# INCRETIN-BASED THERAPIES AND THE RISK OF PANCREATIC CANCER IN PATIENTS WITH TYPE 2 DIABETES

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## BACKGROUND

Preclinical studies have highlighted the existence of metaplasia of ductal cells under the action of incretin-based therapies. Since the marketing of these two new classes of antidiabetic drugs (gliptins and GLP-1 receptor agonists) in 2008-2009, adverse pancreatic effects have been reported thru pharmacovigilance systems, suggesting a potential increased risk of pancreatic cancer associated with these treatments.

However, to date only few pharmacoepidemiological studies have investigated this association.

## OBJECTIVES

To investigate the risk of pancreatic cancer associated with incretin-based therapies in patients with type 2 diabetes.

More specifically, our aims were: 1) to measure the association between exposure to incretin-based therapies and the risk of pancreatic cancer; 2) to characterise this association in terms of dose- and treatment duration-response relationship; 3) to compare this association with that observed between other antidiabetic drugs and the risk of pancreatic cancer.

## MATERIAL AND METHODS

**Study Design:** Observational, longitudinal study

**Data source:** French national health insurance anonymized claim database matched to the national hospital discharge database (SNIIRAM) including individual information on:

- sociodemographic characteristics;
- reimbursement for all outpatient healthcare expenditures;
- hospital discharge diagnoses and medical procedures;
- severe and/or costly long-term diseases (LTD).

**Study Population:** All beneficiaries of the French national health insurance general scheme, aged 40 to 80 years and with a history type 2 diabetes diagnosis in 2010 were included unless they fulfilled one of the following exclusion criteria:

- history of cancer (any location) or pancreatectomy before inclusion;
- incident;
- cancer (any location) or death in the 3 months following inclusion;
- contraindication to incretin-based therapies (pregnancy, lactation, liver failure).

**Follow-up:** From the date of first reimbursement for an antidiabetic treatment in 2010 up to 31 December 2013, date of diagnosis of any cancer or death

**Exposure definition:** Patients were considered exposed to an antidiabetic treatment starting from 3 months following the date of first reimbursement for this treatment

**Statistical Analysis:** Multivariate Cox proportional hazard models

- Exposure to each class of antidiabetic drugs considered as a time-dependant variable
- Adjustment for age, sex, other antidiabetic drugs, severity of diabetes, smoking status, alcohol consumption, obesity, history of pancreatitis, ulcers, lithiasis and hepatitis

## RESULTS

### Characteristics of the study population

Among the 1,346,055 people included, 41.1% were exposed to gliptins and 7.2% to GLP-1 receptor agonists. Mean follow-up was 44 months, during which 3,113 cases of pancreatic cancer occurred (incidence of 62.9 per 100 000 people per year): 1,107 cases in the group exposed to gliptins and 157 cases in the group exposed to GLP-1 receptor agonists.

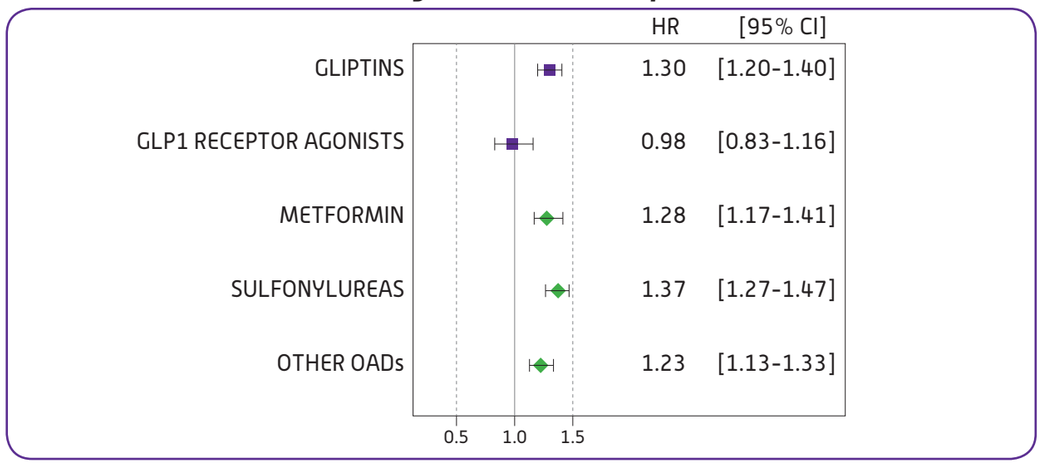
***Table 1. Baseline characteristics according to exposure to incretin-based therapies***

| | Entire cohort N=1,346,055 | Users of gliptins N=554,219 | Users of GLP-1 receptor agonists N=98,101 |
|---|---|---|---|
| **At baseline** | | | |
| Mean age (years) | 63.8 | 62.4 | 58.8 |
| Women, % | 46.0 | 45.4 | 51.8 |
| LTD diagnosis of diabetes*f*, % | 73.0 | 77.8 | 86.3 |
| Complications of diabetes*, % | 17.9 | 15.9 | 28.9 |
| Obesity**, % | 13.5 | 13.4 | 33.2 |

