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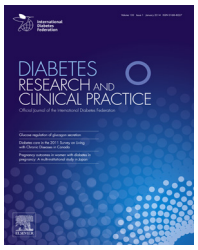

Incretin-based therapies are associated with acute pancreatitis: Meta-analysis of large randomized controlled trials

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ABSTRACT

Previous studies have offered weak and conflicting evidence regarding the impact of incretin-based oral antihyperglycemic agents on risk of acute pancreatitis. This meta-analysis of three recent mega-trials found an 82% increase in the odds of acute pancreatitis with the use of these agents compared to usual care (95% CI, 1.17–2.82).

1. Introduction

The Food and Drug Administration and European Medicines Agency have issued warnings but no firm conclusion regarding the pancreatic safety of incretin-based oral antihyperglycemic agents, pending further evidence [1]. A 2014 meta-analysis of 55 small randomized trials including 37 events in 33,227 patients with type 2 diabetes found no impact of incretins on acute pancreatitis (23/20,127 [0.11%] in intervention groups vs 14/13,100 [0.11%] in control groups; OR, 1.11; 95% CI, 0.57–2.17) [2]. This result was consistent across different types of incretin, types of comparator, and length of follow-up. While a case-control study in that review suggested an increased risk of admissions for acute pancreatitis (OR, 2.24; 95% CI, 1.36–3.68), another 4 did not replicate this association. Other studies in routine databases have also failed to detect an effect [3]. Unfortunately, neither the meta-analysis of many small trials nor the analysis of large routinely collected datasets reliably detects such small effects; the first is hindered by random error and the second by inadequate ascertainment of outcomes and covariates precluding adequate control for confounding and information biases.

Three recent large randomized trials of dipeptidyl peptidase 4 (DPP4) inhibitors were published after the search date of

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Table 1 – Characteristics of included trials. There was no evidence of prognostic imbalance at baseline in any of the trials; thus, intervention group characteristics reported here are nearly identical in the control groups. T2DM, type 2 diabetes mellitus; T1DM, type 1 diabetes mellitus; HbA_{1c}, glycated hemoglobin; eGFR, estimated glomerular filtration rate; ULN, upper limit of normal; ACS, acute coronary syndrome; BMI, body mass index; CVD, cardiovascular disease.

Study	Inclusion criteria	Exclusion criteria	Intervention	Control	Median follow-up, years	BMI in intervention group, kg/m^2	Mean % HbA_{1c} in intervention group	Diabetes duration in intervention group, years	Age in intervention group, years	% Males in intervention group	Pancreatitis definition and adjudication	Pancreatitis cases (treatment vs control)
EXAMINE [4]	>18 years T2DM (HbA_{1c} 6.5–11% or 7–11% if on insulin) on therapy with ACS within 15–90 days	T1DM, unstable cardiac disorders, dialysis within 14 days	Standard of care + alogliptin 25 mg daily (12.5 mg if eGFR <60 ml/min/1.73 m^2, 6.5 mg if eGFR <30 ml/min/1.73 m^2)	Placebo + standard-of-care	1.6	28.7 (median)	8.0	7.1 (median)	61.0 (median)	67.9	If pancreatitis is suspected, or serum amylase or lipase ≥2× ULN; investigators encouraged to obtain imaging and discontinue study drug; supporting evidence adjudicated centrally	12/2701 (0.44%) vs 8/2679 (0.30%)
SAVOR TIMI-53 [5]	>40 years T2DM (HbA_{1c} 6.5–12%) and either established CVD or >55 years (male) or >60 years (female) with multiple vascular risk factors	Incretin within 6 months, on chronic dialysis, have renal transplant, serum creatinine > 6 mg/dL	Standard of care + saxagliptin 5 mg daily (or 2.5 mg if eGFR ≤50 ml/min)	Placebo + standard-of-care	2.1	31.1 (mean)	8.0	10.3 (median)	65.1 (mean)	66.7	[a]Expert adjudicated all cases of pancreatitis. Definite cases must have 2 of typical abdominal pain, serum amylase or lipase >3× ULN, concordant abnormal imaging	23/7332 (0.31%) vs 12/7339 (0.16%)
TECOS [6]	>50 years T2DM with HbA_{1c} 6.5–8.0% on stable doses of ≤2 oral agents or insulin with or without metformin, and established CVD	Incretin or thiazolidinedione (not pioglitazone) within 3 months, ≥2 major hypoglycemic episodes within 12 months, or eGFR <30 ml/min/1.73 m^2	Standard of care + sitagliptin 100 mg daily (or 50 mg daily if eGFR ≥30 and <50 ml/min/1.73 m^2)	Placebo + standard-of-care	3.0	30.2 (mean)	7.2	11.6 (mean)	65.4 (mean)	70.9	Committee and specialty reviewer adjudication. Symptoms of abdominal pain or vomiting, and objective evidence of pancreatic inflammation (amylase or lipase >3× ULN or >2× ULN if have chronic pancreatitis, or evidence on imaging)	17/8280 (0.21%) vs 8/8212 (0.10%)
			Meta-analysis					Primary			1.82 [1.17–2.82]; I^2 = 0%; p = 0.008	52/18,313 (0.28%) vs 28/18,230 (0.15%)
								Secondary			1.57 [1.09–2.26]; I^2 = 12.1%; p = 0.016	75/38,440 (0.2%) vs 42/31,330 (0.13%)

[a] Only 'definite' pancreatitis events were considered for our analysis. Meta-analysis results are presented as 'Odds Ratio [95% Confidence Interval]; I^2, p-value'.