Strengthening Inferential Studies in the U.S. FDA Sentinel Initiative: A Methodological Demonstration Project

Final Results

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1. Overview

Analysis Description:
Through this demonstration project, we aimed to demonstrate the applicability of the FDA Sentinel's Real World Evidence Data Enterprise (RWE-DE) in a use case of the risk of acute pancreatitis following initiation of SGLT2 inhibitors compared to dipeptidyl peptidase-4 inhibitors (DPP-4i) in patients with type 2 diabetes mellitus (T2DM).

Sentinel Routine Querying Module:
Type 2 Cohort Identification and Descriptive Analysis (CIDA) within Query Request Package, with ad hoc programming.

Data Source:
The RWE-DE commercial network comprising two Data Partners, HealthVerity and TriNetX. HealthVerity included ambulatory care electronic healthcare records (EHRs) from three sources linked to closed medical claims from more than 150 payers and closed pharmacy claims from a large pharmacy benefit manager (PBM) from January 2018 to December 2020. TriNetX included inpatient and ambulatory care EHRs from 20 unique health care organizations (HCOS) linked to closed claims data from more than 150 payers for the period of January 2013 to February 2024.[1]

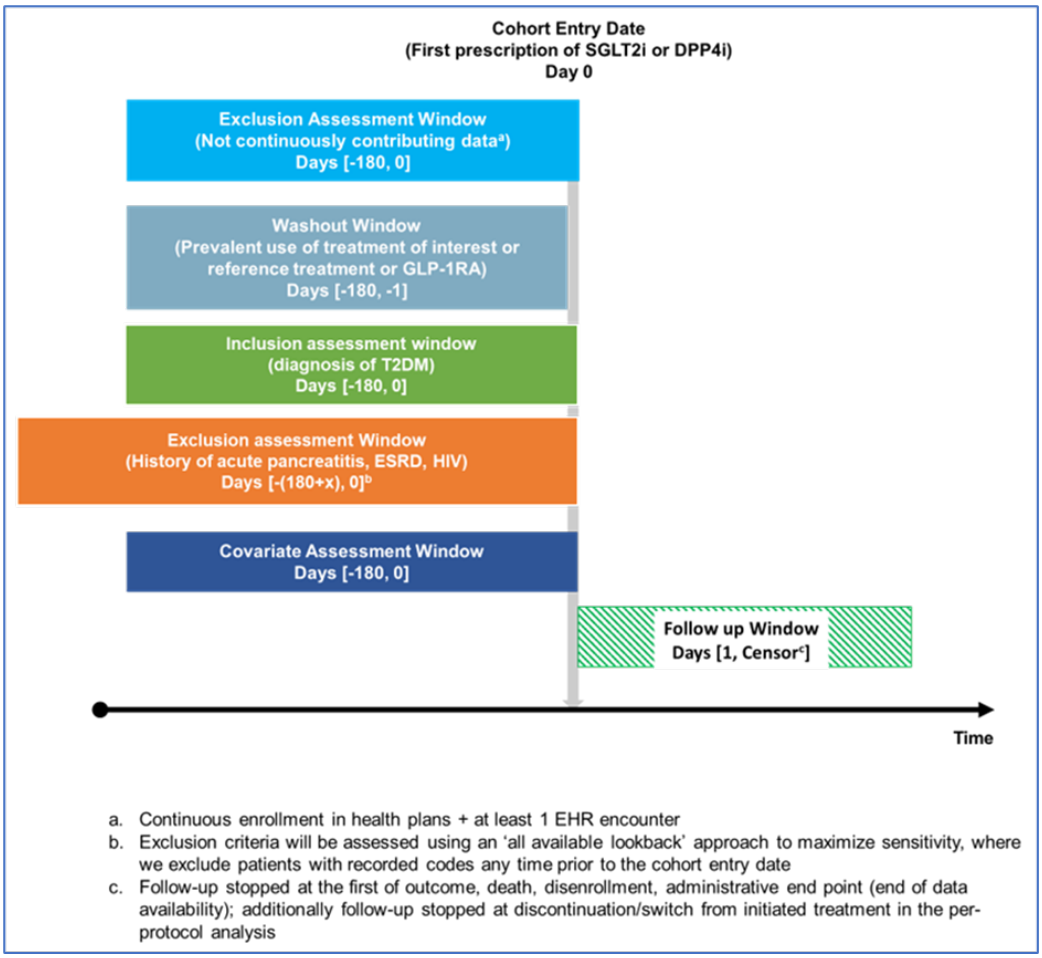

Figure 1. Study Design and Cohort Eligibility Criteria.

