Incretin-Based Drugs and Adverse Pancreatic Events: Almost a Decade Later and Uncertainty Remains

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Over the past few years, substantial clinical data have been presented showing that incretin-based therapies are effective glucose-lowering agents. Specifically, glucagon-like peptide 1 receptor agonists demonstrate an efficacy comparable to insulin treatment with minimal hypoglycemia and have favorable effects on body weight. Thus, many of the unmet clinical needs noted from prior therapies are addressed by these agents. However, even after many years of use, many continue to raise concerns about the long-term safety of these agents and, in particular, the concern with pancreatitis. This clearly remains a complicated topic. Thus, in this issue of *Diabetes Care*, we continue to update our readers on this very important issue by presenting two studies evaluating incretin-based medications and risk of pancreatitis. Both have undergone significant revisions based on peer review that provided significant clarification of the data. We applaud both author groups for being extremely responsive in providing the additional data and revisions requested by the editorial team. As such, because of the critical peer review, we feel both articles achieve the high level we require for *Diabetes Care* and are pleased to now present them to our readers. In keeping with our aim to comprehensively evaluate this topic, we asked for additional commentaries to be prepared. In the narrative outlined below, Dr. Laurent Azoulay provides a commentary about the remaining uncertainty in this area and also discusses the results from a nationwide population-based case-control study. In the narrative preceding Dr. Azoulay's contribution, Prof. Edwin A.M. Gale provides a commentary on the report that focuses on clinical trials of liraglutide in the treatment of diabetes. From the journal's perspective, both of the articles on pancreatitis and incretin-based therapies reported in this issue have been well vetted, and we feel both of the commentaries are insightful.

—William T. Cefalu
Editor in Chief, *Diabetes Care*

Almost a decade after entering the U.S. market, the safety of incretin-based drugs continues to be debated (1,2). Much of the controversy has focused on concerns that these drugs may cause proliferative changes in pancreatic duct cells that lead to acute pancreatitis and possibly pancreatic cancer (3). These concerns have been corroborated by reports from adverse event databases (4,5), although such analyses have well-known limitations. In contrast, the observational studies conducted to date have been conflicting and inconclusive (6–15).

In one of the two studies of the question in this issue of *Diabetes Care*, Thomsen et al. (16) report on a population-based case-control study using the

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Danish administrative databases to assess the association between incretin-based drugs and hospitalized acute pancreatitis. Overall, the authors report no association between the use of incretin-based drugs and acute pancreatitis. While the use of these large comprehensive databases and the use of risk set sampling for the selection of the control subjects are strengths of this study, it does have some important methodological shortcomings that limit the interpretation of the findings. First, it was based on an impressive 12,868 cases and 128,680 matched control subjects, but the actual number of patients with a history of treated diabetes was relatively small (1,091 [8.5%] and 7,868 [6.1%], respectively). Second, the reference category used in the primary analysis was never users of incretin-based drugs. As a result, this reference category likely included a large number of patients without type 2 diabetes. While the use of this large comparator group increased statistical power, it likely introduced confounding by indication given the known association between type 2 diabetes and acute pancreatitis (17). Accordingly, the crude analysis comparing ever users of incretin-based drugs with never users produced a statistically significant association (odds ratio [OR] 1.36 [95% CI 1.08–1.69]); incidentally, similar point estimates were observed for the other antidiabetes drugs, suggesting that this observed association is driven more by the type 2 diabetes itself than the drugs. In a secondary analysis, the authors compared incretin-based drugs with other antidiabetes drugs. While this is an improvement relative to the primary analysis, comparing second- to third-line therapies, such as incretin-based drugs to various other antidiabetes drugs, may introduce time-lag bias, a bias resulting from comparing treatments prescribed at different stages of the disease (18). Finally, the association was no longer significant and closer to the null after adjustment for potential confounders (OR 0.95 [95% CI 0.75–1.21]). The sharp attenuation of the OR appears to have been explained by the adjustment of pancreatitis-associated conditions. With both exposure and the potential confounders measured in the same time window, it is possible the analysis adjusted for variables in the causal pathway, resulting in a potentially biased and underestimated point estimate (19).

