STRENGTHENING INFERENTIAL STUDIES IN THE U.S. FDA SENTINEL INITIATIVE

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BACKGROUND

The U.S. FDA's Sentinel System forms a critical component of the national active post-marketing surveillance of medical products.[1] Historically, Sentinel's reliance on insurance claims data has led to insufficiency in addressing some emerging safety questions requiring more granular clinical information.[2] The FDA Sentinel Real-World Evidence Data Enterprise (RWE-DE), an infrastructure linking large volumes of electronic health records (EHRs) with claims data, was created to address emerging safety questions for which claims data may be insufficient.[3,4]

OBJECTIVES

We aimed to demonstrate the applicability of the RWE-DE in a use case of the risk of acute pancreatitis (AP) following initiation of sodium-glucose cotransporter-2 inhibitors (SGLT-2i) compared to dipeptidyl peptidase-4 inhibitors (DPP-4i) in patients with type 2 diabetes mellitus (T2DM). Specifically, we leveraged a computable phenotyping algorithm using structured and unstructured data from the EHRs to identify AP events, which are not accurately captured using administrative claims alone.

METHODS

- Target trial emulation that compared AP among new users of SGLT-2i versus DPP-4i with T2DM using the PRINCIPLED process framework developed by Sentinel.[5]
- Data source: HealthVerity (HV) [2018-2020] and TriNetX (TNX) [2013-2024] of the RWE-DE commercial network.
- Cohort entry date (CED): Day of first pharmacy dispensing of either drug.
- Eligibility criteria: Presence of T2DM, continuous medical and prescription coverage (enrollment gap: up to 30 days) and ≥1 EHR encounter, no prior use of study medications and glucagon-like peptide-1 receptor agonists, no history of end stage renal disease, Human Immunodeficiency Virus, or AP.
- AP (primary outcome) identified using a previously validated computable phenotyping algorithm[6] using EHRs, with a positive predicted value >0.9, defined probabilistically using diagnosis codes, laboratory findings and natural language processing (NLP)-derived features.
- Patient characteristics assessed at baseline: claims-based (demographics, medications, comorbidities, healthcare utilization and general health indices) and EHR-based (laboratory findings, vitals and lifestyle factors)
- Propensity score (PS) fine stratification weighting to adjust for 130 claims-based and six EHR-based covariates.[7]
- Missingness patterns among partially observed EHR-derived covariates identified using the smdi R package[8].
- Multiple imputation methods for addressing missingness after evaluating the assumption of data missingness at random.[9]
- Adjusted hazard ratios (HR) and 95% confidence intervals (CIs) for both intent-to-treat (ITT) and per-protocol (PP) causal contrasts calculated using Cox proportional hazards regression models. Combined results using inverse variance pooling using Rubin's rule. [10]
- Subgroup analyses: By age (<65 vs. ≥65), sex (male vs. female), and history of risk factors for AP (gallstones, tobacco use, alcohol abuse).
- Sensitivity analyses to reduce EHR-based missingness: 1) Increased baseline window to 12 months before CED, 2) Restricted the analysis to subjects with ≥3 EHR encounters during the 6-month baseline period.

RESULTS

Table 1 summarizes the key patient characteristics of the 72,429 patients (SGLT2i=30,174; DPP-4i=42,255) and 24,690 patients (SGLT2i=11,943; DPP-4i=12,747) from HV and TNX respectively with T2DM. *Table 2* shows a comparison of incidence rates (IRs) of AP in SGLT-2i and DPP-4i initiators in HV and TNX. *Figure 1* compares the unadjusted cumulative incidence of acute pancreatitis in new users of SGLT-2i versus DPP-4i with T2DM, including both ITT and PP analyses in both data sources. *Figure 2* summarizes the treatment effect estimates with 95% confidence intervals for all analyses.

Table 1. Select patient characteristics among patients with type 2 diabetes mellitus initiating SGLT-2 inhibitors or DPP-4 inhibitors.

