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Incretin-Based Therapies and the Short-term Risk of Pancreatic Cancer: Results From Two Retrospective Cohort Studies

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Diabetes Care 2018;41:286–292 | https://doi.org/10.2337/dc17-0280

OBJECTIVE

Concerns have been raised about a possible increased risk of pancreatic cancer associated with incretin-based therapies. We examined the risk of pancreatic cancer among patients with diabetes prescribed incretin drugs.

RESEARCH DESIGN AND METHODS

With the use of public health insurance databases of Belgium and the Lombardy Region, Italy, we created two retrospective cohorts that included adult patients who were first prescribed an incretin drug or another noninsulin antidiabetic drug (NIAD) from 1 July 2008 to 31 December 2013 in Belgium and from 1 January 2008 to 31 December 2012 in the Lombardy Region. The risk of pancreatic cancer was evaluated by multivariate-adjusted Cox models that included time-dependent variables. Adjusted hazard ratios (aHRs) from Belgium and Italy were pooled by using fixed-effects meta-analyses.

RESULTS

The cohorts included 525,733 patients with diabetes treated with NIADs and 33,292 with incretin drugs. Results in both cohorts were similar. Eighty-five and 1,589 subjects who developed pancreatic cancer were registered among the incretin and NIAD new users, respectively, which represented an aHR of pancreatic cancer of 2.14 (95% CI 1.71–2.67) among those prescribed an incretin compared with an NIAD. The aHR with a drug use lag exposure of 6 months was 1.69 (1.24–2.32). The aHR decreased from 3.35 (2.32–4.84) in the first 3 months after the first incretin prescription to 2.12 (1.22–3.66) in months 3–5.9, 1.95 (1.20–3.16) in months 6–11.9, and 1.69 (1.12–2.55) after 12 months. Among those prescribed an NIAD, pancreatic cancer occurred mostly within the year after the first prescription. The risk of pancreatic cancer among patients subsequently prescribed insulin was 6.89 (6.05–7.85).

CONCLUSIONS

The recent prescription of incretin therapy is associated with an increased risk of pancreatic cancer. The reason for such an increase is likely the consequence of an occult pancreatic cancer that provokes or aggravates diabetes. Studies are warranted for assessing the risk of pancreatic cancer associated with long-term use of incretin drugs.

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Received 6 February 2017 and accepted 22 October 2017.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc17-0280/-/DC1.

This article is featured in a podcast available at http://www.diabetesjournals.org/content/diabetes-core-update-podcasts.

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The incretin-based therapies for patients with diabetes include glucagon-like peptide 1 receptor agonists (GLP-1 RAs) and dipeptidyl peptidase 4 (DPP-4) inhibitors. These therapies were introduced at the end of the 2000s and provide several advantages over other antidiabetic therapies. In particular, the metabolic actions of incretin-based therapies include glucoregulatory effects, the preservation of β-cell function, a low incidence of hypoglycemia, and the promotion of weight loss (1).

The pleiotropic effects of incretins on digestive functions and on the exocrine pancreas, such as the stimulation of cellular proliferation, have raised concerns about possible adverse events affecting the pancreas, including pancreatic cancer (2–6). These concerns were boosted by analyses of spontaneous reports to the U.S. Food and Drug Administration and to the German Adverse Reaction Registry suggesting that the use of incretin drugs is associated with an up to sixfold increased risk of pancreatic cancer (7–9). Such spontaneous reporting is highly susceptible to bias (e.g., reported cases are not validated and frequently are reported by nonmedical professionals), and cohort studies have not found an association between the use of incretin drugs and pancreatic cancer occurrence (10–12). However, the latter studies included relatively small numbers of patients with pancreatic cancer (13). A recent meta-analysis of the six largest randomized trials on incretin drugs obtained a summary relative risk of pancreatic cancer of 0.71 (95% CI 0.45–1.11) after 1.5–3.8 years of follow-up (14). However, the six trials analyzed reported a total of only 75 patients with pancreatic cancer, with a high level of heterogeneity of results across trials (I^2 = 61%). Hence, these trials cannot inform on the presence or absence of a small but real increase in risk.

