Tribal Diabetes ECHO

Case Discussion October 2021

Pancreatitis and SGLT2 inhibitors

“Not sure if patient should go back on Jardiance.”

- Potential concerns of resuming Jardiance(SGLT2i) related to bout of pancreatitis:
  - Risk of another bout of pancreatitis
  - Risk of Diabetic Ketoacidosis (DKA)

Is pancreatitis a side effect of Jardiance?

- A review of 15 clinical studies looked at the risk of having pancreatitis while taking Jardiance showed that people taking **Jardiance have less than a 0.1 percent risk of pancreatitis**.
  - If there is a history of pancreatitis in the past, there may be greater risk of having this condition while taking Jardiance.
  - *“A review of the available data for possible associations between SGLT2 inhibitors and acute pancreatitis is ongoing.”*

Adv Ther. **2017**; 34(7): 1707–1726. Safety and Tolerability of Empagliflozin in Patients with Type 2 Diabetes: Pooled Analysis of Phase I–III Clinical Trials

Jardiance: Side effects, dosage, uses, and more - Medical ...

Invokana / Jardiance / Farxiga: Increased Risk Of Pancreatitis, According To Health Canada Safety Review

August 30, 2018

- Health Canada's safety review of sodium-glucose cotransporter-2 (SGLT2) inhibitors -- *e.g.*, Invokana (canagliflozin), Farxiga (dapagliflozin), and Jardiance (empagliflozin) -- concluded in July **2018** with the finding that there *may be a link* between the use of SGLT2 inhibitors and *acute* pancreatitis.
  - However, there was limited evidence to suggest a link with chronic pancreatitis.
  - Health Canada is working with the manufacturers to update the Canadian product monographs, or drug labels, for SGLT2 inhibitors to include this increased risk of pancreatitis.

Summary of Safety Review by Health Canada

Pancreatic safety of sodium-glucose cotransporter 2 inhibitors in patients with type 2 diabetes mellitus: A *systematic review and meta-analysis*

February 2020

- Results: Of the ***35 trials*** involving 44 912 patients with T2DM included, 41 events of acute pancreatitis (19 trials; 32 932 patients), 72 events of overall pancreatitis (including acute pancreatitis, chronic pancreatitis, or nonspecific pancreatitis; 26 trials; 36 688 patients), and 40 events of pancreatic cancer (18 trials; 27 806 patients) were reported during a median follow-up of 52 weeks.
  - SGLT2 inhibitors were not associated with an increased risk of acute pancreatitis compared to controls (placebo or other active drugs; OR, 1.13; 95% CI, 0.60-2.13; moderate quality evidence).
  - A similar result was found for risk of overall pancreatitis (OR, 1.08; 95% CI, 0.67-1.75; moderate quality evidence) and
  - pancreatic cancer (OR, 1.34; 95% CI, 0.71-2.54; very low-quality evidence).

- Conclusions: Moderate quality evidence from RCTs shows ***no significantly increased risk of acute pancreatitis associated with SGLT2 inhibitors***, while
  - there is very low-quality evidence suggesting no significant association between SGLT2 inhibitors and pancreatic cancer among patients with T2DM.

Acute pancreatitis risk in type 2 diabetes patients treated with canagliflozin versus other antihyperglycemic agents: an observational claims database study.

Yuan Z., et al

Current Medical Research and Opinion. 36(7) (pp 1117-1124), 2020. Date of Publication: 02 Jul 2020.

