
بسم الله الرحمن الرحیم

GLP-1 RECEPTOR AGONISTS AND THE RISK OF THYROID CANCER

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Diabetes Care
American Diabetes Association

GLP-1 Receptor Agonists and the Risk of Thyroid Cancer

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ARTICLE HIGHLIGHTS

- Preclinical studies suggest that GLP-1 RA have specific effects on the thyroid gland, potentially involving the development of thyroid cancer.
- Studies on this subject produced conflicting results, potentially due to a lack of statistical power.
- The results of this nationwide population-based study suggest that use of GLP-1 RA is associated with increased risk of thyroid cancer.
- The increased risk was higher in the case of 1–3 years of GLP-1 RA use.
- Clinicians should be aware of this potential risk in initiating a GLP-1 RA and carefully monitor exposed patients.

- GLP-1 receptors are expressed in thyroid tissues, and carcinogenicity studies in rats and mice demonstrated a dose and time-dependent increased risk of medullary carcinomas with GLP-1 RA .

- Based on these findings, the U.S. Food and Drug Administration (but not the European Medicines Agency) contraindicated the use of liraglutide, dulaglutide, exenatide extended release, and semaglutide in patients with a personal or family history of medullary thyroid cancer and multiple endocrine neoplasia type 2 .

- An increased number of thyroid cancers was reported in the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) clinical trial evaluating liraglutide versus placebo, but the risk did not reach statistical significance (hazard ratio [HR] 1.66, 95% CI 0.40–6.95), as well as in a meta-analysis of 12 other clinical trials with liraglutide (odds ratio [OR] 1.54, 95% CI 0.40–6.02) .

