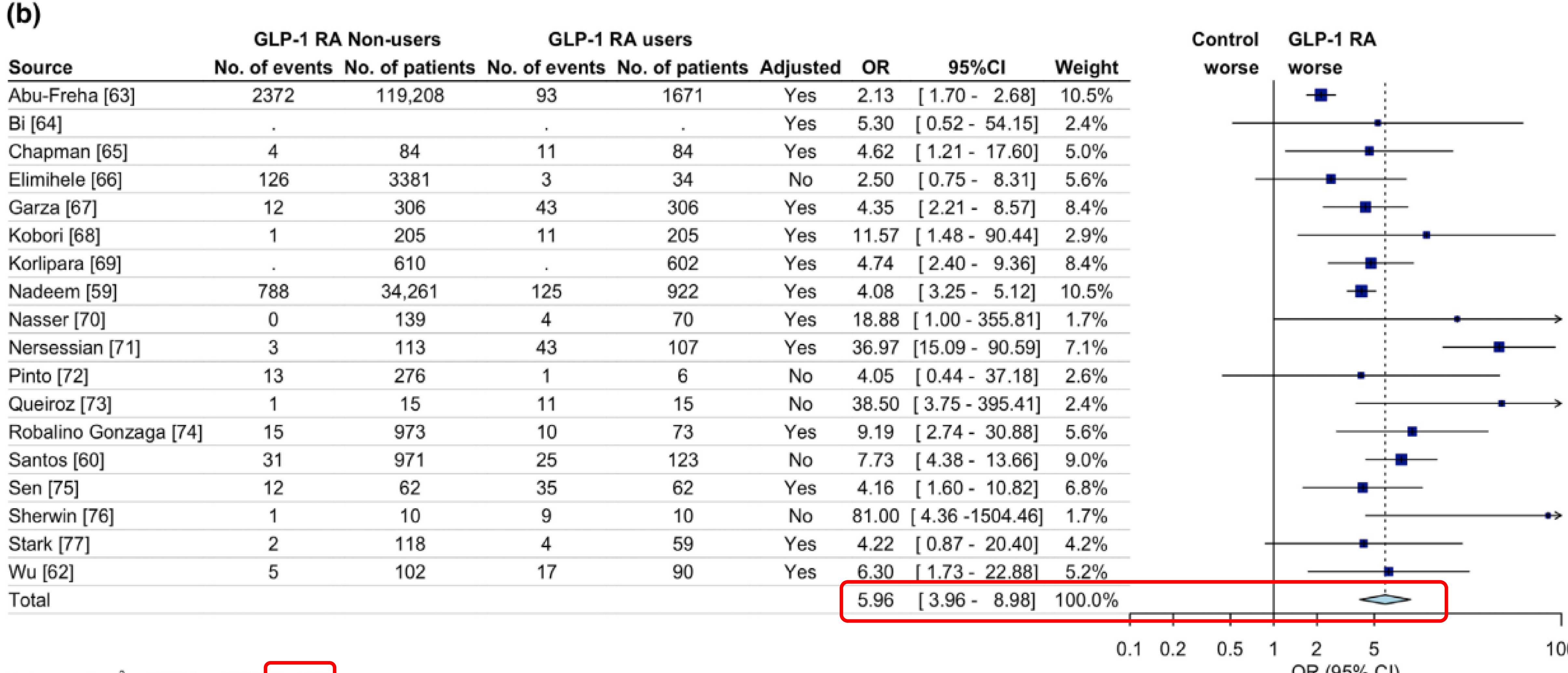
28 observational studies involving 466,373 patients

- **Certainty of evidence:**

low/very low

Elkin J, et al. Anaesthesia 2025;80:846-858.

GLP-1RA exposure was associated with an increased risk of residual gastric contents despite appropriate fasting



(b)

Source	GLP-1 RA Non-users No. of events	GLP-1 RA Non-users No. of patients	GLP-1 RA users No. of events	GLP-1 RA users No. of patients	Adjusted	OR	95%CI	Weight
Abu-Freha [63]	2372	119,208	93	1671	Yes	2.13	[1.70 - 2.68]	10.5%
Bi [64]	.		.	.	Yes	5.30	[0.52 - 54.15]	2.4%
Chapman [65]	4	84	11	84	Yes	4.62	[1.21 - 17.60]	5.0%
Elimihele [66]	126	3381	3	34	No	2.50	[0.75 - 8.31]	5.6%
Garza [67]	12	306	43	306	Yes	4.35	[2.21 - 8.57]	8.4%
Kobori [68]	1	205	11	205	Yes	11.57	[1.48 - 90.44]	2.9%
Korlipara [69]	.	610	.	602	Yes	4.74	[2.40 - 9.36]	8.4%
Nadeem [59]	788	34,261	125	922	Yes	4.08	[3.25 - 5.12]	10.5%
Nasser [70]	0	139	4	70	Yes	18.88	[1.00 - 355.81]	1.7%
Nersessian [71]	3	113	43	107	Yes	36.97	[15.09 - 90.59]	7.1%
Pinto [72]	13	276	1	6	No	4.05	[0.44 - 37.18]	2.6%
Queiroz [73]	1	15	11	15	No	38.50	[3.75 - 395.41]	2.4%
Robalino Gonzaga [74]	15	973	10	73	Yes	9.19	[2.74 - 30.88]	5.6%
Santos [60]	31	971	25	123	No	7.73	[4.38 - 13.66]	9.0%
Sen [75]	12	62	35	62	Yes	4.16	[1.60 - 10.82]	6.8%
Sherwin [76]	1	10	9	10	No	81.00	[4.36 -1504.46]	1.7%
Stark [77]	2	118	4	59	Yes	4.22	[0.87 - 20.40]	4.2%
Wu [62]	5	102	17	90	Yes	6.30	[1.73 - 22.88]	5.2%
Total						5.96	[3.96 - 8.98]	100.0%