- Objective: Observational evidence suggests that **patients with type 2 diabetes mellitus (T2DM) are at increased risk for acute pancreatitis(AP) versus those without T2DM**. A small number of AP events were reported in clinical trials of the sodium glucose co-transporter 2inhibitor canagliflozin, though no imbalances were observed between treatment groups.
  - This observational study evaluated risk of AP among new users of canagliflozin compared with new users of six classes of other antihyperglycemic agents (AHAs).
- Method(s): Three US claims databases were analyzed based on a prespecified protocol approved by the European Medicines Agency.
- Result(s): Across the three databases, there were between 12,023-80,986 new users of canagliflozin; the unadjusted incidence rates of AP(per 1000 person-years) were between **1.5-2.2 for canagliflozin and 1.1-6.6 for other AHAs**.
  - The risk of AP was generally similar for new users of canagliflozin compared with new users of glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, sulfonylureas, thiazolidinediones, insulin, and other AHAs, with no consistent between-treatment differences observed across databases. Intent-to-treat and sensitivity analysis findings were qualitatively consistent with on-treatment findings.
- Conclusion(s): In this large observational study, **incidence rates of AP in patients with T2DM treated with canagliflozin or other AHAs were generally similar, with no evidence suggesting that canagliflozin is associated with increased risk of AP compared with other AHAs**.

An investigation on the association between sodium glucose co-transporter 2 inhibitors use and acute pancreatitis: A VigiBase study.

Frent I., Bucsa C., Leucuta D., Farcas A., Mogosan C.

Pharmacoepidemiology and Drug Safety. 30(10) (pp 1428-1440), 2021. Date of Publication: October 2021.

- Purpose: To characterize acute pancreatitis (AP) related to sodium glucose co-transporter 2 inhibitors and to investigate this relationship through disproportionality analysis in an international pharmacovigilance database.
- Method(s): We analyzed all AP reports for canagliflozin, dapagliflozin and/or empagliflozin from the **WHOs Global adverse drug reactions database VigiBase** up to July 2019.
- Result(s): Of the 19 834 180 individual case safety reports in VigiBase, in 600 reports containing 618 AP group reactions, gliflozins were suspected/ interacting drugs.
  - Men were affected in 52.3% of the cases and 59.6% of the patients were in the 45-64 years age group. The reporters were in 417 cases healthcare professionals. Most of the reactions were reported for canagliflozin (59.7%), followed by empagliflozin (21%) and dapagliflozin (19.2%) and were serious (98.6%). Most of the reactions' outcomes (84% of the patients) were favorable. Ketoacidosis was frequently associated with the AP (21.3%). Significant PRR and IC were found for pancreatitis and pancreatitis acute for all three gliflozins, pancreatitis necrotizing for canagliflozin and Empagliflozin and pancreatitis relapsing for empagliflozin.
- Conclusion(s): Most of the AP cases were serious and with favorable outcome. ***We identified possible alternative*** causes for AP, like concomitant medication, hypertriglyceridemia, and cholelithiasis and a **frequent association with ketoacidosis**. We ***found a significant association between AP and the use of canagliflozin, dapagliflozin, and Empagliflozin that would need further investigation.***

Several case reports attributing SGLT2i meds as cause of acute pancreatitis

- https://www.bumc.bu.edu/im-residency/acute-pancreatitis-as-a-rare-side-effect-of-empagliflozin/
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7044483/

- ***Drug induced pancreatitis: A systematic review of case reports to determine potential drug associations***
  - Much of the case report evidence upon which drug-induced pancreatitis associations are based is *tenuous*.
  - A greater emphasis on *exclusion of all non-drug causes* of acute pancreatitis and on quality reporting would improve the evidence base.
  - It should be recognized that reviews of case reports, are valuable scoping tools but have limited strength to establish drug-induced pancreatitis associations.

Drug-induced Acute Pancreatitis: A Review

- The diagnosis of drug-induced acute pancreatitis first requires a diagnosis of acute pancreatitis.
- The next step in diagnosing drug-induced pancreatitis requires **ruling out more common etiologies** such as **gallstone pancreatitis** and **ethanol-induced acute pancreatitis**.
  - A thorough medical history and the patient's medications must be recorded. The history should focus on **previous symptoms** and any record of **gallstones**, **ethanol abuse**, **hypercalcemia, hypertriglyceridemia, and trauma**.
  - Serum amylase, lipase, triglyceride level, calcium level, and liver function tests should be ordered.
  - Abdominal and endoscopic ultrasounds should be performed to evaluate for gallstones and other obstructive possibilities such as tumors of the pancreas head.

