4th September 2023

Study protocol

To examine the impact of additional confounder adjustment for the potential association between second line T2DM therapy and thyroid cancer: a nested case-control study

Administrative details of the data analysis	
Substance(s)	GLP-1 RA
Condition/ADR(s)	T2DM
Short title of topic	T2DM therapy and thyroid cancer association
TDA-DAT lead analyst and team	Daniel Morales, Alexandra Pacurariu

1. Rationale and background

Thyroid cancer was thought to have an average estimated age standardized incidence in Europe of 12.7 per 100 000 person years in 2020.[1] The US Food and Drug Administration has contraindicated Glucagon-like peptide-1 agonists (GLP-1 RA) in patients with a personal or family history of medullary thyroid cancer based on preclinical and clinical findings.[2,3] GLP-1 receptor are expressed in thyroid tissues, and carcinogenicity studies in rodents have demonstrated a dose- and duration-dependent risk of medullary thyroid cancer with GLP-1 RA exposure.[4,5] However the association is not clearly established in humans given the long latency period for cancer induction and relatively low incidence of thyroid cancer.

GLP-1 RAs, including exenatide, liraglutide, dulaglutide, and semaglutide, are second-line drugs commonly used in the management of type 2 diabetes mellitus (T2DM). They induce direct activation of the GLP-1 receptor, which stimulates pancreatic insulin secretion in a glucose-dependent manner, while also inhibiting glucagon secretion.[6] A recent nested case-control analysis performed in the French national health care insurance system (SNDS) database (Bezin et al, 2023) showed an association with an increased risk of all thyroid cancer and medullary thyroid cancer with use of Glucagon-like peptide-1 agonists (GLP-1 RA) in people with T2DM, in particular after 1–3 years of cumulative treatment.[7] However, it was not possible to adjust for certain potential confounders in the association with thyroid cancer that were not captured in that database, such as smoking status or body mass index. Such risk factors generally have well known associations with cancer incidence.[8] In a UK study, nearly four in ten cancer cases have been attributed to known risk factors and understanding modifiable risk factors is therefore a key driver of changing cancer incidence.[9] Other known risk factors for thyroid cancer include exposure to radiation, family history, and other thyroid related conditions.

Our study aims to examine the potential impact of adjusting for missing confounders on the association with thyroid cancer in people with T2DM by attempting to reproduce the design of the French NCCS study.

2. Research question and objectives

To examine the impact of additional confounder adjustment for the association between T2DM therapy and thyroid cancer.

1. To calculate crude and adjusted effect estimates for GLP1-agonists (and other second-line T2DM therapy) and the association with thyroid cancer based upon the design for confounding adjustment in the study by Bezin et al study.

2. To determine the impact of additional adjustment for smoking status, BMI, history of alcohol use/abuse on the effect estimates for GLP1-agonists (+/- other second-line T2DM therapy) and the association with thyroid cancer thyroid cancer.

3. Research methods

3.1. Study design

This primary analysis will be a nested case control study, whereby controls will be matched to cases of thyroid cancer, within in a cohort of patients diagnosed with T2DM treated with second-line antidiabetic therapy.

3.2. Data sources

The following databases will be used: IQVIA™ Medical Research Data (IMRD) UK. A brief description of this database is provided in Annex 1.

3.3. Setting and study population eligibility criteria

For the primary analysis, the cohort population will be identified from the general population (UK) registered with general practices using the following inclusion criteria applied for the creation of underlying cohort:

Inclusion criteria

- type II diabetes mellitus diagnosis
- previously treated with metformin
- currently treated with second line therapy such as: GLP1 RA, DPP-4, SGLT2 inhibitors, Sulfonylureas, meglitinides, alpha-glucosidase inhibitors, thiazolidinediones

