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Incretin-based drugs and risk of acute pancreatitis: A nested-case control study within a healthcare database

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ABSTRACT

To assess the association between use of incretin-based drugs for diabetes mellitus and the occurrence of acute pancreatitis.

A population-based, nested case-control study was performed within a cohort of 166,591 patients from the Lombardy region (Italy) aged 40 years or older who were newly treated with oral antihyperglycaemic agents between 2004 and 2007. Cases were 666 patients who experienced acute pancreatitis from April 1, 2008 until December 31, 2012. For each case patient, up to 20 controls were randomly selected from the cohort and matched on gender, age at cohort entry, and date of index prescription. Conditional logistic regression was used to model the risk of acute pancreatitis associated with use of incretin-based drugs within 30 days before hospitalization, after adjustment for several risk factors, including the use of other antihyperglycaemic agents. Sensitivity analyses were performed in order to account for possible sources of systematic uncertainty.

Use of incretin-based drugs within 30 days was reported by 17 (2.6%) cases of acute pancreatitis versus 193 (1.5%) controls. The corresponding multivariate odds ratio was 1.75 (95% confidence interval, 1.02 to 2.99). Slightly lower and no significant excess risks were observed by shortening (15 days) and increasing (60 and 90 days) the time-window at risk.

This study supports a possible increased risk of acute pancreatitis in relation to use of incretin-baseddrugs reported in a few previous studies. However, given the potential for bias and the inconsistency with other studies, additional investigations are needed to clarify the safety of incretin-based-drugs.

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1. Introduction

Glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors are two classes of incretin-based treatments for type 2 diabetes mellitus [1]. They act either by mimicking the effects of GLP-1 (e.g., exenatide and liraglutide) or by inhibiting the enzyme DPP-4 that degrades endogenous GLP-1 (e.g., sitagliptin and linagliptin). These agents are effective in glycaemic control, do not increase weight [2], and may reduce major cardiovascular events [3,4]. However, safety concerns have arisen because of possible pancreatic adverse events [5,6]. In particular, several cases of acute pancreatitis have been reported following the use of exenatide, sitagliptin, and other incretin-based drugs [7–9]. A recent case-control study nested within a large US claim database also reported an almost 2-fold increased risk of acute pancreatitis in users of exenatide and sitagliptin [10]. However, other observational studies based on insurance claim or health databases did not confirm such association [11–17], in agreement with meta- and pooled-analyses of clinical trials (mainly sitagliptin) [18–20]. A recent meta-analysis of randomized and non-randomized studies also suggested that incretin-based drugs do not increase the risk of *pancreatitis* [21]. Due to methodological *weaknesses*, however, additional carefully designed and conducted observational studies are warranted as also suggested by the FDA and EMA [22].

To further investigate this issue, we have thus analysed the data from the healthcare databases of the Lombardy Region (Italy), providing information on a large unselected population representative of the real clinical practice.

2. Methods

Data were retrieved from the healthcare utilization databases of the Italian Lombardy Region. In Italy, the population is covered by a National Health Service (NHS), and Lombardy provides an automated system of databases to collect a variety of information. Full details of the databases and the merging procedure have been reported elsewhere [23].

2.1. Study population

The target population consists of all beneficiaries of the NHS, resident in Lombardy and aged 40 years or more. We identified those who received at least one prescription of drug for diabetes treatment (ATC code: A10) from January 1, 2004, until December 31, 2007 and we defined the first prescription as the index prescription. Because incretin-based drugs were registered in Italy at the end of 2007, the period of recruitment ensured that patients had not started antihyperglycaemic therapy with an incretin-based drug. Since in fact incretin-based drugs are usually prescribed to type 2 diabetic patients as a second choice antidiabetic, patients who start with incretin-based drugs may differ from those who switch from other antidiabetics in clinical and other features which we are not able to measure. Patients were excluded from data analysis if they: (i) had received any antihyperglycaemic agent and/or were hospitalized for diabetes within the four years before the index prescription, to ensure inclusion of only newly treated individuals; (ii) were hospitalized for any pancreatic disease within four years before the index prescription, to ensure inclusion of only incident acute pancreatitis during follow-up; and/or (iii) were hospitalized for acute pancreatitis before April 1, 2008, to ensure a sufficient time span of potential exposure to the drugs of interest. Each member of the cohort accumulated person-months of follow-up from the date of the index prescription until the earliest among the dates of hospitalization for acute pancreatitis (see below), death, migration, or end of follow-up (December 31, 2012).

2.2. Selection of cases and controls

A case-control study was nested within the cohort of incident antihyperglycaemic users. Nested case-control design is an efficient alternative to cohort design when the effect of time-dependent exposure on rare events needs to be investigated using large databases [24,25].

Cases were members of the cohort who were hospitalized for acute pancreatitis (ICD-9 code 577.0). For each case patient, up to 20 controls at risk for the outcome at the time when the matched case had the event were randomly selected from the cohort and matched for gender, age at cohort entry, and date of index prescription. In this way, every set constituted by the index case and corresponding controls had the same period of observation.

2.3. Exposure variable and covariates

We identified all prescriptions of antihyperglycaemic drugs, including incretin-based drugs (ATC codes: A10BD07, A10BH01, A10BH02, A10BH03, A10BX04, A10BX07), biguanides (A10BA), sulphonylurea (A10BB and A10BC), other oral antihyperglycaemic agents (A10BD, A10BF, A10BG, A10BH, A10BX, with exclusion of A10BX04, A10BX07, A10BH01, A10BD07, A10BH02, A10BH03), and insulin (A10A) dispensed to each case-controls set during the corresponding time-window of observation.

Case patients and controls were classified according whether they were prescribed incretin-based drugs any time in the 30 days period before the date of hospital admission of the index case of each case-control set (time-window at risk). With the aim of avoiding the arbitrary nature of this time-window, shorter (15 days) and longer (60 and 90 days) time-windows of exposure were considered in a sensitivity analysis.

Information additionally considered were: (1) current exposure to other oral antihyperglycaemic, agents and/or to insulin in the 30 days before the date of hospital admission; (2) recent use (i.e., in the six months before the event date) of drugs known or suspected of increasing the risk of acute pancreatitis [26,27], such as ACE-inhibitors (C09A, C09B), angiotensin receptors blockers (C09C, C09D), furosemide (C03CA01, C03CB01, C03EB01), statins (C10AA), fibrates (C10AB), and valproic acid (N03AG01); (3) previous use (i.e., in the four years prior the date of the index prescription) of cardiovascular drugs (C) and antidepressants (N06A); (4) hospital discharge for gallstones, including diagnosis of either cholelithiasis (ICD-9-CM 574, 575.2) or cholangiography (51.10–51.11) or cholecystectomy (51.2), hypertriglyceridemia

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