The diagnosis of DIP is mostly a diagnosis of exclusion in the setting of convincing drug exposure.

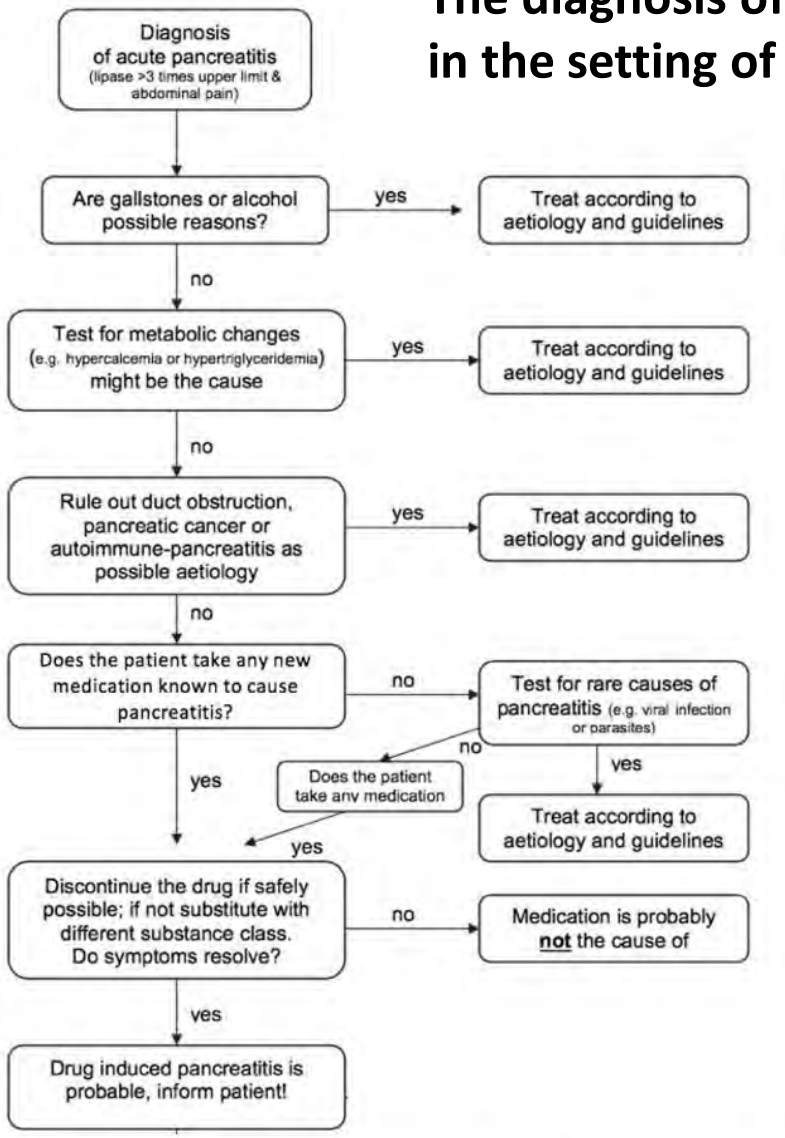


Figure 1: Diagnostic approach to identify possible cases of DIP, adapted from Nitsche et al. (6)