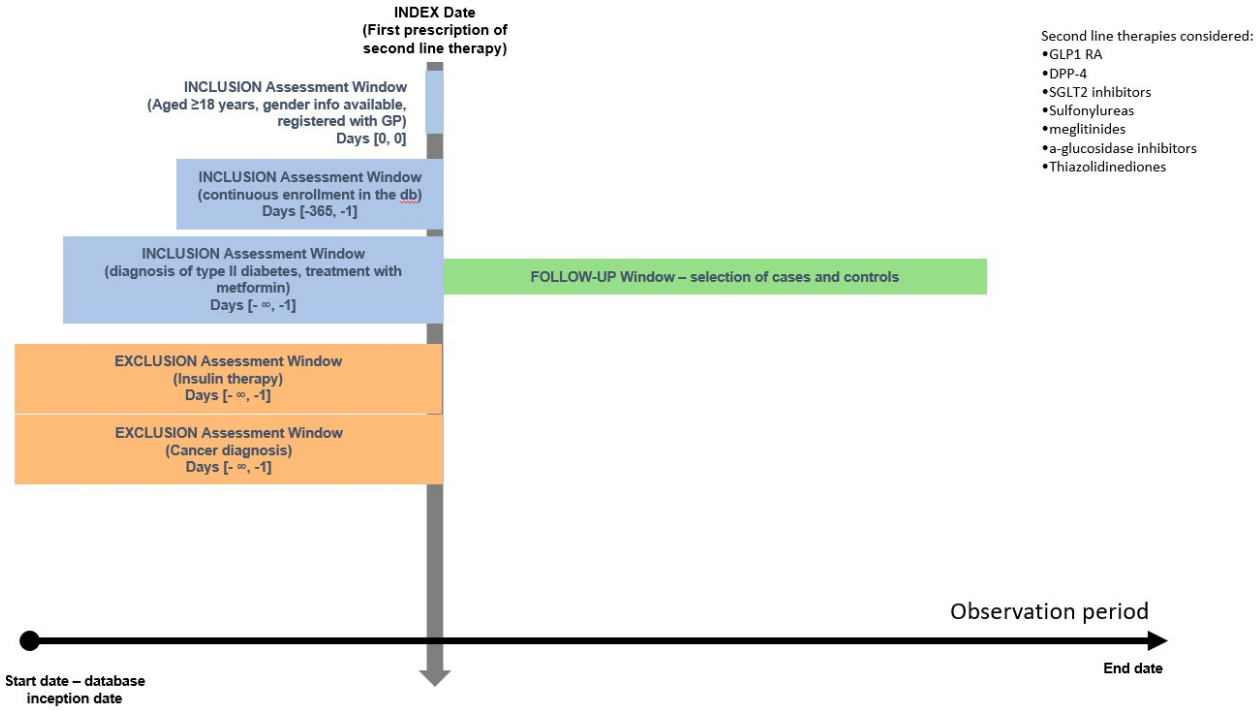
Exclusion criteria

- Any use of insulin therapy prior to cohort entry
- Patients with a thyroid cancer diagnosis prior to cohort entry

Cohort entry will consist of the latest of the following: study start date (1st January 2007), one year after the date of registration with a general practice, date of T2DM diagnosis, date of exposure to second-line antidiabetic therapy. Cohort exit will consist of the earliest of the following: study end date (31st December 2022), date of deregistration for the general practice, date of last data collection at the general practice, date of death.

Cases will then be identified from within the cohort. Cases will be the first thyroid cancer diagnosis after cohort entry. Up to 50 controls per case will be then selected through incidence density sampling method.

Figure 1. The design of parent cohort



3.4. Study period

Study period will be 1st January 2007 until 31st December 2022.

3.5. Variables

Outcome:

Any thyroid cancer diagnosis

Second-line therapy exposure:

Exposure for the following classes will be considered as second-line T2DM therapy: GLP1 receptor agonists, DPP-4 inhibitors, SGLT2 inhibitors, Thiazolidinediones and sulfonylureas, meglitinides, or a-glucosidase inhibitors (with prior metformin therapy). A list of drug substances used to define each class of T2DM treatment is contained in Annex 2.

For each exposure class type we will define the following definitions:

Definition 1

- Nonuser = no prior exposure record
- Current user = prescription within 90 days prior to the lag time period
- Past user = exposure >90 days before the lag time period
- Any history of use

Definition 2

- Nonuser = no prior exposure record

- Cumulative duration of use
    - o <1year of use
    - o 1-3 years of use
    - o >3 years of use

Confounders:

Adjustment based upon the design by Bezin et al.

- indices of multiple deprivation (IMD)
- goiter, hypo- and hyperthyroidism in the last year
- use of other antidiabetes drugs by therapeutic class

The primary additional confounders to be adjusted for will include:

- smoking status
- BMI
- history of alcohol abuse/misuse

Furthermore the following will also be considered depending upon the impact of the primary additional confounders on the effect estimates and available time to conduct the analysis: Exposure to ciclosporin/tacrolimus, and history of HIV/AIDs, chronic kidney disease, rheumatoid arthritis and inflammatory bowel disease.

Lag time: A six-month lag time period prior to index date will be implemented whereby exposure recorded during this lag period will not be counted in the analysis.

3.6. Statistical analysis

3.6.1. Main statistical methods

Controls will be sampled through risk set sampling, matched for age, gender, cohort follow-up, and diabetes duration. The matching approach may be refined depending on the feasibility to identify controls. Conditional logistic regression will be used to examine the association between each exposure and outcome. Odds ratios in this context can be considered akin to rate ratios.