This study evaluates the risk of pancreatic cancer associated with incretin-based therapies. It is part of a risk management plan approved by the European Medicines Agency (EMA) to evaluate the risk of pancreatic cancer associated with incretin use of a new incretin-based therapy, lixisenatide. This study covers a period before lixisenatide use in the general population.

RESEARCH DESIGN AND METHODS

Study Design

The study used patient data from public health care insurance databases in Belgium (11 million inhabitants) and in the Lombardy Region of Italy (10 million inhabitants). In both settings, the same protocol was used (i.e., similar methods for subject selection, drug exposure assessment, statistical analysis). A new users design was implemented in both settings. The risk of pancreatic cancer in subjects newly prescribed an incretin drug was compared with that in subjects who were newly prescribed another noninsulin antidiabetic drug (NIAD). In both settings, secondary data were used without transfer of individual or identifiable data to another study partner; therefore, prior approval by an ethics committee was not needed.

Data Sources

Registration of individuals living in Belgium and Italy to public health insurance is compulsory. In Belgium, public health insurance data contain prescription data and hospitalization information. These data are linked to governmental population registries and the national Belgian cancer registry with a unique identifier that allows extraction of migration status, living status, and occurrence of pancreatic cancer.

The health care utilization databases of the Lombardy Region comprise the outpatient drug prescription database, which stores all drug prescriptions reimbursed by the National Health Service and dispensed by Lombardy Region pharmacies, and the hospital discharge database, which contains all hospitalization data from public and private hospitals. These databases are linked to demographic data with a unique identifier to build the full pathway of care and health status of patients with diabetes. Study subjects with pancreatic cancer were identified from hospital discharge data.

The validity of the databases as well as the recording and coding of data have been described previously (15–17). Date of delivery and formulation of antidiabetic drugs were identified in the public health insurance records by their Anatomical Therapeutic Chemical Classification System codes.

Study Cohorts

Because a 2- to 3-year lag exists between data collection at the individual level and availability of complete data sets for the entire population, the statistical analyses were performed in 2015–2016 on two cohorts of subjects for whom data had been collected from 2008 to 2013 in Belgium and from 2000 to 2012 in Italy. The date of study start was 1 January 2008, which corresponds to the date both settings started to reimburse for incretin drugs.

In Belgium, the cohort included all patients ≥18 years of age who had no prescription of an antidiabetic drug from 1 January 2008 until 30 June 2008 and to whom an NIAD or incretin drug was prescribed for the first time from 1 July 2008 onward. In the Lombardy Region, the cohort included all patients ≥18 years of age who never received a prescription for an antidiabetic drug from January 2000 to December 2007 and to whom an NIAD or incretin drug was prescribed for the first time from 1 January 2008 onward.

In both settings, patients who received insulin as primary antidiabetic therapy were excluded. Those with a record of pancreatic cancer before 1 January 2008 also were excluded. In both settings, GLP-1 RA was marketed later than DPP-4 inhibitor drugs. Lixisenatide was not studied in the retrospective cohort because its approval by the EMA was too recent and it was not available in the Lombardy Region during the study period. The 23 Belgian patients who had at least one prescription of lixisenatide were excluded from the analyses.

Exposure Definition

The incretin drugs included the GLP-1 RAs exenatide and liraglutide and the DPP-4 inhibitors sitagliptin, vildagliptin, saxagliptin, alogliptin, and linagliptin. NIADs included metformin, sulfonylureas, thiazolidinediones, and repaglinide.

Outcome

Third-revision *International Classification of Diseases for Oncology* codes C25.0–C25.9 were used to identify pancreatic cancer cases in the Belgian Cancer Registry. In the Lombardy Region, the hospital discharge records were used to identify pancreatic cancer through ICD-9 code 157 and all subcategories.

Data Analysis

The medical trajectory of each study subject was reconstituted with the succession of events and prescriptions relevant to the study. Person time-at-risk starting from the first prescription was computed for each subject. The person time-at-risk included the duration of drug use until occurrence of one of the following events: diagnosis of pancreatic cancer, death, emigration, or study end date, whichever

came first. Because the reimbursement of drugs and medical services depends on the correct registration of data by health insurance companies, missing data are known to be rare and are not apparent in the databases.