	HealthVerity (January 2018 – December 2020)		TriNetX (January 2013 – February 2024)	
	SGLT-2i initiators	DPP-4i initiators	SGLT-2i initiators	DPP-4i initiators
Patient Characteristics	N(%)/mean (SD)	N(%)/mean (SD)	N(%)/mean (SD)	N(%)/mean (SD)
Unique Patients	30174 (100)	42255 (100)	11943 (100)	12747 (100)
Age (Years), mean (SD)	56.9 (11.1)	59.6 (12.9)	55.4 (11.4)	55.6 (11.5)
Sex				
Female	14634 (48.5)	23106 (54.7)	5743 (48.1)	6521 (51.2)
Claims-Based Frailty Index (CFI)	0.1 (0)	0.2 (0)	0.2 (0)	0.2 (0)
Combined comorbidity Index (CCI)	1.2 (1.8)	1.4 (2)	1.5 (2.1)	1.2 (2)
Prior Metformin users	22764 (75.4)	29922 (70.8)	7894 (66.1)	7792 (61.1)
Prior Sulfonylureas users	9770 (32.4)	15940 (37.7)	2885 (24.2)	3562 (27.9)
Prior Insulin users	7168 (23.8)	7271 (17.2)	2607 (21.8)	1898 (14.9)
ACE inhibitors/ARBs	20899 (69.3)	29163 (69)	7716 (64.6)	7484 (58.7)
Beta Blockers	10570 (35)	14594 (34.5)	4305 (36)	3702 (29)
Hypertension	22724 (75.3)	31973 (75.7)	9309 (77.9)	9606 (75.4)
Hyperlipidemia	21737 (72)	29063 (68.8)	8533 (71.4)	8749 (68.6)
Myocardial Infarction (MI)	510 (1.7)	470 (1.1)	442 (3.7)	155 (1.2)
Heart Failure (HF)	1813 (6)	2498 (5.9)	1589 (13.3)	725 (5.7)
Stable angina	1295 (4.3)	1543 (3.7)	572 (4.8)	291 (2.3)
Mean number of ambulatory encounters	8.9 (9.2)	8.5 (9.8)	8.9 (9.5)	8.3 (8.7)
Mean number of filled prescriptions	26 (21.2)	26.5 (22.1)	23.8 (20.3)	22.5 (20.9)
Count of antidiabetic medications	1.4 (0.8)	1.3 (0.8)	1.2 (0.8)	1.1 (0.8)
Hemoglobin A1c recorded in percent	8874 (29.4)	11518 (27.3)	5802 (48.6)	6560 (51.5)
HbA1c, mean (SD)	8.7 (1.9)	8.6 (1.9)	8.6 (2)	8.5 (1.9)
Serum Creatinine recorded in mg/dL	7298 (24.2)	10020 (23.7)	6364 (53.3)	7377 (57.9)
serum creatinine, mean (SD)	0.9 (0.5)	0.9 (0.5)	0.9 (0.3)	0.9 (0.4)
Body Mass Index (BMI) recorded in kg/m2	18326 (60.7)	26239 (62.1)	5950 (49.8)	6055 (47.5)
BMI, mean (SD)	32.4 (5.5)	31.6 (5.7)	34.8 (8)	34.5 (7.9)
Diastolic Blood Pressure (DBP), recorded in mmHg	24896 (82.5)	34932 (82.7)	7884 (66)	7830 (61.4)
DBP, mean (SD)	79 (10.2)	78.3 (10.3)	79.8 (12.2)	79.5 (11.6)
Systolic Blood Pressure (SBP), recorded in mmHg	24896 (82.5)	34933 (82.7)	7834 (65.6)	7752 (60.8)
SBP, mean (SD)	131.3 (16.5)	131.3 (16.8)	134.6 (19.6)	134.2 (19)
Tobacco Use, recorded as yes	4384 (14.5)	5663 (13.4)	1535 (12.9)	1608 (12.6)
Total Number of Encounters	3.4 (2.8)	3.5 (2.9)	3.9 (4.7)	3.9 (4.8)

Figure 1. Cumulative incidence of acute pancreatitis among patients with type 2 diabetes mellitus initiating SGLT-2 or DPP-4i inhibitors

