COMMENT ON THOMSEN ET AL.

# Incretin-Based Therapy and Risk of Acute Pancreatitis: A Nationwide Population-Based Case-Control Study. Diabetes Care 2015;38:1089–1098

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We read with great interest the article by Thomsen et al. (1), which is the latest study fueling the ongoing discussion on acute pancreatitis (AP) associated with incretin-based therapies. This controversy on drug safety started with conflicting animal and clinical data shortly after marketing approval of glucagon-like peptide 1 receptor agonists (GLP-1RA) and dipeptidyl peptidase-4 inhibitors (DPP-4I). Recently, regulatory authorities reviewed the available data and concluded no increased AP risk, yet they called for further studies (2). Thomsen et al. underlined this conclusion with results from the Danish Civil Registration System (CRS) database. In their case-control study, a history of incretin-based drug use was identified in 89 first-time hospitalization AP cases and 684 matched control subjects. After correction for confounders, incretin-based therapy did not increase AP risk, with an odds ratio (OR) of 0.95 (95% CI 0.75–1.21).

Although this is the largest observational study to address this issue so far, and the high-quality CRS database facilitates accurate conclusions, we are not convinced these results will provide enough clinical certainty to reassure health care providers. A recurring concern is the residual confounding that is inherent to the nature of database studies. Moreover, at closer inspection, only 30 and 68 AP cases ever used GLP-1RA and DPP-4I, respectively. We question whether these numbers are sufficient to adequately correct for confounding without hampering statistical power and thereby missing a potential risk. Also, when analyses were restricted to primary AP diagnoses, which enhances validity, a history of DPP-4I use was associated with increased AP risk (OR ~1.40), an observation only briefly touched upon by the authors.

Confounding and diagnostic uncertainty are less problematic in a randomized clinical trial (RCT). However, given the low incidence of AP, an enormous amount of subjects need to be studied for a long period of time. In the largest RCTs available, the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) and Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trials, use of DPP-4I was not associated with increased AP risk (3,4). When pooling all RCT data, nonsignificant ORs of 1.39 (95% CI 0.67–2.88) for GLP-1RA and 1.07 (0.72–1.58) for DPP-4I for AP development were found (4). Importantly, these conclusions also were based on a low number of cases, 38 and 57, respectively.

What if incretin-based therapies do increase AP risk, to what clinical risk are we exposing our patients? On the basis of meta-analysis data from RCTs, over 1,800 (GLP-1RA) and 10,200 (DPP-4I) patients with type 2 diabetes must be treated for 1 year to prompt one extra AP case (background AP incidence rate: 1.4 cases per 1,000 person-years) (4). Whether this (low) risk is outweighed by the potential benefits on cardiovascular outcome still needs to be determined.

Finding or dismissing a (patho)physiological basis underlying the potential AP risk in humans could guide the discussion and strengthen conclusions. Interestingly, treatment with incretin-based drugs increases serum lipase and amylase levels, although the cause and clinical relevance remain unclear (5).

We expect that the pooled results from the ongoing cardiovascular safety trials will be the only means to definitely settle the debate on the pancreatic safety of incretin-based therapies (expected ~2020). Until then, we believe that high-quality database studies, such as the current study, and well-performed human mechanistic studies are needed to reassure clinicians that their patients are not harmed.

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## References

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