Medications implicated in Drug-induce Pancreatitis

ACE inhibitors	Cyproheptadine	Linagliptin	Liraglutide
Macrolides	Rifapentine	Acetaminophen	Cytosine
Mefenamic acid	Rivastigmine	ACTH	Danazol
6-MP	Ropinirole	Alendronate	Dapsone
Mesalamine	Saw palmetto	Saxagliptin	All-trans-retinoic acid
Alogliptin	DDP-4 inhibitors	Metformin	SSRIs
Alpha-methyldopa	Diazoxide	Methimazole	Sirolimus
Sitagliptin	Aminosalicylates	Diphenoxylate	Methyldopa
Sodium stibogluconate	Amiodarone	Dipyridamole	Divalproex sodium
Metronidazole	Somatropin	Amlodipine	Doxercalciferol
Mirtazapine	Statins	Ampicillin	Doxorubicin
Montelukast	Sulfamethoxazole	Antivirals	Ertapenem
Mycophenolate	Sulfasalazine	Aspirin	Estrogens
Exenatide	Nitrofurantoin	Sumatriptan	Atypical antipsychotics
Fibrates	NSAIDs	Tacrolimus	Azathioprine
Finasteride	Octreotide	Tamoxifen	Bupropion
Fluoroquinolones	Paclitaxel	Tetracyclines	Calcitriol
5-Fluorouracil	Pegaspargase	Thiazide diuretics	Cannabis
Furosemide	Penicillin	Thrombolytic agents	Capecitabine
Gabapentin	Pentamidine	TNF-alpha inhibitors	Carbamazepine
GLP-1 analogs	Pergolide	Topiramate	Ceftriaxone
Gold	Phenolphthalein	Valproic acid	Cimetidine
HAART agents	Pilocarpine	Venlafaxine	Cisplatin
Ifosfamide	Prazosin	Vincristine	Clomiphene
Indomethacin	Procainamide	Voriconazole	Codeine
Interferon/ribavirin	Propofol	Zolmitriptan	Colchicine
Interleukin-2	Propoxyphene	Corticosteroids	Irbesartan
PPIs	Co-trimoxazole	Isoniazid	Quinupristin/dalfopristin
COX-2 inhibitors	Isotretinoin	Ranitidine	Cyclophosphamide
Lamotrigine	Repaglinide	Cyclosporine	L-asparaginase
Rifampin			

6-MP, 6-mercaptopurine; ACE, angiotensin-converting enzyme; ACTH, adrenocorticotropic hormone; COX, cyclooxygenase; DDP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide-1; HAART, highly active antiretroviral therapy; NSAIDs, nonsteroidal antiinflammatory drugs; PPI, proton pump inhibitor; SSRIs, selective serotonin reuptake inhibitors; TNF, tumor necrosis factor.
(Table adapted with permission from Kaurich.[26])

Medications (commonly used in treatment of diabetes) implicated in Drug-induce Pancreatitis

- Some association exists between the occurrence of pancreatitis and biguanide agents such as **metformin**, as well as with **dipeptidyl peptidase 4 inhibitors**, including sitagliptin, vildagliptin, and saxagliptin.
- **Angiotensin-converting enzyme (ACE) inhibitors** – acute pancreatitis proposed mechanism is local angioedema of the pancreatic duct.
- **Statins** -the onset of acute pancreatitis induced by statins has been observed from *hours to years after treatment* - may be related to a direct toxic effect to the pancreas and the accumulation of a toxic metabolite or speculated to be associated with rhabdomyolysis, myalgia, and/or metabolism or drug interactions through cytochrome P-450 3A4 (CYP3A4).
  - Because pravastatin does not metabolize CYP3A4, it may have fewer case reports of drug-induced acute pancreatitis than other statins.

Drug-Induced Acute Pancreatitis: A Review

- Any drugs with the potential to cause pancreatitis should be discontinued or exchanged for a drug of a different class, if possible.
  - If the pancreatitis resolves after discontinuation of the drug, suspicion for drug-induced pancreatitis increases.
  - This connection proves difficult to establish, however, as the resolution of disease may be linked *coincidentally* with cessation of the inciting agent.
  - A *firm diagnosis* can be *reasonably established* with a **rechallenge** of the offending drug that **results in the recurrence of pancreatitis symptoms**.