* retinopathy or kidney failure or arterial disease of lower limbs or diabetic neuropathy
** recorded during hospitalisation - *f* missing data: 14.8%

### Comparison of the risk of pancreatic cancer between patients exposed versus non-exposed to incretin-based therapies and to other classes of oral antidiabetic drugs

***Figure 1. Associations (adjusted* Hazard Ratios [HR] and 95% CI) between each class of antidiabetic drugs and the risk of pancreatic cancer***



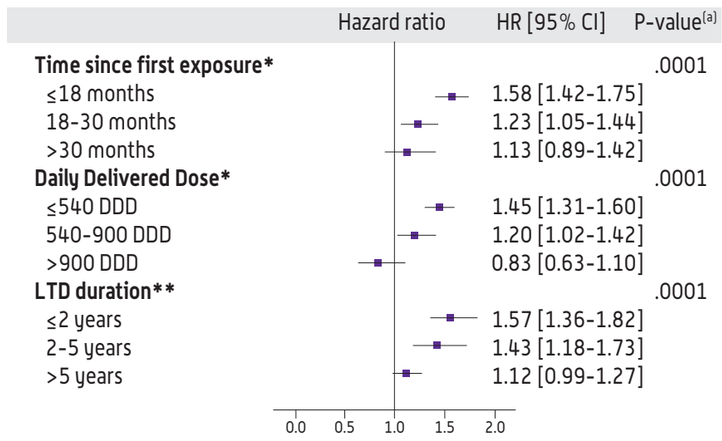

* Adjusted for age, sex, use of other antidiabetic drugs, complications of diabetes, history of pancreatitis, ulcers, lithiasis and hepatitis, smoking status, alcohol consumption and morbid obesity

The risk of pancreatic cancer was significantly higher among people ever vs. never exposed to gliptins (adjusted Hazard Ratio [aHR]: 1.30; 95% CI: [1.20-1.40]).

Exposure to other oral antidiabetic drugs (metformin/ Sulfonylureas / others) was also associated with an increased risk of pancreatic cancer. The increase in the risk of pancreatic cancer associated with gliptins was of similar magnitude as for other oral antidiabetic drugs (aHR between 1.23 and 1.37).

Exposure to GLP-1 receptor agonists was not associated with pancreatic cancer risk (aHR: 0.98 [0.83-1.16]).

***Figure 2. Associations between gliptins and the risk of pancreatic cancer according to time since 1st exposure, daily delivered dose (DDD) and LTD duration*****




* in patients strating gliptin treatment for the 1st time - ** at entry in the cohort - (a) tests for trend

The risk of pancreatic cancer was particularly marked early after initiation of gliptin treatment, and subsequently decreased with time since first exposure to gliptins (≤18 months: aHR 1.58 [1.42-1.75]; >30 months: aHR 1.13 [0.89-1.42]), with gliptins doses (≤540 DDD: aHR 1.45 [1.31-1.60]; >900 DDD: aHR 0.83 [0.63-1.10]) and with LTD duration (≤2 years: aHR 1.57 [1.36-1.82]; >5 years: aHR 1.12 [0.99-1.27]).

### Comparison of the risk of pancreatic cancer associated with gliptins versus with other classes of oral antidiabetic drugs

The risk of pancreatic cancer associated with gliptins did not differ from the risk of pancreatic cancer associated with other classes of oral antidiabetic drugs:

- Gliptins vs. Metformin: aHR 0.93 [0.75-1.16];
- Gliptins vs. Sulfonylureas: aHR 0.89 [0.79-1.00];
- Gliptins vs. other oral antidiabetic drugs: aHR 0.90 [0.79-1.02].

### Comparison of the risk of non-pancreatic cancers between patients exposed versus non-exposed to incretin-based therapies

Exposure to gliptins was not associated with an increased risk of non-pancreatic cancers: aHR 1.00 [0.98-1.01].

## CONCLUSION

- The risk of pancreatic cancer is increased in people exposed to gliptins with a recently initiated treatment or a low level of exposure, but not in those with a long-lasting or a high level of exposure to gliptins nor in those exposed to GLP-1 receptor agonists.
- The association found between exposure to gliptins and the risk of pancreatic cancer is similar to that observed for other classes of oral antidiabetic drugs.
- These results do not support a causal association between incretin-based treatments and the risk of pancreatic cancer.
- A longer follow-up is needed to confirm these reassuring results.

**Conflict of interest:** None of the authors have any conflicts of interest to declare.