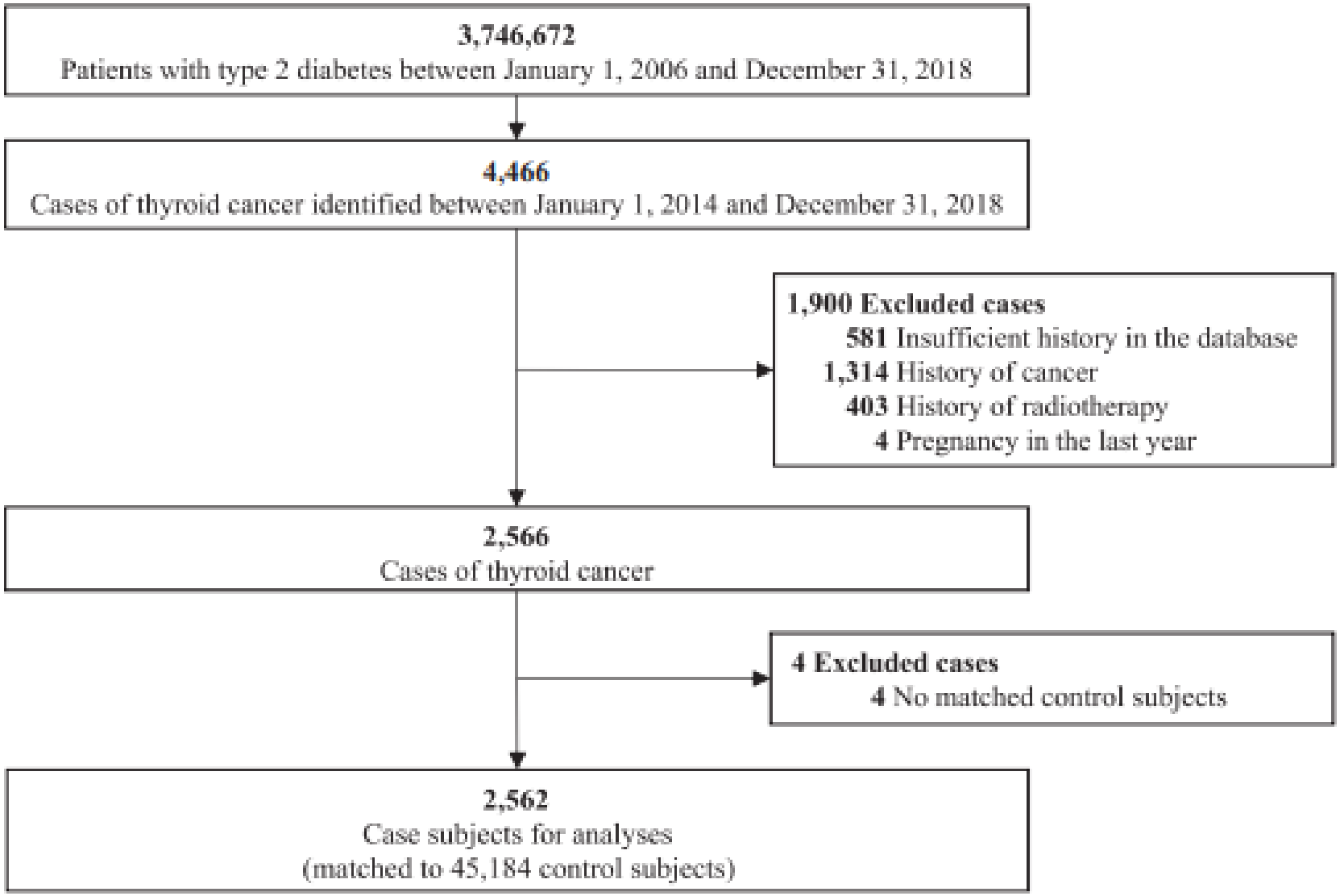

Figure 1—Flowchart of included case and control subjects.

- Each case subject was matched to a maximum of 20 control subjects by age (in years), sex, and duration of diabetes (in 2-year class between 0 and 8 years, and then > 8 years) with the risk-set sampling procedure.

Table 1—Baseline characteristics of case and control subjects at the beginning of the lag time period

	Case subjects, *n* = 2,562	Control subjects, *n* = 45,184
Age, years, median (IQR)	64 (56–71)	64 (57–71)
Sex		
Male	845 (33.0)	14,813 (32.8)
Female	1,717 (67.0)	30,371 (67.2)
Duration of diabetes (years)		
0–1	296 (11.5)	4,345 (9.6)
2–3	316 (12.3)	4,744 (10.5)
4–5	352 (13.7)	5,565 (12.3)
6–7	313 (12.2)	5,275 (11.7)
≥8	1,285 (50.2)	25,255 (55.9)

Antidiabetes drugs		
GLP-1 RA	307 (12.0)	4,348 (9.6)
DPP-4 inhibitors	1,040 (40.6)	17,778 (39.3)
Insulins	494 (19.3)	9,124 (20.2)
Metformin	2,037 (79.5)	35,700 (79.0)
Sulfonylureas	1,118 (43.6)	20,462 (45.3)
Repaglinide	387 (15.1)	6,182 (13.7)
α-Glucosidase inhibitors	193 (7.5)	3,683 (8.2)
Thiazolidinediones	159 (6.2)	3,582 (7.9)
Comorbidities		
Goiter	95 (3.7)	125 (0.3)
Hypothyroidism	613 (23.9)	5,933 (13.1)
Hyperthyroidism	144 (5.6)	220 (0.5)
Coronary heart disease	206 (8.0)	3,667 (8.1)
Stroke	63 (2.5)	1,085 (2.4)
Hypertension	1,926 (75.2)	31,144 (68.9)
Peripheral artery occlusive disease	71 (2.8)	1,299 (2.9)
Chronic kidney disease	58 (2.3)	893 (2.0)
Obesity	302 (11.8)	3,812 (8.4)

Table 2—Adjusted HRs for association between use of GLP-1 RA or DPP-4 inhibitors and risk of all thyroid cancer or medullary thyroid cancer

	All thyroid cancer			Medullary thyroid cancer		
	Case subjects, *n* = 2,562	Control subjects, *n* = 45,184	Adjusted HR (95% CI)*	Case subjects, *n* = 398	Control subjects, *n* = 6,993	Adjusted HR (95% CI)*
Current exposure model						
GLP-1 RA						
Nonuser	2,255 (88.0)	40,836 (90.4)	Reference	343 (86.2)	6,347 (90.8)	Reference
Past user	100 (3.9)	1,628 (3.6)	1.20 (0.96–1.50)	20 (5.0)	237 (3.4)	1.45 (0.84–2.50)
Current user	207 (8.1)	2,720 (6.0)	1.46 (1.23–1.74)	35 (8.8)	409 (5.9)	1.76 (1.16–2.69)
DPP-4 inhibitors						
Nonuser	1,522 (59.4)	27,406 (60.7)	Reference	231 (58.0)	4,217 (60.3)	Reference
Past user	387 (15.1)	6,462 (14.3)	1.07 (0.94–1.22)	66 (16.6)	999 (14.3)	1.12 (0.81–1.55)
Current user	653 (25.5)	11,316 (25.0)	1.10 (0.99–1.22)	101 (25.4)	1,777 (25.4)	1.15 (0.88–1.50)