Dapagliflozin-Induced Acute Pancreatitis: A Case Report and Review of Literature

- Case Presentation: A 51-year-old male with type 2 diabetes, dyslipidemia, and status-post cholecystectomy presented to the emergency room with a four-day history of periumbilical pain radiating to the back. He denied any history of recent alcohol intake or prior episodes of pancreatitis.
  - Physical examination: abdomen diffusely tender to palpation without guarding or rebound. Labs: WBC 9.3, creatinine 0.72, calcium 9.5, lipase 262 U/L, triglyceride 203, HbA1c 8.5%. CT scan of his abdomen and pelvis: consistent with acute pancreatitis with no biliary ductal dilatation.
  - Review of his medications revealed he was started on **dapagliflozin** five days prior to admission in addition to his longstanding regimen of insulin detemir, **sitagliptin**, **metformin**, and **rosuvastatin**. His symptoms resolved after discontinuation of sitagliptin and dapagliflozin.
  - A year later, due to increasing HbA1c levels, a decision was made to **rechallenge the patient with dapagliflozin**, after which **he developed another episode of acute pancreatitis**. His symptoms resolved upon cessation of dapagliflozin.
- Conclusion. This case highlights the ***possible association of SGLT-2 inhibitors and pancreatitis***.
  - Patients should be informed about the symptoms of acute pancreatitis and advised to discontinue SGLT-2 inhibitors in case such symptoms occur.

“Not sure if patient should go back on Jardiance.”

- Potential concerns of resuming Jardiance(SGLT2i):
  - Risk of another bout of pancreatitis - ??
    - Rx profile suggests history of significant hypertriglyceridemia
      - Fatty meal can precipitate if impaired triglyceride clearance
    - Other risks (gallstones, calcium, etc.)?
    - Rx profile – suggestive of PEI - ? Chronic vs severe acute pancreatitis
- Are there other potential concerns for this patient?
  - Risk of Diabetic Ketoacidosis (DKA)

https://www.drugs.com/pro/jardiance.html

Ketoacidosis

- Reports of ketoacidosis have been identified in postmarketing surveillance.
  - In some but not all cases, **factors predisposing to ketoacidosis** such as insulin dose reduction, acute febrile illness, reduced caloric intake, surgery, ***pancreatic disorders suggesting insulin deficiency*** (e.g., type 1 diabetes, ***history of pancreatitis*** or pancreatic surgery), and alcohol abuse were identified.
  - Before initiating Jardiance, consider factors in the patient history that may predispose to ketoacidosis including ***pancreatic insulin deficiency from any cause***, caloric restriction, and alcohol abuse.

PANCREATITIS AND SGLT2 INHIBITOR-ASSOCIATED KETOACIDOSIS

- Reports of ketoacidosis have been identified in patients receiving SGLT2i, including canagliflozin. In some, but not all cases, ***pancreatic disorders suggesting insulin deficiency*** (e.g., type 1 diabetes [T1DM], ***history of pancreatitis***, or pancreatic surgery) were identified as factors predisposing to ketoacidosis.
- Advise patients to inform their healthcare professional if there are or have been problems with the pancreas, including ***pancreatitis*** or surgery on the pancreas.
- Before initiating canagliflozin, consider factors in the patient history that may predispose to ketoacidosis, including pancreatic insulin deficiency from any cause. Monitor for ketoacidosis and temporarily discontinuing in clinical situations known to predispose to ketoacidosis.

Patients with diabetes secondary to pancreatitis or pancreatectomy were excluded from phase 3 and phase 4 INVOKANA clinical studies.

