GLP-1RAs: No Increased Risk of Acute Pancreatitis vs. Sulfonylureas

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The potential association between glucagon-like peptide-1 receptor agonists (GLP-1RAs) and acute pancreatitis has been a subject of clinical interest, particularly given the expanding use of these agents in type 2 diabetes and obesity management. A recent target trial emulation aimed to clarify whether initiating GLP-1RAs, compared with sulfonylureas, is associated with an increased risk of all-cause and cause-specific acute pancreatitis. The study found no evidence of increased risk for any form of acute pancreatitis with GLP-1RA use.1

KEY TAKEAWAYS

- The Pivot: This study directly compared GLP-1RA initiation to sulfonylurea initiation, addressing previous observational limitations.
- The Data: The hazard ratio (HR) for all-cause acute pancreatitis was 0.99 (95% CI, 0.90-1.09) for GLP-1RAs versus sulfonylureas.1
- The Action: Clinicians can be reassured that GLP-1RA initiation does not appear to increase the risk of acute pancreatitis compared to sulfonylureas.

Concerns regarding acute pancreatitis risk with GLP-1RAs have largely stemmed from early post-marketing surveillance and observational studies, which often struggled with confounding by indication and other biases inherent in real-world data. The current study sought to overcome these limitations by employing a target trial emulation design, a method intended to mimic a hypothetical randomised controlled trial using observational data.1

What the study did

Researchers emulated a target trial to assess the risk of acute pancreatitis associated with initiating GLP-1RAs compared with sulfonylureas. The study population included individuals with type 2 diabetes who initiated either a GLP-1RA or a sulfonylurea. The primary outcomes were all-cause acute pancreatitis and cause-specific acute pancreatitis, including biliary, alcoholic, and idiopathic forms. The study also examined temporal risk patterns.1

The analysis involved a large cohort of patients, with 1,008,797 individuals initiating GLP-1RAs and 2,017,594 initiating sulfonylureas. The median follow-up was 1.5 years for GLP-1RAs and 1.7 years for sulfonylureas. The study used propensity score matching to balance baseline characteristics between the two treatment groups, aiming to reduce confounding.1

Key Findings

The target trial emulation found no statistically significant increase in the risk of all-cause acute pancreatitis among patients initiating GLP-1RAs compared with those initiating sulfonylureas. The hazard ratio (HR) for all-cause acute

pancreatitis was 0.99 (95% CI, 0.90-1.09).1

When examining cause-specific acute pancreatitis, the results remained consistent. For biliary acute pancreatitis, the HR was 0.97 (95% CI, 0.85-1.11). For alcoholic acute pancreatitis, the HR was 1.03 (95% CI, 0.82-1.29). For idiopathic acute pancreatitis, the HR was 0.96 (95% CI, 0.81-1.13). None of these hazard ratios indicated a statistically significant increased risk.1

The study also investigated temporal risk patterns, finding no evidence of an increased risk of acute pancreatitis at any specific time point following GLP-1RA initiation compared to sulfonylureas. This suggests that the risk does not appear to be concentrated in the early phases of treatment.1

The study's strengths include its large sample size and the use of target trial emulation, which provides a more robust approach to causal inference in observational studies. However, limitations include the reliance on administrative data, which may not capture all relevant clinical details, and the potential for residual confounding despite rigorous matching. The study also focused on a comparison with sulfonylureas, and the risk profile against other antidiabetic agents or in populations without diabetes was not assessed.1

Clinical Implications and Context

The findings from this target trial emulation offer significant reassurance for healthcare professionals prescribing GLP-1RAs. Given the increasing adoption of these agents for type 2 diabetes and, more recently, for weight management, a clear understanding of their safety profile is paramount. The consistent lack of an increased risk across all-cause and cause-specific acute pancreatitis, and the absence of temporal risk patterns, strengthens the evidence base supporting the safety of GLP-1RAs in this regard.

This study's robust methodology, particularly the target trial emulation, addresses many of the methodological challenges that plagued earlier observational studies. By mimicking a randomized controlled trial, it provides a higher level of evidence than traditional observational designs, helping to disentangle true associations from confounding factors. The comparison with sulfonylureas is also clinically relevant, as these represent a common alternative second-line therapy for type 2 diabetes, providing a meaningful comparator group.

While the study provides strong evidence, clinicians should remain vigilant for signs and symptoms of acute pancreatitis in all patients, regardless of their antidiabetic medication. Patient education regarding potential symptoms, such as severe abdominal pain radiating to the back, nausea, and vomiting, remains crucial. Furthermore, individual patient risk factors for pancreatitis, such as a history of gallstones, hypertriglyceridemia, or excessive alcohol consumption, should always be considered during treatment selection and monitoring.

Future Research Directions

Despite the comprehensive nature of this study, several avenues for future research emerge. Expanding the comparison to other antidiabetic agents, such as DPP-4 inhibitors or SGLT2 inhibitors, could provide a more complete picture of GLP-1RA safety across the broader spectrum of diabetes treatments. Additionally, investigating the risk profile in specific patient subgroups, such as those with pre-existing pancreatic conditions or a strong family history of pancreatitis, would be valuable.

Further research could also explore the long-term risk of pancreatitis beyond the median 1.5-1.7 years of follow-up, particularly as GLP-1RAs are often used for extended periods. While administrative data are excellent for large-scale analyses, supplementing these with more detailed clinical data from electronic health records or prospective registries could help to capture subtle nuances in patient characteristics and outcomes that might influence pancreatitis risk.

CLINICAL IMPLICATIONS

This target trial emulation offers a reassuring perspective for clinicians prescribing GLP-1RAs. The consistent finding of no increased risk for all-cause or cause-specific acute pancreatitis, when compared to sulfonylureas, should help to alleviate some long-standing concerns. It reinforces the safety profile of this class of medicine, particularly as their use expands beyond type 2 diabetes into weight management.

The methodology employed, target trial emulation, represents a significant step forward in leveraging real-world data to answer complex clinical questions. It provides a more robust framework for causal inference than traditional observational studies, which often leave room for doubt regarding confounding. This precision is vital for informing prescribing decisions and patient counselling, especially given the high prevalence of diabetes and obesity.

For the pharmaceutical industry, these data further solidify the safety narrative for GLP-1RAs, potentially supporting broader uptake and reducing regulatory scrutiny on this specific adverse event. While no medicine is without risk, clearly delineated safety profiles, backed by rigorous comparative effectiveness research, are essential for maintaining clinician confidence and patient adherence. This study contributes to a growing body of evidence that supports the judicious use of GLP-1RAs in appropriate patient populations.

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REFERENCES

1. 1. Xie Y, Choi T, Al-Aly Z. GLP-1 receptor agonists and risk of all cause and cause specific acute pancreatitis: target trial emulation. BMJ Med. 2026. doi:10.1136/bmjmed-2025-002183

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