Cumulative exposure model						
GLP-1 RA						
Nonuser	2,255 (88.0)	40,836 (90.4)	Reference	343 (86.2)	6,347 (90.8)	Reference
≤1 year	117 (4.6)	1,767 (3.9)	1.22 (0.99–1.50)	23 (5.8)	278 (4.0)	1.57 (0.96–2.55)
1–3 years	112 (4.4)	1,419 (3.1)	1.58 (1.27–1.95)	20 (5.0)	203 (2.9)	1.78 (1.04–3.05)
>3 years	78 (3.0)	1,162 (2.6)	1.36 (1.05–1.74)	12 (3.0)	165 (2.4)	1.61 (0.85–3.06)
DPP-4 inhibitors						
Nonuser	1,522 (59.4)	27,406 (60.7)	Reference	231 (58.0)	4,217 (60.3)	Reference
≤1 year	333 (13.0)	5,209 (11.5)	1.12 (0.99–1.28)	58 (14.6)	798 (11.4)	1.33 (0.97–1.84)
1–3 years	310 (12.1)	5,918 (13.1)	0.96 (0.84–1.10)	48 (12.1)	882 (12.6)	0.98 (0.69–1.39)
>3 years	397 (15.5)	6,651 (14.7)	1.19 (1.04–1.35)	61 (15.3)	1,096 (15.7)	1.11 (0.79–1.55)

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

- To our knowledge, this is the first study with investigation of the risk of thyroid cancer with the main GLP-1 RAs in a large administrative database.

- in this nationwide population-based study, use of GLP-1 RA was found to be associated with higher risk of thyroid cancer.

- Our results suggest that thyroid cancer risk should be considered with GLP-1 RA, particularly in patients treated for 1–3 years.

- the role of GLP-1 RA in increasing calcitonin release and upregulating calcitonin gene expression resulting in C-cell hyperplasia was thought to be specific to rodents .

- Although GLP-1 receptor expression in humans is lower than in rodents .

- Our findings clearly raise concerns about the relevance of this risk to humans.

- Higher HRs were found for the period of 1–3 years of GLP-1 RA use (especially for male patients).

- Although the potential carcinogenic effect of GLP-1 RA on the thyroid is not well understood, this finding suggests either that induced thyroid cancers could develop after a relatively short period of GLP-1 RA exposure or that GLP-1 RA could promote thyroid precancerous lesions .

Conclusion:

- In summary, the results of this nationwide population-based study suggest that use of GLP-1 RA is associated with increased risk of thyroid cancer and medullary thyroid cancer in particular. The increased risk was higher for 1–3 years of GLP-1 RA use and remained elevated for >3 years of use.

- Clinicians should be aware of this potential risk in initiating a GLP-1 RA and carefully monitor exposed patients, especially in the presence of other risk factors for thyroid cancer

COMMENT 1 :

- We read the article by Bezin et al and would like to point out several flaws that make the interpretation unreliable.
- The control group has 9.6% of individuals treated with a glucagon-like peptide receptor agonist (GLP-1 RA) for various durations, thereby making it difficult to suggest causality.

COMMENT ON BEZIN ET AL: (Ronald M. Goldenberg[1] and Akshay B. Jain)

- An ideal comparison would be to look at incidence of thyroid cancer in those on a GLP-1 RA versus those not on a GLP-1 RA and a third arm to compare with the incidence of thyroid cancers in individuals without diabetes and not on a GLP-1 RA.

- There is no exclusion of thyroid nodules/cancer prior to initiation on GLP-1 RA therapy, and therefore it is unknown if these individuals already had thyroid cancer.

- The most common type of thyroid cancer (papillary thyroid carcinoma) is extremely slow growing, with tumor doubling time ≥ 5 years .

- the duration of exposure to a GLP-1 RA was too short to cause drug-induced cancer development per current evidence .

- Medullary thyroid cancer in this study formed 15.5% of all cases (compared with <3% seen in the literature , suggesting that methods used by the authors to assume medullary thyroid cancer are too simplistic, leading to gross overestimation.

COMMENT 2 :

- In this commentary, we discuss three issues: misuse of P values,limitations of case-control designs in this setting, and overdiagnosis of thyroid cancer.
- Estimates for duration of use ≤1 year and >3 years are very similar in magnitude.
- Only highlighting statistically significant results and, conversely, ignoring any non–statistically significant results is a common mistake in medical research.