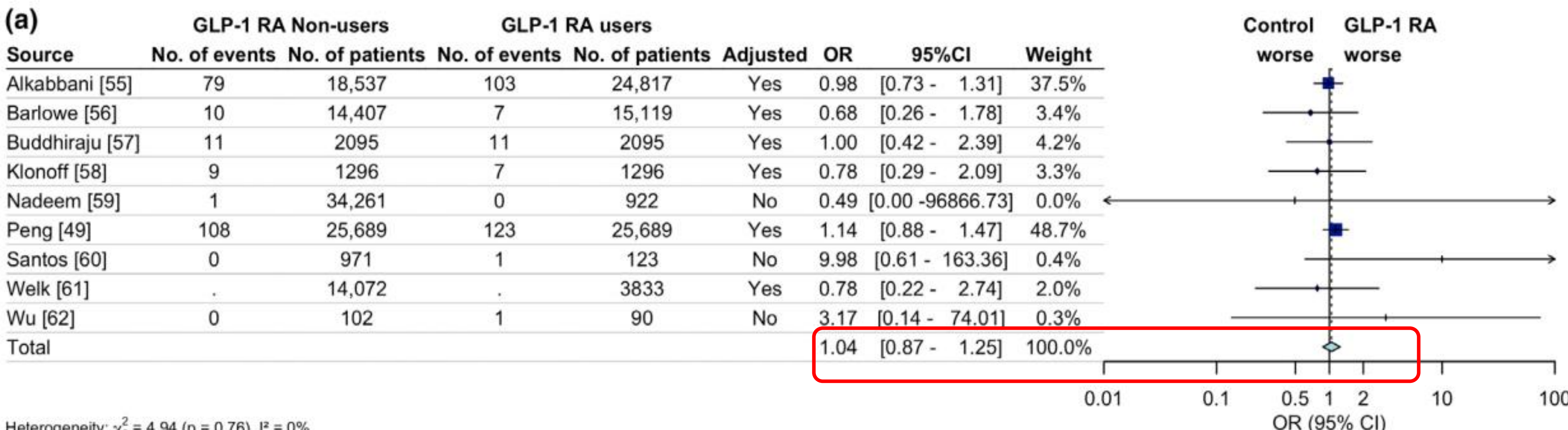
Heterogeneity: $\chi^2_{17} = 69.79$ ($p < 0.001$) $I^2 = 76\%$

Test for overall effect: $z = 8.54$ ($p < 0.001$)

Risk of bias: very serious

Elkin J, et al. Anaesthesia 2025;80:846-858.

GLP-1RA exposure was not associated with pulmonary aspiration


(a)

Source	GLP-1 RA Non-users		GLP-1 RA users		Adjusted	OR	95%CI	Weight
	No. of events	No. of patients	No. of events	No. of patients				
Alkabbani [55]	79	18,537	103	24,817	Yes	0.98	[0.73 - 1.31]	37.5%
Barlowe [56]	10	14,407	7	15,119	Yes	0.68	[0.26 - 1.78]	3.4%
Buddhiraju [57]	11	2095	11	2095	Yes	1.00	[0.42 - 2.39]	4.2%
Klonoff [58]	9	1296	7	1296	Yes	0.78	[0.29 - 2.09]	3.3%
Nadeem [59]	1	34,261	0	922	No	0.49	[0.00 -96866.73]	0.0%
Peng [49]	108	25,689	123	25,689	Yes	1.14	[0.88 - 1.47]	48.7%
Santos [60]	0	971	1	123	No	9.98	[0.61 - 163.36]	0.4%
Welk [61]	.	14,072	.	3833	Yes	0.78	[0.22 - 2.74]	2.0%
Wu [62]	0	102	1	90	No	3.17	[0.14 - 74.01]	0.3%
Total						1.04	[0.87 - 1.25]	100.0%

Heterogeneity: $\chi^2_8 = 4.94$ (p = 0.76), $I^2 = 0\%$
Test for overall effect: z = 0.47 (p = 0.64)

Elkin J, et al. Anaesthesia 2025;80:846-858.