A subject contributed in a time-dependent manner to the incretin or NIAD group. Subjects newly prescribed an NIAD could switch to an incretin drug or be prescribed an incretin drug in addition to NIAD treatment. Hence, a subject's duration of exposure to a specific antidiabetic regimen was measured individually and expressed in days. If the antidiabetic regimen changed, then the switch to a new regimen had another duration starting the day of the regimen change. Subjects contributed to the NIAD group during the period with never exposure to an incretin drug. Subjects who took both a GLP-1 RA and a DPP-4 inhibitor were classified in the GLP-1 RA group. Subjects who switched to an incretin drug remained in this category for the rest of the follow-up regardless of additional changes in prescription or coexposure with an NIAD.

The incidence rates of pancreatic cancer among new users of an incretin drug were compared with rates observed in new users of an NIAD. Crude and standardized incidence rates for pancreatic cancer were calculated. The European Standard Population was the reference (18).

Risk of pancreatic cancer between incretin and NIAD use was reported as a hazard ratio (HR) from a Cox proportional hazards regression model that included time-dependent variables for drug prescriptions to account for changes in exposure during the follow-up. To minimize the risk of confounding, stratification was performed on age and sex. Age was defined as the age at study entry and stratified into four categories: 18–49, 50–59, 60–69, and $\geq$70 years. Statistical adjustments were done on insulin prescription. Data from Belgium also were adjusted for a history of gallstones or bariatric surgery. Similarly to metformin, incretin drugs are sometimes prescribed for short periods to patients without diabetes for weight-loss purposes. Thus, we performed sensitivity analyses with the exclusion of subjects with a drug prescribed for $<$90 days. To assess the influence on the risk of pancreatic cancer of the first months after drug prescription, we also performed an analysis excluding the 6 months of exposure to antidiabetic drugs immediately preceding the diagnosis of pancreatic cancer (i.e., a lagged analysis) (19). A lag exposure of 6 months was taken so that the analysis could be based on decent numbers of pancreatic cancer cases among incretin users in each setting. Results from Belgium and the Lombardy Region were pooled by using meta-analytic methods on the basis of a fixed-effects model. Heterogeneity of results between Belgium and the Lombardy Region was assessed with the I^2 statistic. A test for the assumption of proportional hazards was not required because all covariates used in the model were time dependent. All analyses were carried out with SAS 9.4 statistical software (SAS Institute, Cary, NC).

RESULTS

The subject selection is detailed in Supplementary Table 1. In Belgium, 345,672 new NIAD and 22,982 new incretin users were included in the cohort. In the Lombardy Region, 180,061 new NIAD and 10,310 new incretin users were included. In Belgium, the mean duration of follow-up was 1.81 years (total of 41,645 person-years [PYs]) for incretin users and 2.83 years (978,708 PYs) for NIAD users. In the Lombardy Region, the corresponding durations were 1.25 years (12,848 PYs) for incretin users and 2.55 years (458,172 PYs) for NIAD users.

Compared with subjects prescribed an NIAD, those prescribed incretin-based therapies were younger and more frequently male (Table 1). Shifts to insulin therapy during follow-up were approximately two times more frequent among incretin users than among NIAD users. Few subjects had a record of gallbladder disorder, bariatric surgery, pancreatic surgery, or a laparoscopic procedure.

A diagnosis of pancreatic cancer was reported for 885 subjects in Belgium and 789 subjects in the Lombardy Region. Of the 1,674 pancreatic cancer cases observed overall, 882 occurred in men and 792 in women. The incidence rate standardized on the age structure of the European population was 45.5 and 83.7 per 100,000 PY in the Belgian NIAD and incretin groups, respectively, and 76.5 and 126.6 per 100,000 PY in the Lombardy Region NIAD and incretin groups, respectively. In both settings, after multiple adjustments for age, sex, and subsequent insulin prescription, the risk of pancreatic cancer was doubled among subjects who ever received an incretin drug compared with those who only received an NIAD, with a pooled adjusted HR (aHR) of 2.14 (95% CI 1.71–2.67) (Table 2). In Belgium, additional adjustments for a history of gallstones, bariatric surgery, or a laparoscopic procedure did not alter results (aHR 2.30 [1.74–3.06]). With only 55 pancreatic cancer cases observed among incretin users in Belgium and 30 in the Lombardy Region, the analysis could not be conducted separately by sex. The 6-month lag analysis of a smaller number of pancreatic cancer cases obtained an aHR of 1.69 (1.24–2.32).