In the other study in this issue, Jensen et al. (20) pooled data from 18 randomized controlled trials (RCTs) conducted by the manufacturer of the glucagon-like peptide 1 analog liraglutide. The authors report eight events of acute pancreatitis in the liraglutide group versus one event in the comparator group, generating incidence rates of 1.6 and 0.7 per 1,000 patient-years, respectively (relative risk 2.1 [95% CI 0.3–16.0]). It is unclear why this analysis excluded 825 patients who had been randomized to placebo in these trials (patients on other antidiabetes drugs). The exclusion of such patients is inappropriate. All patients, including those randomized to placebo, should have contributed to the analysis, as they would surely have been included if a case of acute pancreatitis had occurred in this group. Thus, the 397 patient-years of follow-up generated by these placebo patients should have been included in the denominator when calculating the rate in the comparator group. The addition of these patient-years of follow-up lowers the incidence rate in the comparator group to 0.6 per 1,000 patient-years, and thus increases the relative risk to 2.8 (95% CI 0.3–22.0). Another limitation of this analysis is that most of the included RCTs were less than 6 months in duration. This short duration of follow-up may have been insufficient to detect the association of interest, given that six out of the eight reported acute pancreatitis events in the liraglutide group occurred between 6 and 24 months after treatment initiation. Finally, the authors report that a large proportion of the acute pancreatitis events on liraglutide had a history of risk factors. However, by the virtue of the randomization process, all known and unknown risk factors of acute pancreatitis should have been well balanced between the exposure groups. On this basis, the findings are not confounded but rather suggest that certain risk factors may have a contributory role on the development of acute pancreatitis in patients using liraglutide—a line of inquiry that should be investigated in future studies. Overall, these findings do raise concerns that liraglutide may increase the risk of acute pancreatitis but do not provide, on their own, conclusive evidence that liraglutide, other glucagon-like peptide 1 analogs, or the wider class of incretin-based drugs are associated or not with an increased risk of acute pancreatitis.

The two studies in this issue of the journal add to the several that have investigated the potential association between incretin-based drugs and adverse pancreatic events, including acute pancreatitis (6–15) and pancreatic cancer (9,12,21,22). Several of these had important methodological limitations, including the lack of an appropriate comparator, confounding by indication and other variables, time-lag bias, and short durations of follow-up; methodological recommendations for future observational studies examining these associations are summarized in Table 1. In addition to these limitations, all observational studies conducted to date were not adequately powered to detect modest increased risks of these outcomes. Indeed, as relatively new drugs, incretin-based drugs have not yet achieved their full market potential. Moreover,

Table 1—Methodological considerations for future observational studies assessing the association between incretin-based drugs and adverse pancreatic events

• Study population should be limited to patients with type 2 diabetes
• Study population should be limited to new users of antidiabetes drugs
• Incretin-based drugs should be compared with active comparators for which there is clinical equipoise (i.e., other second- or third-line therapies)
• For pancreatic cancer, exposure should be lagged for latency considerations and to minimize protopathic bias
• Analyses should control for diabetes-related variables, such as duration of diabetes, hemoglobin A_{1c}, and diabetes-related complications
• Appropriate study design and analytic approaches should be used to avoid time-related biases (18)
• Given the rarity of the outcomes, studies need large sample sizes and sufficient durations of follow-up

acute pancreatitis and pancreatic cancer are rare events, even in patients with type 2 diabetes. Thus, the rarity of both the exposure and the outcomes of interest poses an interesting methodological challenge. As such, there is a need for additional, well-designed studies that would be sufficiently large enough to rule out modest increased risks of acute pancreatitis and pancreatic cancer. One such effort is a series of ongoing studies being conducted by the Canadian Network for Observational Drug Effect Studies (CNODES), a distributed network with access to data on more than 40 million individuals across three countries (23). With one study protocol replicated across different jurisdictions covering nearly 2 million patients with type 2 diabetes, these CNODES studies will benefit from low heterogeneity and, when meta-analyzed, will have the necessary precision to detect modest, but clinically important, effect measures. Such distributed networks may be the way forward for the assessments of the safety of new pharmacotherapies such as incretin-based drugs.

Compared with other antidiabetes therapies, incretin-based drugs have been shown to decrease hemoglobin A_{1c} levels, lower the risk of hypoglycemia, and have favorable effects on body weight (24). As a result, they have become attractive treatment options for patients with type 2 diabetes. However, there remains a cloud of uncertainty regarding their safety, and additional, well-conducted studies using real-world data are urgently needed to determine whether these concerns are substantiated.

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