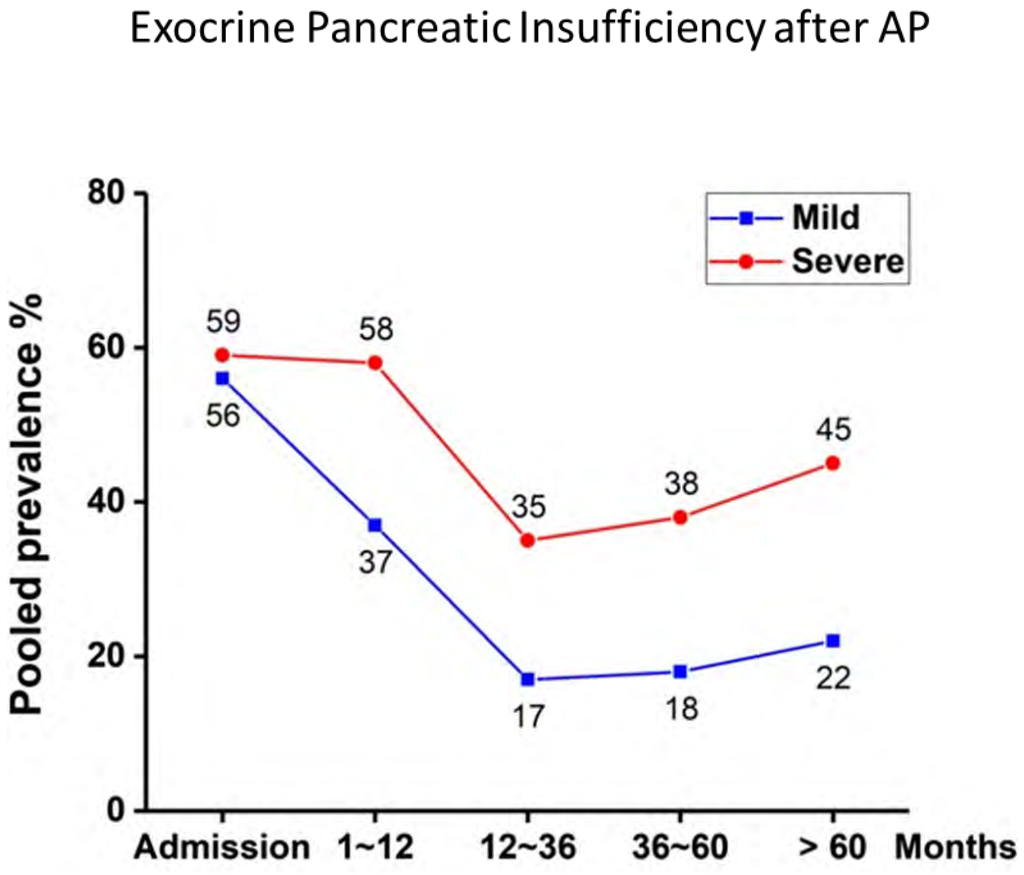
Type 3c (Pancreatogenic) diabetes

- Early in the disease - **mild hyperglycemia** - periods of glucose intolerance may *only be evident during stress, illness or high dose glucocorticoid* treatment.
- Later - progression to **brittle diabetes** characterized by **marked glycemic lability** and **frequent hypoglycemia**
  - due to **loss of islet β-cell secretion of insulin**
  - Also, loss of counterregulatory glucagon secretion from islet α-cells such that replacement doses of insulin unpredictably predispose to hypoglycemia.

Pathogenesis of T3cDM is ultimately due to decreased insulin secretion caused by both a reduction in the number of islets and their functional capacity from extensive fibrosis and sclerosis (or resection)replacing the pancreatic tissue by scar tissue leading to loss of vascularity

Acute Pancreatitis – residual effects

- Clinical resolution of acute pancreatitis as judged by standard clinical measures may not detect some **residual damage to beta-cell mass & exocrine function**
- Rather, this may manifest later in life with the coexistence of other diabetes risk factors.
  - The average age of diabetes diagnosis was younger by 4 years among those with a history of acute pancreatitis (**reduced beta cell reserve)**
  - Also nutritional status compromise from EPI
- This may suggest a **lower capacity** to overcome the individual's underlying degree of insulin resistance and that a **shorter duration is sufficient to induce beta-cell failure and hyperglycemia**
- Need to think of, do assessment & monitoring



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GENERAL MECHANISMS OF DRUG-INDUCED ACUTE PANCREATITIS

- Drug-induced acute pancreatitis mechanisms are currently based on theories extracted from case reports, case-control studies, animal studies, and other experimental data.
  - Potential mechanisms for drug-induced acute pancreatitis include pancreatic duct constriction, cytotoxic and metabolic effects, accumulation of a toxic metabolite or intermediary, and hypersensitivity reactions.
  - Negative effects of drugs, such as hypertriglyceridemia and chronic hypercalcemia, are also mechanisms for drug-induced acute pancreatitis, as these effects are risk factors for acute pancreatitis.
  - Other possible mechanisms of action are localized angioedema effect in the pancreas and arteriolar thrombosis.