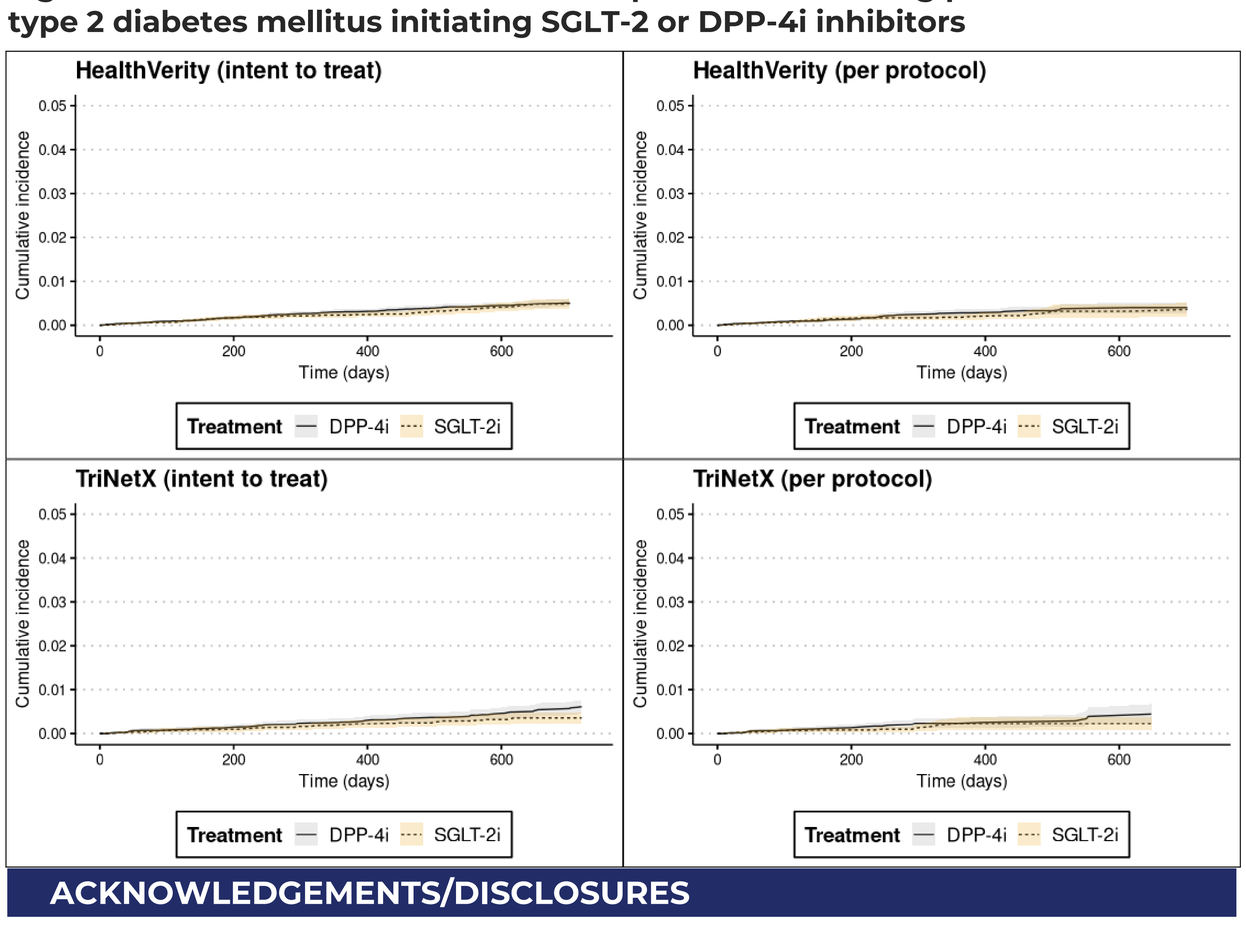
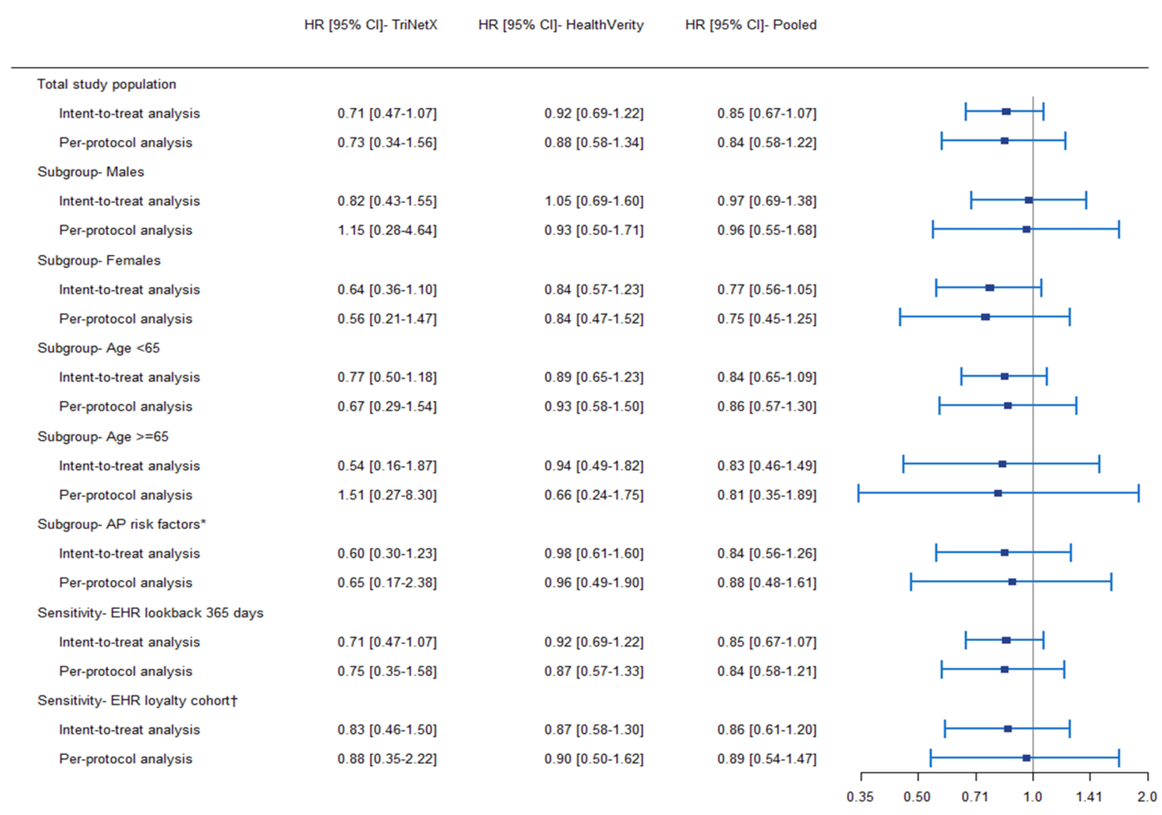