Figure 1 provides a visual summary of the study design. Initiation of the medications of interest (SGLT2i or DPP-4i) was defined as cohort entry date (day 0). We required six months of medical and prescription coverage prior to cohort entry with an allowable enrollment gap of up to 30 days as well as at least one EHR encounter operationalized by any entry in the lab or vital signs table of the Sentinel Common Data Model (SCDM). To restrict the cohort to new users, we excluded patients with evidence of SGLT2i or DPP-4i use 180 days prior to and including cohort entry date. We also excluded prior use of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) 180 days prior to and including cohort entry date as they shared similar mechanism with DPP-4is and given the uncertainty regarding the risk of pancreatitis after their use with some studies suggesting increased risk.[2,3] We restricted the cohort to patients with T2DM, and no evidence of T1DM. We also excluded patients with a history of pancreatitis, end stage renal disease (ESRD), or human immunodeficiency virus (HIV) as these patients had elevated risk of future acute pancreatitis event which may not be attributable to the treatment.[4] Patient characteristics were assessed during a window of 180 days prior to and including cohort entry date which were defined using multiple code types (please refer to the code list in the protocol appendix).[5] Follow-up started at one day (day 1) following the cohort entry date and stopped at the first occurrence of outcome (i.e., acute pancreatitis), death or end of data availability; additionally, follow-up stopped at discontinuing or switching from initiated treatment in the per protocol analysis.

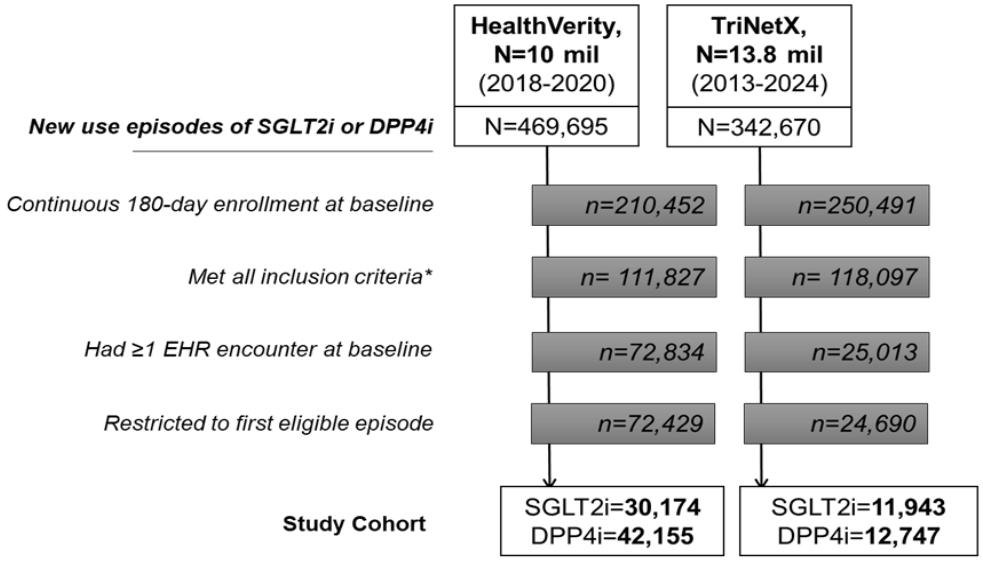

Figure 2. Cohort Attrition Flowchart.

Figure 2 provides a summary of patient-level cohort attrition for SGLT2i and DPP-4i initiators with type 2 DM for HealthVerity and TriNetX. There were a total of ten million and 13.8 million unique patients enrolled at any point throughout the query period of HealthVerity (2018-2020) and TriNetX (2013-2024) respectively. From these, a total of 469,695 and 342,670 new users of SGLT2i or DPP-4i were identified from HealthVerity and TriNetX respectively. After applying the eligibility of continuous 180 day enrollment at baseline, at least one EHR encounter at baseline, inclusion criteria (no prior use of SGLT2i, DPP-4i or GLP-1 RA; no history of pancreatitis, ESRD, HIV or Type 1 DM; diagnosis of Type 2 DM) and restricting to the first eligible episode, the final cohorts had 72,429 patients in HealthVerity (30,174 SGLT2i initiators;

42,155 DPP-4i initiators) and 24,690 patients in TriNetX (11,943 SGLT2i initiators; 12,747 DPP-4i initiators).

Exposures of Interest:
New use of SGLT2i or DPP-4i was defined as no prior use of either study drugs in the baseline period. Exposures of interest were defined using National Drug Codes (NDCs). Please refer to the code list from the protocol appendix for a detailed list of NDCs used to define the exposures of interest in this analysis.[5]

Baseline Characteristics:
We measured demographic characteristics such as age, sex, race, region, and year of cohort entry for all individuals who entered the study cohort on the day of cohort entry. Additionally, we measured several claims and EHR-based health characteristics as listed below.