Putting GLP-1 RAs and Thyroid Cancer in Context: Additional Evidence and Remaining Doubts (Caroline A. Thompson and Til Sturmer)

- LEADER (liraglutide)Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results] hazard ratio 1.66 [95% CI 0.40–6.95].

- When making treatment decisions, clinicians need to weigh potential benefit and harm.

- For outcomes that have vastly different incidences (e.g., cardiovascular disease versus thyroid cancer) , A protective relative risk of 0.9 for a high incidence outcome (e.g., cardiovascular disease) can largely outweigh a relative risk of 2 for a very low incidence adverse outcome (e.g., thyroid cancer).

- Globally, thyroid cancer is ranked 9th for incidence but not in the top 20 for mortality burden .

Clinicians and patients need to always balance benefit and harm of treatments in light of their alternatives. In a population without specific risk factors for thyroid cancer, the benefits of GLP-1 Ras will largely outweigh the harm……

ORIGINAL ARTICLE

WILEY

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

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- The principal endpoint was the incidence of any thyroid cancer during the study; secondary endpoints were the incidence of PTC, the incidence of MTC, the incidence of follicular thyroid cancer, and the incidence of overall differentiated thyroid cancer .

- We included all RCTs with a duration of follow-up of at least 52 weeks.

- The number of studies fulfilling the inclusion criteria was 64, overall enrolling 46 228 patients on GLP-1RA treatment, and 38 399 subjects on placebo or a comparator.

• often performed for the treatment of diabetes (48 trials), while 16 were performed for the treatment of obesity .

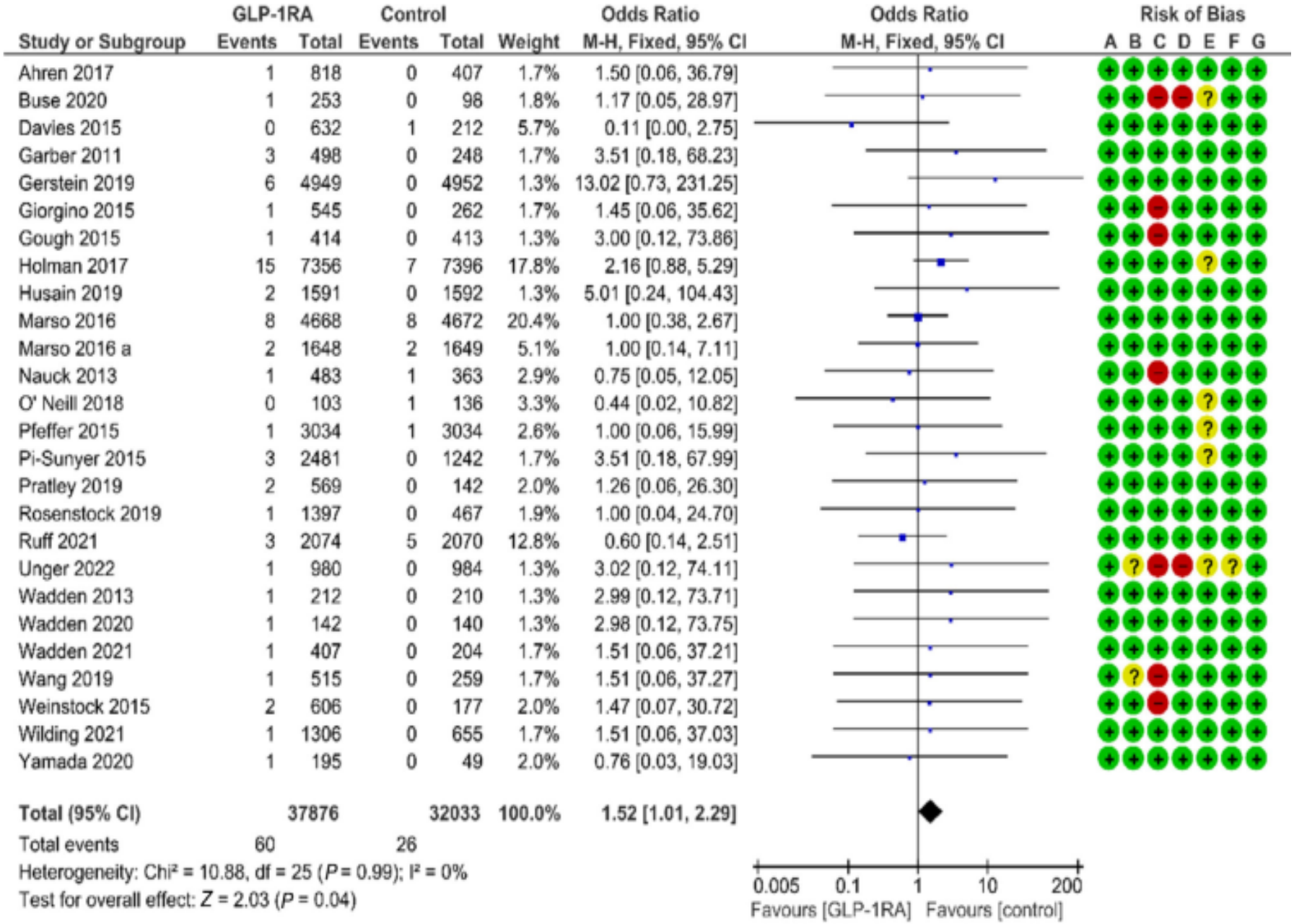
• Twenty-six trials, enrolling 69 909 patients overall, reported at least one incident case of thyroid cancer.