Table 2. Incidence rates of acute pancreatitis among patients with type 2 diabetes mellitus initiating SGLT-2i compared to DPP-4i.

Data source	Treatment group	Measure	Intent to treat follow-up (as-started)	Per protocol follow-up (on-treatment)
HealthVerity (Jan 2018-Dec 2020)	SGLT-2i initiators (n=30,174)	Number of events/person years	88/33,889	40/16,374
		Incidence rate/1,000 person years	2.6 (2.1-3.2)	2.4 (1.7-3.3)
	DPP-4i initiators (n=42,255)	Number of events/person years	148/51,561	67/24,608
		Incidence rate/1,000 person years	2.9 (2.4-3.4)	2.7 (2.1-3.5)
TriNetX (Jan 2013-Feb 2024)	SGLT-2i initiators (n=11,943)	Number of events/person years	44/22,756	15/7,891
		Incidence rate/1,000 person years	1.9 (1.4-2.6)	1.9 (1.1-3.1)
	DPP-4i initiators (n=12,747)	Number of events/person years	94/36,783	26/10,499
		Incidence rate/1,000 person years	2.6 (2.1-3.1)	2.5 (1.6-3.6)

Figure 2. Relative risk of acute pancreatitis among patients with type 2 diabetes mellitus initiating SGLT-2 inhibitors compared to DPP-4 inhibitors.



CONCLUSION

This study within Sentinel's RWE-DE network serves as a proof-of-concept for future protocol-based assessments highlighting the value of diverse data types including claims and EHR data from numerous data sources for efficient capture of health-related information. Analytic pipelines and packages developed by the FDA Sentinel System provide key building blocks to achieve scalable and timely execution of complex analyses using claims-EHR linked data assets.

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Dr. Weberpals is now an employee of AstraZeneca and owns stocks in AstraZeneca.
Other authors have no conflicts of interest to disclose.

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