3.6.2. Sensitivity analysis

1. Varying the definition of the T2DM cohort:

   As the number of thyroid cancer cases will be low, we may undertake the analysis by broadening the definition of the T2DM population to include:

   1) first-line treated T2DM or second-line treated T2DM, or

   2) diet controlled T2DM or first-line treated T2DM or second-line treated T2DM.

2. Varying the lag period from 3 months, 12 months, 24 months (depending upon the impact of confounder adjustment on the primary analysis).

3.6.3. Consideration of small numbers suppression

Considering the outcome of thyroid cancer is rare there is a risk that for some strata, the number of patients will be below 5. These cells will be masked in the final report to avoid patient reidentification.

3.7. Quality control

The study will be conducted according to the ENCePP code of conduct (European Medicines Agency 2018).

Standard operating procedures or internal process guidance will be adhered to for the conduct of the study. These procedures include rules for secure and confidential data storage, quality-control procedures for all aspects of the study from protocol development to the reporting of the results.

All documents will undergo at least one round a review by an experienced reviewer, while the results from the statistical analysis will be either reviewed or checked via double coding.

The quality control of the data is the responsibility of the data holder.

3.8. Limitations of the research methods

The main limitations of this study will be the database size and the number of incident thyroid cancer cases that are detected in the T2DM population. This study may therefore be underpowered to specifically quantify the association between GLP1 RAs and thyroid cancer. Also, whilst additional confounding adjustment is being proposed, residual confounding for the association between GLP1 receptor agonists and thyroid cancer is still possible. However, the aim is primarily to understand the impact of additional confounder adjustment on the association with thyroid cancer in the T2DM population (on the direction and degree of change in any association), which should be feasible. Whilst other study designs such as a comparator cohort study could also potentially be used to study this association, the nested case-control study is an established design useful to address multiple time-varying confounders that has been chosen in order to contextualise the impact of confounder findings in the context of the study by Bezin et al. For this reason, the study design will aim to be replicated. We will also consider a broader T2DM in order to examine the impact of additional confounder adjustment on the association, with the understanding that this deviates from the study by Bezin et al. Whilst this study will be closely aligned to that of Bezin et al. some differences will still be apparent such as the use of additional classes of drug-substances and second-line medications used in T2DM in the UK.

4. Protection of human subjects

Patient confidentiality will be protected according to the EU General Data Protection Regulation (GDPR) on the protection of individuals.

5. Management and reporting of adverse events/adverse reactions

Pursuant to the requirements for reporting of adverse events for secondary data (GVP module VI, VI.C.1.2.1.2), adverse event reporting will not be conducted as part of this study given the study objectives will be met through the use of secondary data.

6. Plans for disseminating and communicating study results

The analysis plan and study results will be published in EUPAS registries upon completion.

7. References

1. ECIS - European Cancer Information System, webpage https://ecis.jrc.ec.europa.eu/ , accessed 30th August 2023

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3. Bulchandani D, Nachnani JS, Herndon B, et al. Effect of exendin (exenatide)–GLP 1 receptor agonist on the thyroid and parathyroid gland in a rat model. Eur J Pharmacol 2012;691:292–296.

4. Bjerre Knudsen L, Madsen LW, Andersen S, et al. Glucagon-like peptide-1 receptor agonists activate rodent thyroid C-cells causing calcitonin release and C-cell proliferation. Endocrinology 2010;151:1473–1486

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9. Brown KF, Rumgay H, Dunlop C, Ryan M, Quartly F, Cox A, Deas A, Elliss-Brookes L, Gavin A, Hounsome L, Huws D, Ormiston-Smith N, Shelton J, White C, Parkin DM. The fraction of cancer attributable to modifiable risk factors in England, Wales, Scotland, Northern Ireland, and the United Kingdom in 2015. Br J Cancer. 2018 Apr;118(8):1130-1141. Epub 2018 Mar 23.

Annexes

Annex 1 - Information on Databases and Healthcare systems included

IQVIA™ Medical Research Data (IMRD) UK

IQVIA™ Medical Research Data (IMRD) UK is a primary care database from the UK. GPs play a gatekeeper role in the healthcare system in the UK, as they are responsible for delivering primary health care and specialist referrals. Over 98% of the UK-resident population is registered with a GP, so that GP patient records are broadly representative of the UK population in general. Patients are affiliated to a practice, which centralizes the medical information from GPs, specialist referrals, hospitalizations, and tests.

Annex 2 – Drug substances used to define each T2DM medication class.