TABLE 1 Characteristics of the included trials with at least one event of thyroid cancer.

Study name	Drug	Dose (mg)	Comparator	Ind	Dur	Age	F%	HbA1c	BMI	P-y drug	P-y control
Ahren 2017[30] (SUSTAIN-2)	Semaglutide	0.5–1 QWK	Sita	DM	56	55	49.4	8.1	32.5	Nr	nr
Buse 2020[31] (PIONEER-7	Semaglutide	7–14 QD	Sita	DM	52	57	43.5	7.9	31.0	nr	nr
Davies 2015[32] (SCALE D)	Liraglutide	1.8 QD	Placebo	DM	56	55	49.8	7.9	37.4	570	180
Garber 2011 (LEAD)[33]	Liraglutide	1.8 QD	Glimepiride	DM	104	53	50.3	8.3	33.0	1366	538
Gerstein 2019 (REWIND)[34]	Dulaglutide	1.5 QWK	Placebo	DM	281	66	46.3	7.3	32.3	25 277	24 925
Giorgino2015 (AWARD-2)[35]	Dulaglutide	1.5 QWK	Glarg	DM	78	57	48.7	8.1	31.3	nr	nr
Gough 2015 (DUAL-I)[36]	Liraglutide	1.8 QD	Degludec	DM	52	55	49.2	8.3	31.2	nr	nr
Holman 2017 (EXSCEL)[37]	Exenatide	2 QWK	Placebo	DM	166	62	38.0	8.0	31.7	22 676	22 625
Husain 2019 (PIONEER 6)[38]	Semaglutide	14 QD	Placebo	DM	68	66	31.6	8.2	32.0	2103	2055
Marso 2016 (SUSTAIN-6)[39]	Semaglutide	0.5–1 QWK	Placebo	DM	109	65	39.3	8.7	32.8	3333	3318
Marso 2016 (a) (LEADER)[40]	Liraglutide	1.8 QD	Placebo	DM	198	64	35.7	8.7	32.5	17 882	17 795
Nauck 2013 (LEAD-2)[41]	Liraglutide	1.8 QD	Glim/met	DM	104	57	41.3	8.6	31.2	nr	nr
O'Neill 2018 (NN9536)[42]	Liraglutide	3 QD	placebo	OB	52	47	64.1	5.5	39.3	nr	nr
Pfeffer 2015 (ELIXA)[43]	Lixisenatide	20 QD	Placebo	DM	107	60	30.7	7.6	30.1	6334	6444
Pratley 2019 (PIONEER-4)[44]	Liraglutide	1.8 QD	Placebo	DM	52	56	48.0	8.0	33.0	nr	nr
Pi-sunyer 2015 (SCALE OB)[45]	Liraglutide	3.0 QD	Placebo	OB	70	45	78.5	5.6	38.3	2237	1067
Rosenstock 2019 (PIONEER-3)[46]	Semaglutide	7–14 QD	Sita	DM	78	58	47.2	8.3	32.5	nr	nr
Ruff 2021 (FREEDOM)[47]	Exenatide	ITCA 0.06 QD	Placebo	DM	62	63	36.7	8.0	32.3	2879	2925
Unger 2022 (LIRA-PRIME)[48]	Liraglutide	1.8 QD	Any OAD	DM	104	57	47.6	8.2	33.5	1356	1258
Wadden 2013 (SCALE M)[49]	Liraglutide	3.0 QD	Placebo	OB	56	46	81.3	5.6	37.9	nr	nr
Wadden 2020 (SCALE IBT)[50]	Liraglutide	3.0 QD	Placebo	OB	56	47	82.9	5.5	39.0	nr	nr
Wadden 2021 (STEP-3)[51]	Semaglutide	2.4 QD	Placebo	OB	68	46	81.0	5.7	38.0	nr	nr
Wang 2019 (AWARD-C)[52]	Dulaglutide	0.75/1.5 QWK	Glargine	DM	52	55	64.1	8.4	26.0	nr	nr
Weinstock 2015 (AWARD-5)[53]	Dulaglutide	1.5 QWK	Sita	DM	104	54	53.5	8.1	31.0	nr	nr
Wilding 2021 (STEP-1)[54]	Semaglutide	2.4 QWK	Placebo	OB	68	46	74.0	5.6	37.9	1708	829
Yamada 2020 (PIONEER-9)[55]	Semaglutide	7–14 QD	Placebo	DM	52	61	22.3	8.2	26.0	192	49