Analyses after leaving out prescriptions for $<$90 days resulted in an aHR of 2.24 (95% CI 1.68–2.99) in Belgium and 2.21 (1.51–3.22) in the Lombardy Region (pooled aHR 2.23 [1.77–2.80]). GLP-1 RAs represented 12.9% and 22.4% of incretin prescriptions in Belgium and the Lombardy Region, respectively. Ten pancreatic cancer cases were found among GLP-1 RA users (seven in Belgium, three in the Lombardy Region). After stratification for age and sex and adjustment for subsequent insulin prescription, the risk of pancreatic cancer was 1.87 (1.00–3.51) times greater among subjects who were ever prescribed a GLP-1 RA compared with new NIAD users. In all analyses, no heterogeneity of results was found between the two settings (I^2 = 0%).

To examine changes in risks according to the duration of incretin use, we fitted multivariable Cox models in which the duration of incretin drug use was modeled as a time-dependent variable, with risks estimated for four distinct categories of time since first prescription of incretin (Table 3). The analysis showed that in both settings, compared with those newly prescribed an NIAD, the risk of pancreatic cancer among subjects newly prescribed incretin therapy was 3.35 (95% CI 2.32–4.84) times greater in the first 3 months immediately after the first prescription, after which the risk gradually diminished to 1.69 (1.12–2.55) 1 year after the first prescription. The analyses found no heterogeneity in results between the two settings (I^2 = 0%).

We performed other analyses for the sake of further exploring the time relationship between the prescription for an antidiabetic therapy and pancreatic cancer. First, among subjects newly prescribed an NIAD, pancreatic cancer cases were more frequent after the first prescription, although this association was less marked than for the incretin drugs

Table 1—Characteristics of subjects included in the retrospective cohorts

	Belgium			Lombardy Region		
	Incretins (*n* = 22,982)	NIAD (*n* = 345,672)	*P* value*	Incretins (*n* = 10,310)	NIAD (*n* = 180,061)	*P* value*
Baseline						
Sex			<0.001			<0.001
Male	13,342 (58.1)	161,167 (46.6)		5,829 (56.5)	96,598 (53.6)	
Female	9,640 (41.9)	184,505 (53.4)		4,481 (43.5)	83,463 (46.4)	
Age-group			<0.001			<0.001
<50 years	6,345 (27.6)	88,512 (25.6)		2,507 (24.3)	26,922 (15.0)	
50–59 years	7,340 (31.9)	79,092 (22.9)		3,141 (30.5)	35,534 (19.7)	
60–69 years	5,555 (24.2)	81,371 (23.5)		2,832 (27.5)	51,520 (28.6)	
≥70 years	3,742 (16.3)	96,697 (28.0)		1,830 (17.8)	66,085 (36.7)	
Follow-up						
Use of insulin			<0.001			<0.001
Yes	4,969 (21.6)	34,082 (9.9)		950 (9.2)	7,719 (4.3)	
No	18,013 (78.4)	311,590 (90.1)		9,360 (90.8)	172,342 (95.7)	
Gallbladder disorder			0.50			0.051
Yes	420 (1.8)	6,532 (1.9)		116 (1.1)	2,435 (1.4)	
No	22,562 (98.2)	339,140 (98.1)		10,194 (98.9)	177,626 (98.6)	
Bariatric surgery			<0.001			—
Yes	314 (1.4)	5,750 (1.7)		NA	NA	
No	22,668 (98.6)	339,922 (98.3)		NA	NA	
Pancreatic surgery			0.66			—
Yes	34 (0.1)	553 (0.2)		NA	NA	
No	22,948 (99.9)	345,119 (99.8)		NA	NA	
Laparoscopic procedure			0.018			—
Yes	75 (0.3)	1,492 (0.4)		NA	NA	
No	22,907 (99.7)	344,180 (99.6)		NA	NA	

Data are *n* (%). NA, not available. *χ^2 *P* value.

