Incretin based drugs and risk of cholangiocarcinoma among patients with type 2 diabetes: population based cohort study

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ABSTRACT

OBJECTIVE

To determine whether use of dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists are associated with an increased risk of cholangiocarcinoma in adults with type 2 diabetes.

DESIGN

Population based cohort study.

SETTING

General practices contributing data to the UK Clinical Practice Research Datalink.

PARTICIPANTS

154 162 adults newly treated with antidiabetic drugs between 1 January 2007 and 31 March 2017, followed until 31 March 2018.

MAIN OUTCOME MEASURES

Use of DPP-4 inhibitors and GLP-1 receptor agonists was modelled as a time varying variable and compared with use of other second or third line antidiabetic drugs. All exposures were lagged by one year to account for cancer latency and to minimise reverse causality. Cox proportional hazards models were used to estimate hazard ratios and 95% confidence intervals of incident cholangiocarcinoma associated with use of DPP-4 inhibitors and GLP-1 receptor agonists, separately. A post hoc pharmacovigilance analysis was conducted using the World Health Organization's global individual case safety report database, VigiBase, to estimate reporting odds ratios of cholangiocarcinoma.

RESULTS

During 614 274 person years of follow-up, 105 incident cholangiocarcinoma events occurred (rate 17.1 per 100 000 person years). Use of DPP-4 inhibitors was associated with a 77% increased hazard of cholangiocarcinoma (hazard ratio 1.77, 95% confidence interval 1.04 to 3.01). Use of GLP-1 receptor agonists was associated with an increased hazard with a wide confidence interval (hazard ratio 1.97, 0.83 to 4.66). In the pharmacovigilance analysis, the use of DPP-4 inhibitors and GLP-1 receptor agonists were both associated with increased reporting odds ratios for cholangiocarcinoma, compared with use of sulfonylureas or thiazolidinediones (1.63, 1.00 to 2.66, 4.73, 2.95 to 7.58, respectively).

CONCLUSION

Compared with use of other second or third line antidiabetic drugs, use of DPP-4 inhibitors, and possibly GLP-1 receptor agonists, might be associated with an increased risk of cholangiocarcinoma in adults with type 2 diabetes.

WHAT IS ALREADY KNOWN ON THIS TOPIC

The glucagon-like peptide-1 (GLP-1) incretin hormone has been shown to have proliferative and anti-apoptotic effects on cholangiocytes—cells that line the biliary tree

This raises the possibility that the incretin based drugs dipeptidyl peptidase-4 (DPP-4) inhibitors and GLP-1 receptor agonists could increase the risk of cholangiocarcinoma, a rare but highly fatal cancer

Although imbalances in hepatobiliary cancers have been observed in some of the large randomised controlled trials of incretin based drugs, no observational study has investigated this association in the real world setting

WHAT THIS STUDY ADDS

Use of DPP-4 inhibitors was associated with a near doubling of the risk of cholangiocarcinoma

An association of similar magnitude was observed with GLP-1 receptor agonists, but this did not reach statistical significance

Incretin based drugs therefore might be associated with an increased risk of cholangiocarcinoma in people with type 2 diabetes

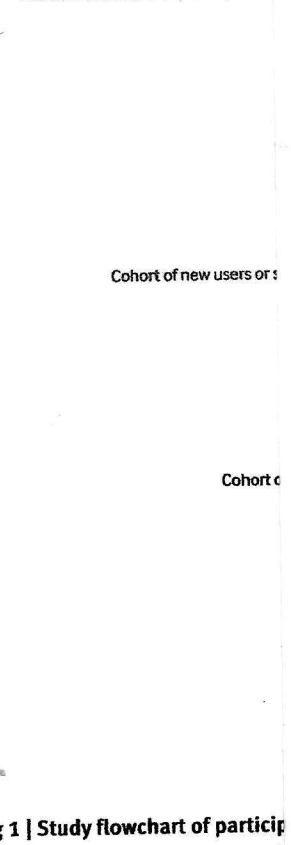

Fig 1 | Study flowchart of particip

Table 1 | Baseline characteristics of cohort and by antic (percentages) unless stated otherwise

Characteristics	Cohort (n=154 16
Mean (SD) age (years)	64.1 (11.6)
Men	89 234 (57.9)
Body mass index:	
<30	63 364 (41.1)
≥30.0	88 204 (57.2)
Unknown	2594 (1.7)
Smoking status:	
Ever	94 364 (61.2)
Never	59 189 (38.4)
Unknown	609 (0.4)
Alcohol related disorders	23 274 (15.1)
Mean (SD) Charlson comorbidity index score	1.9 (1.8)
Inflammatory bowel disease	1974 (1.3)
Gallbladder disease	4565 (3.0)
Glycated haemoglobin (HbA1c) (%):	
≤7.0	22 428 (14.6)
>7.0	114 003 (74.0)
Unknown	17 731 (11.5)
Mean (SD) duration of diabetes (years)	4.3 (5.5)
Antidiabetic drugs†:	
Metformin	43 233 (28.0)
Sulfonylureas	26 319 (17.1)
Thiazolidinediones	13 396 (8.7)
Insulin	4853 (3.2)
Others	2660 (1.7)

DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1.
*Suppressed: Numbers fewer than five are not displayed, as per confidenti
†Non-mutually exclusive groups, measured any time before (not including)