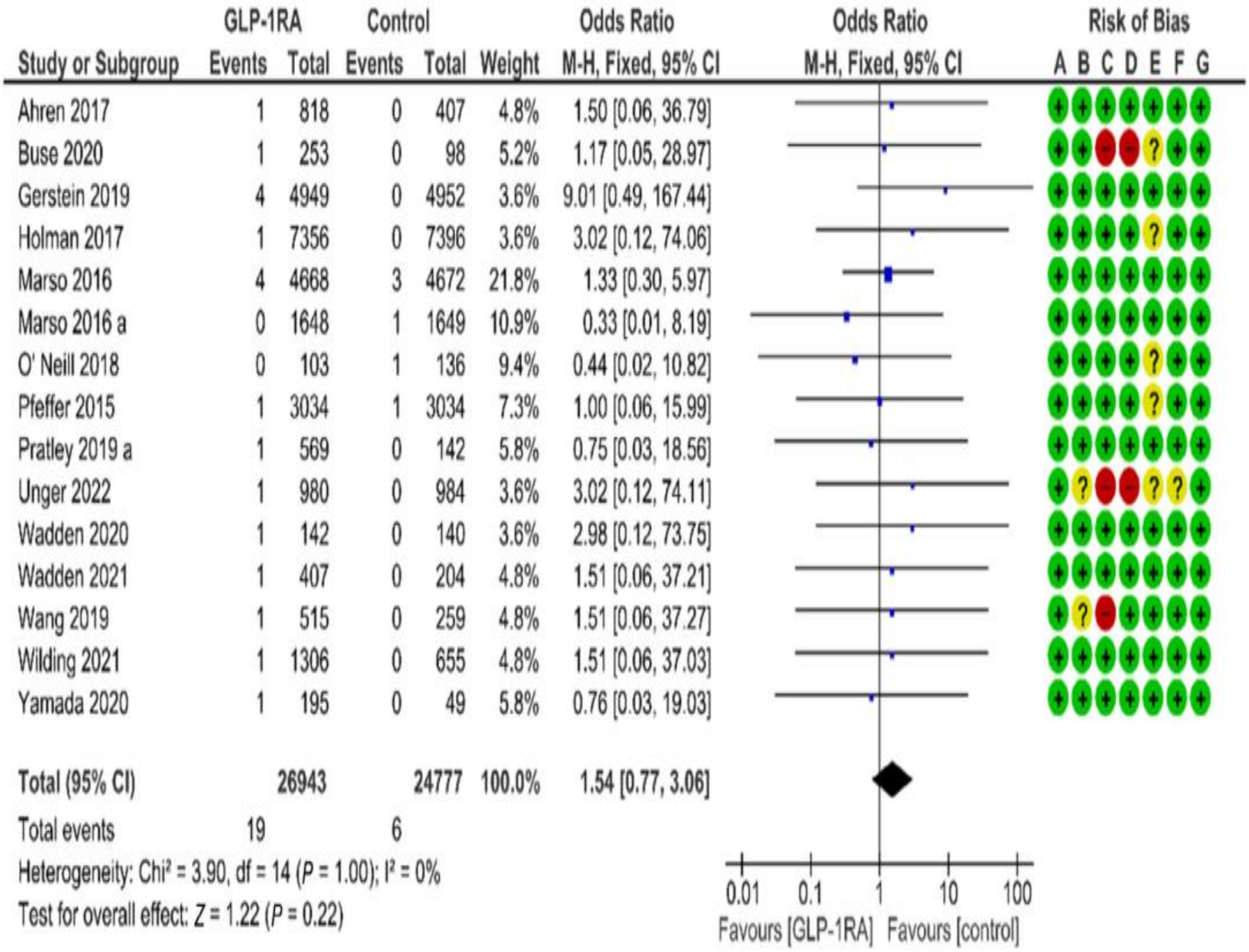
- Of the 86 cases of thyroid cancer retrieved (60 and 26 in the GLP-1RA and comparator arms, respectively), 25 (19 in the GLP-1RA arm vs. 6 in comparator arms) were reported as PTCs and three as MTCs (two with GLP-1RAs and one with comparators .