(data not shown). Second, in the subgroup of subjects taking an NIAD who subsequently received a prescription of incretin or insulin, the time from first prescription of the NIAD to the first prescription of incretin or insulin was shorter in those diagnosed with pancreatic cancer (Supplementary Table 2). Third, we examined the risk of pancreatic cancer among subjects who received an insulin therapy during follow-up (Table 4). An insulin therapy during follow-up was prescribed to 10.6% of subjects in Belgium and 4.6% of subjects in the Lombardy Region (Table 4). A diagnosis of pancreatic cancer was at least 10 times more frequent among subjects who shifted to insulin therapy. After stratification for age and sex, the risk of pancreatic cancer was found to be 6.89 (95% CI 6.05–7.85) times greater in subjects who were prescribed an insulin therapy during follow-up.

CONCLUSIONS

This study indicates a doubling of the risk of pancreatic cancer after prescription of incretin-based therapies, with the same

Table 2—Risk of pancreatic cancer associated with incretin use

	Belgium		Lombardy Region		Belgium and Lombardy Region combined	
Exposure group	NIAD	Incretin	NIAD	Incretin	NIAD	Incretin
All subjects						
Pancreatic cancer (*n*)	830	55	759	30	1,589	85
PYs	978,708	41,645	458,172	12,848	1,436,880	54,493
IR* (crude)	84.8	132.1	165.7	233.5	110.6	156.0
IR* (standardized to the EU population)	45.5	83.7	76.5	126.6	55.4	94.4
HR† (95% CI)	1.00‖	2.32 (1.76–3.07)	1.00‖	1.85 (1.28–2.67)	1.00‖	2.14 (1.71–2.67)¶
HR‡ (95% CI)	1.00‖	2.55 (1.92–3.37)	1.00‖	2.44 (1.69–3.52)	1.00‖	2.51 (2.01–3.14)¶
HR§ (95% CI)	1.00‖	2.12 (1.60–2.81)	1.00‖	2.17 (1.50–3.13)	1.00‖	2.14 (1.71–2.67)¶
Lagged exposure of 6 months						
Pancreatic cancer (*n*)	469	50	428	17	897	67
PYs	774,499	31,052	369,228	8,225	1,143,727	39,277
IR* (standardized to the EU population)	33.71	103.79	54.69	113.89	40.60	106.09
HR† (95% CI)	1.00‖	2.01 (1.39–2.90)	1.00‖	1.36 (0.75–2.49)	1.00‖	1.81 (1.32–2.47)¶
HR‡ (95% CI)	1.00‖	2.20 (1.52–3.19)	1.00‖	1.85 (1.02–3.38)	1.00‖	2.10 (1.53–2.87)¶
HR§ (95% CI)	1.00‖	1.74 (1.20–2.52)	1.00‖	1.59 (0.87–2.91)	1.00‖	1.69 (1.24–2.32)¶

EU, European; IR, incidence rate. *Per 100,000 PY. †Crude. ‡Stratified by age and sex. §Stratified by age and sex and adjusted for use of insulin as a time-dependent variable. ‖Reference category. ¶Summary HR calculated by fixed-effects meta-analysis.

Table 3—Risk of pancreatic cancer associated with incretin use by time since first prescription

	Belgium		Lombardy Region		Belgium and Lombardy Region combined	
Incretin exposure category	Pancreatic cancer (*n*)	HR (95% CI)	Pancreatic cancer (*n*)	HR (95% CI)	Pancreatic cancer (*n*)	Summary HR (95% CI)
<3 months	16	3.31 (1.98–5.52)	14	3.39 (2.00–5.78)	30	3.35 (2.32–4.84)
3 to <6 months	8	2.34 (1.16–4.71)	5	1.80 (0.74–4.35)	13	2.12 (1.22–3.66)
6 to <12 months	11	2.13 (1.17–3.88)	6	1.66 (0.74–3.73)	17	1.95 (1.20–3.16)
≥12 months	20	1.74 (1.10–2.76)	5	1.52 (0.62–3.69)	25	1.69 (1.12–2.55)