DRUG SUBSTANCE	CLASS
ACARBOSE	ALPHA-GLUCOSIDASE INHIBITORS
METFORMIN	BIGUANIDE ANTIDIABETICS PLAIN
ALOGLIPTIN	DPP-IV INHIBITOR ANTIDIABETICS
LINAGLIPTIN	DPP-IV INHIBITOR ANTIDIABETICS
SAXAGLIPTIN	DPP-IV INHIBITOR ANTIDIABETICS
SITAGLIPTIN	DPP-IV INHIBITOR ANTIDIABETICS
VILDAGLIPTIN	DPP-IV INHIBITOR ANTIDIABETICS
NATEGLINIDE	GLINIDE ANTIDIABETICS PLAIN
REPAGLINIDE	GLINIDE ANTIDIABETICS PLAIN
PIOGLITAZONE	GLITAZONE ANTIDIABETICS PLAIN
ROSIGLITAZONE	GLITAZONE ANTIDIABETICS PLAIN
TROGLITAZONE	GLITAZONE ANTIDIABETICS PLAIN
DULAGLUTIDE	GLP-1 AGONIST ANTIDIABETICS
EXENATIDE	GLP-1 AGONIST ANTIDIABETICS
LIRAGLUTIDE	GLP-1 AGONIST ANTIDIABETICS
LIXISENATIDE	GLP-1 AGONIST ANTIDIABETICS
SEMAGLUTIDE	GLP-1 AGONIST ANTIDIABETICS
INSULIN BOVINE BASE	INSULINS
INSULIN BOVINE BASE/INSULIN PORCINE BASE	INSULINS
INSULIN BOVINE ISOPHANE	INSULINS
INSULIN BOVINE PROTAMINE ZINC	INSULINS
INSULIN BOVINE ZINC SUSPENSION (COMPOUND)	INSULINS
INSULIN BOVINE ZINC SUSPENSION (CRYSTALLINE)/INSULIN PORCINE ZINC SUSPENSION (AMORPHOUS)	INSULINS
INSULIN PORCINE BASE	INSULINS
INSULIN PORCINE ISOPHANE	INSULINS
INSULIN PORCINE ISOPHANE/INSULIN PORCINE BASE	INSULINS
INSULIN PORCINE ZINC SUSPENSION (AMORPHOUS)	INSULINS
INSULIN UNSPECIFIED BASE	INSULINS
INSULIN UNSPECIFIED ISOPHANE	INSULINS
INSULIN ASPART/INSULIN ASPART PROTAMINE CRYSTALLINE	INSULINS
INSULIN HUMAN BASE/INSULIN HUMAN ISOPHANE	INSULINS
INSULIN LISPRO/INSULIN LISPRO PROTAMINE	INSULINS
INSULIN ASPART	INSULINS
INSULIN GLULISINE	INSULINS
INSULIN HUMAN BASE	INSULINS
INSULIN LISPRO	INSULINS
INSULIN HUMAN ISOPHANE	INSULINS
INSULIN HUMAN ZINC SUSPENSION (COMPOUND)	INSULINS
INSULIN DEGLUDEC	INSULINS
INSULIN DETEMIR	INSULINS
INSULIN GLARGINE	INSULINS
INSULIN HUMAN ZINC SUSPENSION (COMPOUND)	INSULINS
INSULIN HUMAN ZINC SUSPENSION (CRYSTALLINE)	INSULINS

INSULIN DEGLUDEC/LIRAGLUTIDE	INSULINS
LIXISENATIDE/INSULIN GLARGINE	INSULINS
CANAGLIFLOZIN	SGLT2 INHIBITOR ANTIDIABETICS
DAPAGLIFLOZIN	SGLT2 INHIBITOR ANTIDIABETICS
EMPAGLIFLOZIN	SGLT2 INHIBITOR ANTIDIABETICS
ERTUGLIFLOZIN	SGLT2 INHIBITOR ANTIDIABETICS
CHLORPROPAMIDE	SULPHONYLUREA ANTIDIABETICS
GLIBENCLAMIDE	SULPHONYLUREA ANTIDIABETICS
GLICLAZIDE	SULPHONYLUREA ANTIDIABETICS
GLIMEPIRIDE	SULPHONYLUREA ANTIDIABETICS
GLIPIZIDE	SULPHONYLUREA ANTIDIABETICS
GLIQUIDONE	SULPHONYLUREA ANTIDIABETICS
TOLAZAMIDE	SULPHONYLUREA ANTIDIABETICS
TOLBUTAMIDE	SULPHONYLUREA ANTIDIABETICS