- GLP-1RA treatment was associated with a significant increase in the risk of overall thyroid cancer in the fixed-effect analysis (MH-OR 1.52 [95% CI 1.01, 2.29]; P = 0.04) .


GLP-1RA
Control
Odds Ratio
Odds Ratio
Risk of Bias
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
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)
0.005 0.1 1 10 200
Favours [GLP-1RA] Favours [control]

- When analysing separately trials with different durations, the association of GLP-1RA with thyroid cancer was statistically significant only in trials of at least 104 weeks (MH-OR 1.76 [95% CI 1.00, 3.12]; P = 0.05) .

- PTCs were reported in 15 trials, overall enrolling 51 720 patients; the association with GLP- 1RA treatment was not significant (MH-OR 1.54 [95% CI 0.77, 3.06]; P = 0.22, I2 = 0%) .
- As an exploratory post hoc analysis, we also grouped all the thyroid cancers excluding those reported as MTCs, observing a significant effect of GLP-1RA treatment (MH-OR 1.51 [95% CI 1.00, 2.29]; P = 0.05, I2 = 0%)


GLP-1RA
Control
Odds Ratio
Odds Ratio
Risk of Bias
Study or Subgroup
Events
Total
Events
Total
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M-H, Fixed, 95% CI
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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)
0.01
0.1
1
10
100
Favours [GLP-1RA]
Favours [control]

- Only three trials reported cases of MTC; the association between GLP-1RA treatment and MTC was not significant (MH-OR 1.44 [95% CI 0.23, 9.16]; P = 0.55, I2 = 0%).

DISCUSSION :

- confounders; in the case of GLP-1RAs, the relatively high proportion of obese patients among those receiving treatment could produce a bias, since excess weight is a risk factor for thyroid malignancies .

- the corresponding 5-year NNH was 1349.

- the estimated NNH, as calculated using data from clinical trials, is well above 1000 patients for 5 years.

- Conversely, figures for the number needed to treat to prevent a major cardiovascular event among high-risk patients with diabetes are considerably smaller.

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

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- Scandinavian cohort study.