HR stratified by age and sex and adjusted for gallbladder events and insulin use as time-dependent variables; the reference group is NIAD users. Summary HR was calculated by fixed-effects meta-analysis.

order of magnitude of risk observed in Belgium and the Lombardy Region. The straightforward interpretation that incretin-based therapies could cause pancreatic cancer is not supported by several findings. A direct causal effect could be suspected if a steadily increasing risk of pancreatic cancer was associated with a steadily longer exposure to incretin drugs. However, the increased risk is observed primarily in the months immediately following prescription, and results from the Cox model in Table 3 demonstrate that the declining cancer occurrence after the first prescription is not solely due to decreasing numbers of subjects being followed. Moreover, exclusion of the 6 months of antidiabetic drug use immediately preceding the diagnosis of pancreatic cancer leads to a lower risk, although it remains significantly elevated. These time relationships between incretin prescription and the diagnosis of pancreatic cancer do not support a causal association.

The diagnosis of pancreatic cancer shortly after new-onset diabetes is a common clinical observation (20), and the diagnosis of pancreatic cancer is three to five times more frequent in the year immediately following the diabetes diagnosis than ≥2 years after diagnosis (21–23). The quicker recourse to incretin or insulin therapy in subjects diagnosed with pancreatic cancer and the higher risk of pancreatic cancer among subjects who received insulin therapy suggest that the prescription of a new antidiabetic drug or a switch to more potent antidiabetic therapy could be the consequence of yet undiagnosed pancreatic cancer that induced or aggravated diabetes.

This peculiar time relationship also suggests that incretin-based therapy promotes the last steps for progression from a subclinical pancreatic cancer to a clinically evident disease shortly after treatment initiation. This promotional effect would be unrelated to the cumulative doses taken. However, a similar inverse correlation with time since first prescription was observed with the new prescriptions of NIADs. In addition, a shift to insulin therapy during follow-up was the strongest risk factor for pancreatic cancer found in this study. Hence, these data do not support an incretin-specific effect on pancreatic cancer growth, whereas they do support the influence of occult pancreatic cancers on diabetes onset and aggravation.

This reverse causation phenomenon is termed the protopathic bias (24) and occurs when a pharmaceutical agent is prescribed for an early manifestation of a disease that has not yet been detected. The influence of the protopathic bias has been raised by other studies on use of oral antidiabetic drugs, insulin (25), and incretin drugs (12,26). In an attempt to reduce the influence of the protopathic bias, the large study of Azoulay et al. (27) excluded all exposures to antidiabetic drugs in the year preceding the diagnosis of pancreatic cancer, which resulted in a pooled aHR of 1.02 (95% CI 0.84–1.23).

The risk of pancreatic cancer in the current study was still significantly raised after 1 year of incretin drug use and after the 6-month lag analysis, which could be due to the same protopathic bias that would influence risks over a relatively long period. But this finding could point to the possibility of an increased risk of pancreatic cancer associated with long-term incretin drug use.

The biological plausibility that incretin-based therapies could be involved in the occurrence of pancreatic cancer has been raised by studies in animals and human tissue, suggesting that these drugs could induce pancreatic inflammation and proliferation of exocrine and endocrine pancreatic cells, two phenomena known to increase the risk of pancreatic cancer (28–30). Other studies in animals, including in baboons, do not provide evidence that incretin-based therapies cause pancreatic injury and remodeling that could give rise to more severe malignant processes (31,32). One recent study in human tissues found no influence of

Table 4—HR for the risk of pancreatic cancer associated with insulin prescriptions during follow-up

	Belgium		Lombardy Region		Belgium and Lombardy Region combined	
	Without insulin prescription	With insulin prescription	Without insulin prescription	With insulin prescription	Without insulin prescription	With insulin prescription
No pancreatic cancer (*n*)	329,236	38,533	181,241	8,341	510,477	46,874
Pancreatic cancer (*n*)	367	518	461	328	828	846
Cumulative incidence per 100,000	111	1,344	254	3,932	162	1,805
HR* (95% CI)	1.00	6.61 (5.63–7.77)	1.00	7.46 (6.00–9.35)	1.00	6.89 (6.05–7.85)†

*Use of insulin as time-dependent variable through Cox model stratified by age and sex. †Summary HR calculated by fixed-effects meta-analysis.

incretin-based therapies on pancreatic tissue morphology (33). However, uncertainties about the adverse biological influence of incretin-based therapies remain partly because of the variability in results obtained across various strains of mice and the difficulty with conducting studies on human tissue (31,33).