Risk factors for delayed gastric emptying and aspiration with the periprocedural use of GLP-1RA

- Escalation phase (vs the maintenance phase)
- Higher dose
- Weekly dosing
- Presence of gastrointestinal symptoms

  (nausea, vomiting, abdominal pain, dyspepsia, and constipation)
- Medical conditions which may also delay gastric emptying

  (bowel dysmotility, gastroparesis, Parkinson's disease)

Kindel TL, et al. Surgery for Obesity and Related Diseases 2024:1-4.

Aspiration Risk and Perioperative Management of GLP-1 Receptor Agonists Patients Undergoing Elective Surgery

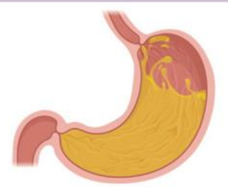
Current Challenge

GLP-1

- Controversy in the perioperative management of GLP-1 RA
- The associated aspiration risk is not reported with the delayed gastric emptying
- Holding and bridging Recommendations may not be feasible to all patients
- Holding duration and its impact on delayed gastric emptying

Summary of the Findings

Aspiration Risk

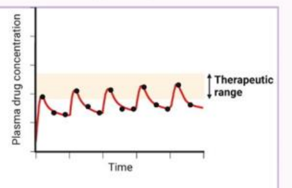


- Controversy of the findings on aspiration risk
- 8 studies reported an increase in aspiration risk in GLP-1 RA users versus non-users, while 4 studies reported no difference

Holding Duration

- GLP-1 RA half-life is one week for daily and weekly formulations
- Holding for GLP-1 RA to achieve return to normal gastric emptying ranges from 3-16 weeks
- This duration is not feasible before surgery or for diabetes management

Tachyphylaxis



- Tachyphylaxis develops after 20 weeks of therapy
- Patients may be immune to the delayed gastric emptying effects of the drug
- Lower aspiration risk after prolonged use of the same dose
- Weigh loss versus DM indications

2024 Guidelines

- It is reasonable to continue GLP-1 RA use perioperatively
- Benefits of continuing outweigh the risk
- Start clear liquids 24 hours before surgery
- Gastric ultrasound on the day of surgery

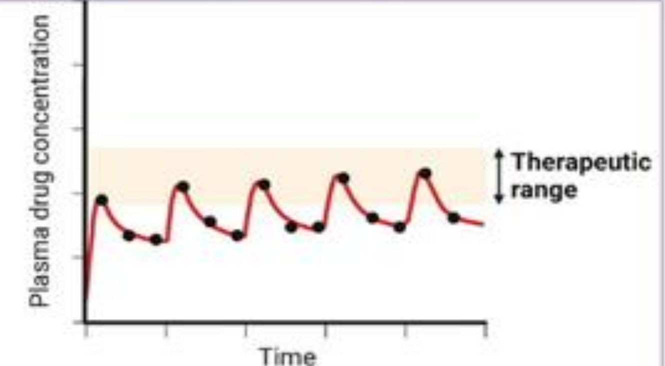
Conclusion: patients' response to GLP-1 RA varies based on multiple factors
Day-of-surgery evaluation of patients on GLP-1 RAs should be performed on a case-by-case basis, taking into account factors such as symptoms and gastric ultrasound

Created in BioRender. Mohamed, B. (2025) https://BioRender.com/m45g345

Holding Duration

- GLP-1 RA half-life is one week for daily and weekly formulations
- Holding for GLP-1 RA to achieve return to normal gastric emptying ranges from 3-16 weeks
- This duration is not feasible before surgery or for diabetes management

Tachyphylaxis



- Tachyphylaxis develops after 20 weeks of therapy
- Patients may be immune to the delayed gastric emptying effects of the drug
- Lower aspiration risk after prolonged use of the same dose
- Weigh loss versus DM indications

2024 Guidelines

- It is reasonable to continue GLP-1 RA use perioperatively
- Benefits of continuing outweigh the risk
- Start clear liquids 24 hours before surgery
- Gastric ultrasound on the day of surgery

Li J, et al. Curr Med Res Opin 2025;41(4):699-712.

Anaesthesia and airway management

- Reducing the risk of pulmonary aspiration on induction of anaesthesia, during maintenance and after emergence of anaesthesia:
  - administering prokinetics
  - using a tracheal tube
  - modified rapid sequence intubation (with or without cricoid force, depending on local practice)
  - head-up position for induction of anaesthesia
  - potential use of gastric tubes to empty the stomach before induction of anaesthesia and tracheal extubation
  - Awake tracheal extubation

El-Boghdadly K, et al. Anaesthesia 2025;80:412-424.
Kindel TL, et al. Surgery for Obesity and Related Diseases 2024:1-4.

Take-home messages

- The perioperative management of patients using GLP-1RAs remains a topic of debate. While several multisociety statements have been published recently, the recommendations vary significantly in terms of medication management and preoperative fasting protocols for these patients.

- In the majority of cases, the patient may continue these drugs before surgery; they should have full risk assessment and stratification; and receive peri-operative techniques that may mitigate risk of pulmonary aspiration before, during and after sedation or general anaesthesia.

Thanks for your attention

Photo by M. Valizadeh, MD