SETTING

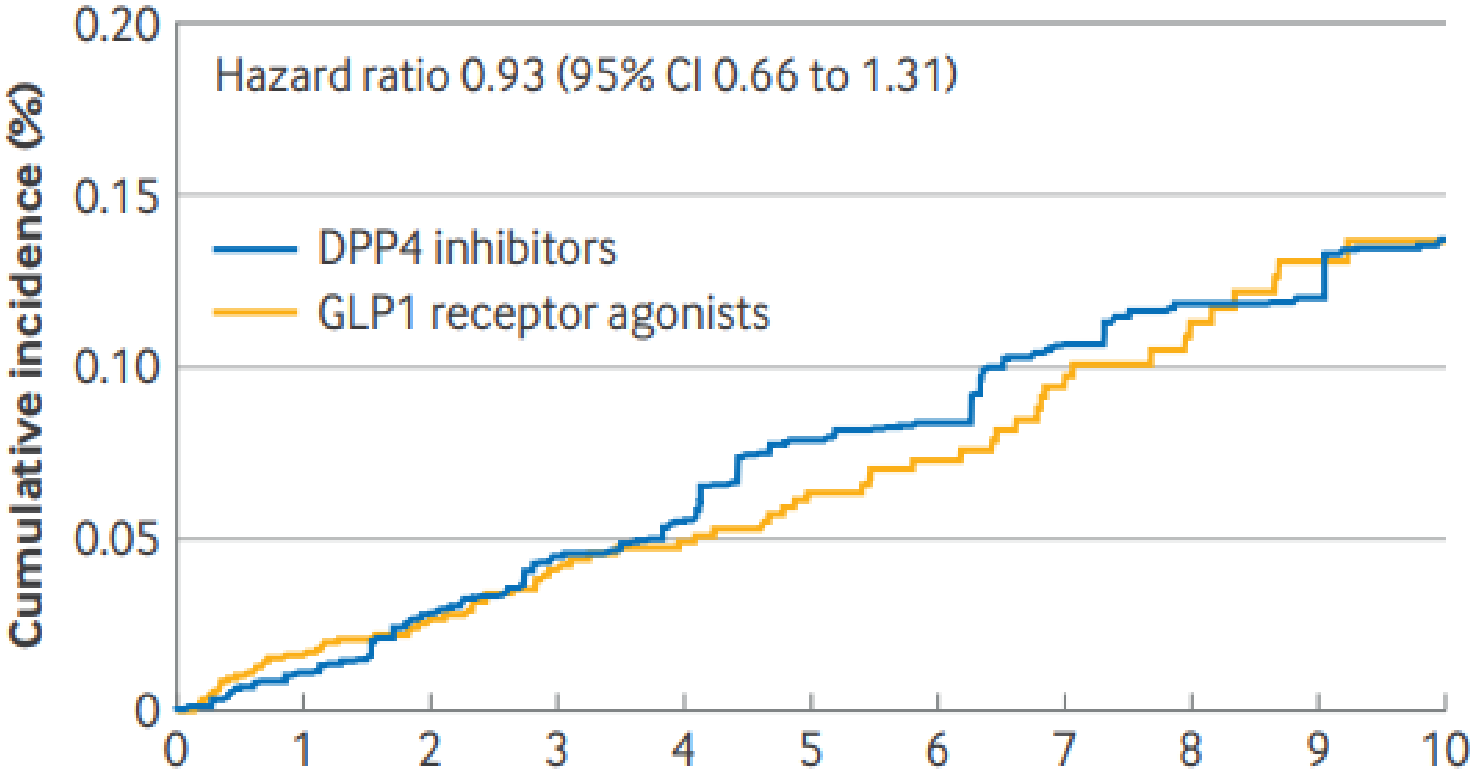
- Denmark, Norway, and Sweden, 2007-2021

- The mean follow-up time was 3.9 years (standard deviation 3.5 years) in the GLP1 receptor agonist group and 5.4 years (standard deviation 3.5 years) in the DPP4 inhibitor group.

- The most common individual GLP1 receptor agonist was liraglutide (57.3%), followed by semaglutide (32.9%), dulaglutide (4.9%), exenatide (4.1%), and lixisenatide (0.9%)

Table 2 | GLP1 receptor agonist use and risk of thyroid cancer

	GLP1 receptor agonists (n=145 410)		DPP4 inhibitors (n=291 667)			
Analysis	No of events	Rate per 10 000 person years*	No of events	Rate per 10 000 person years*	Hazard ratio (95% CI)*	Rate difference (95% CI) per 10 000 person years*
Main analysis (any thyroid cancer)	76	1.33	184	1.46	0.93 (0.66 to 1.31)	−0.13 (−0.61 to 0.36)
Subtypes of thyroid cancer						
Papillary	53	0.93	114	1.04	0.92 (0.61 to 1.39)	−0.11 (−0.53 to 0.31)
Follicular	16	0.28	47	0.27	0.99 (0.47 to 2.08)	0.01 (−0.19 to 0.21)
Medullary	4	0.07	11	0.07	1.19 (0.37 to 3.86)	0.00 (−0.09 to 0.09)
Other	5	0.09	15	0.05	1.51 (0.44 to 5.20)	0.04 (−0.05 to 0.12)



No at risk

GLP1 receptor agonists	145 410	85 070	55 506	37 277	24 369	13 771
DPP4 inhibitors	291 667	237 308	175 024	115 062	67 927	35 871

Additional analyses	No of patients	No of events	Rate per 10 000 person years*	Hazard ratio (95% CI)*
SGLT2 inhibitors as comparator group				
GLP1 receptor agonists	111744	40	1.21	1.16 (0.65 to 2.05)
SGLT2 inhibitors	148179	26	1.07	Reference

- In conclusion, this large cohort study found that GLP1 receptor agonist treatment was not associated with a substantially increased risk of thyroid cancer over a mean follow-up of 3.9 years . However, the study cannot exclude a small increase in risk.

Conclusion:

- results of RCTs seem to confirm a possible moderate increase in the risk of thyroid cancer in patients treated with GLP- 1RAs .
- Clinicians and patients need to always balance benefit and harm of treatments in light of their alternatives.
- In a population without specific risk factors for thyroid cancer, the benefits of GLP-1 Ras will largely outweigh the harm.