The current study has several strengths. The same methods were applied on two independent databases of patients of all ages residing in Belgium or the Lombardy Region, and the results in both settings were consistent. The methods were strictly based on a new user design (i.e., patients with no history of antidiabetic medication before their inclusion in cohorts, which precluded possible biases as a result of differences in antidiabetic therapy duration before incretin use). The study included 1,674 subjects with pancreatic cancer. Other studies that were based on a new user design included 221 (26), 309 (12), and 1,221 (27) patients.

The current study also has a number of limitations. First, the duration of incretin drug use was short, which on average was 1.8 years in Belgium and 1.25 years in the Lombardy Region, assuming that these drugs were taken during most of the time after prescription. This short duration precluded statistical analyses on the basis of long lag times (e.g., $\geq$1 year). Therefore, studies are needed with longer follow-up to enable the use of variable lag periods as recommended by methodological studies (19,34). Second, no population-based cancer registry exists in the Lombardy Region. However, pancreatic cancer is a serious condition that usually leads to hospitalization. Indeed, some cases of pancreatic cancer may have been missed if subjects died as a result of pancreatic cancer not managed in a hospital. Third, risk estimations relied on prescription data and not on dispensed medication, with no control for adherence to treatment, but as suggested by meta-analytic studies, adherence to treatment would not vary according to the type of antidiabetic drug (35). Fourth, we did not consider whether patients were taking one or more antidiabetic therapies at the same time. However, when an incretin therapy is prescribed in Belgium, the concomitant prescription of metformin or a sulfonylurea is compulsory. In Italy, incretins may be prescribed alone. The similarity of results in both areas is a sign that the simultaneous use of antidiabetic therapies does not affect associations found in this study. Finally, data were absent on well-documented risk factors for pancreatic cancer, such as heavy alcohol consumption, smoking, a family history of chronic pancreatic diseases, and other confounders like physical activity, adiposity, and information on diabetes severity other than the recourse to insulin. Thus, residual confounding may partly explain some of the observed associations.

We conclude that the protopathic bias would be an adequate hypothesis for explaining the increased risk of pancreatic cancer associated with the use of incretin drugs on the basis of spontaneous report. However, because the risk of pancreatic cancer remained slightly but significantly increased after 1 year of incretin drug use, studies that assess the risk of pancreatic cancer associated with long-term incretin drug use are needed, with examination of timing and duration while taking into account the various factors possibly involved in the occurrence of pancreatic cancer.

Acknowledgments. The data in Belgium belong to the InterMutualistic Agency (www.aim-ima.be) and the Belgian Cancer Registry, and the data in the Lombardy Region belong to the Health Directorate of Lombardy Region.

Funding. This study was part of the postauthorization safety study of GLP-1 Receptor Agonists and Risk of Acute Pancreatitis, Pancreatic Cancer and Medullary Thyroid Cancer requested by EMA (London, U.K.). The protocol was developed through interaction between the International Prevention Research Institute and the Committee for Medicinal Products for Human Use of the EMA.

Duality of Interest. The postauthorization safety study was funded by Sanofi. G.C. reports grants from Roche, Amgen, and Bristol-Myers Squibb outside the submitted work. No other potential conflicts of interest relevant to this article were reported.

Sanofi had no influence on the study design, conduct, analysis, and reporting.

Author Contributions. M.Bon., M.F., M.Bot., A.L., J.G., N.v.D., G.C., P.A., and P.B. interpreted the data and edited the final version of the manuscript. M.Bon., M.F., and M.Bot. analyzed the data. M.Bon., P.A., and P.B. contributed to the study concept and design. M.F., A.L., J.G., and N.v.D. handled the data. P.A. drafted the manuscript. P.A. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented in abstract form at the 77th Scientific Sessions of the American Diabetes Association, San Diego, CA, 9–13 June 2017.

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