Claims-based health characteristics included- claims-based frailty index; combined comorbidity score; prior and current use of metformin, sulfonylureas, insulin, alpha glucosidase inhibitors, thiazolidinediones, amylin analogs and meglitinides; anticoagulants; antiarrhythmics; angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs); beta blockers; calcium channel blockers; thiazides; diuretics; digoxin; non-steroidal anti-inflammatory drugs (NSAIDs) without aspirin; aspirin; opioids; statin; other lipid lowering drugs; anticonvulsants; antidepressants; antiosteoporosis medications; anxiolytics/hypnotics; antipsychotics; antiparkinsonian medications; benzodiazepine; dementia medications; proton pump inhibitors; sigmoidoscopy/colonoscopy; flu vaccination; mammography; pap smear; pneumococcal vaccine; prostate specific antigen (PSA)/prostate exam; bone mineral density test; blood chemistry test; hypertension; hyperlipidemia; myocardial infarction; obesity; alcohol abuse/dependence; stable angina; unstable angina; coronary revascularization; coronary atherosclerosis; other chronic ischemic heart disease (IHD); history of coronary artery bypass graft (CABG)/ percutaneous transluminal angioplasty (PCTA); any stroke; transient ischemic attack (TIA); late effects of cerebrovascular disease; peripheral vascular disease; heart failure; atrial fibrillation; other cardiac dysrhythmia; cardiomyopathy; hypertensive nephropathy; acute kidney injury; chronic kidney disease (stages 1 through 5); anemia; miscellaneous renal disease; chronic obstructive pulmonary disease; obstructive sleep apnea; asthma; osteoporosis; osteoarthrosis; syncope; falls; non-alcoholic steatohepatitis (NASH)/ non-alcoholic fatty liver disease (NAFLD); Alzheimer's disease; Parkinson's disease; psychosis; delirium; depression; anxiety; vertebral and non-vertebral fractures; diabetic nephropathy; diabetes with peripheral circulatory disorders; diabetic foot; diabetic neuropathy; diabetic retinopathy; type 2 diabetes mellitus without mention of complications; lower limb amputation; hypoglycemia; cancer; valve disorders; hyperkalemia; hypotension; deep vein thrombosis/pulmonary embolism; edema; history of autoimmune diseases; gallstones; fecal occult blood test; pneumonia; other dementia types; type 2 diabetes mellitus with unspecified complications; urinary tract or fungal infection history; hyperosmolar hyperglycemic nonketotic syndrome; hyperglycemia; hypertriglyceridemia; pulmonary hypertension; tobacco use. Health service utilization metrics included mean number of-ambulatory encounters; emergency room encounters; inpatient encounters; non-acute institutional encounters; other ambulatory encounters; filled prescriptions; generics dispensed; antidiabetic medications.

EHR-based patient characteristics included- lab characteristics (HbA1c, creatinine, triglycerides, microalbuminuria tests); vitals and lifestyle factors (body mass index (BMI), blood pressure tobacco use); mean number of EHR encounters.

Please refer to the protocol appendix for a detailed list of ICD-9, ICD-10, NDCs, LOINCs, SOC-defined lab codes, and HCPCS codes used to define baseline characteristics in this analysis.[5]

Outcome of Interest:
The primary outcome of interest was acute pancreatitis (AP) which was defined using a computable phenotyping algorithm. Briefly, among the cases initially identified using a diagnosis code, we identified additional features including laboratory test results as well as NLP concepts extracted from clinical notes in a time window of 7 days around the diagnosis date to calculate a probability score based on a previously developed and validated algorithm (Bahn et al. In Review). Additional details on the phenotyping algorithm including structured diagnosis codes, laboratory test results and NLP features used for defining AP can be found in the attached AP model application guide (Appendix).

Follow-up:
We determined follow-up time based on the length of exposure episodes and censored upon prespecified criteria met. Follow-up began on the day after exposure initiation and continued until the first occurrence of any of the following: 1) outcome occurrence (acute pancreatitis); 2) health plan disenrollment; 3) recorded death; 4) end of available data; 5) discontinuation/switching from initiated treatment (only for per-protocol analysis). Only the first qualifying exposure episode that occurred during the study period was included per patient.

Analysis Plan:
We used propensity score (PS) based fine-stratification weighting method with 50 strata for confounding adjustment by measured factors.[6] PS were estimated as the probability of initiating SGLT2i versus DPP-4i given the baseline patient characteristics using multivariable logistic regression models. Fifty strata were created based on the distribution of PS in SGLT2i-treated patients, and DPP-4i initiators were assigned into these strata based on their PS resulting in 50 unequally sized strata. In the weighting step, DPP-4i initiators in each stratum were weighted proportional to the number of SGLT2i patients to account for stratum membership and achieve balance. As diagnostics for PS models, we evaluated distributional overlap, weight distribution, and covariate balance using standardized differences post-weighting. In the weighted population, we estimated the hazard ratio for SGLT2i versus DPP-4 inhibitor on acute pancreatitis using a Cox proportional hazards model. Cumulative incidence was calculated using cumulative incidence functions and reported stratified by treatment groups.[7]

In addition to claims-based variables, we used numerous EHR based variables for confounding adjustment. Missingness in these EHR based variables is common and expected. We used a recently developed R package, smdi, for principled missing data investigations on partially observed confounders and implemented functions to visualize, describe, and infer potential missingness patterns and mechanisms based on observed data.[8] After verifying assumptions based on this diagnostic evaluation, we proceeded to use multiple imputation methods to analytically address missingness in all EHR based confounding variables**.** ***Figure 3*** provides an overview of the analytic workflow. In summary, we created 20 imputed datasets where missing confounders were imputed based on random forest algorithms. In each of the imputed dataset, we fit the PS models and conduct fine stratification to calculate adjusted treatment effect estimates using the *MatchThem* package.[9] The final results were reported after pooling results using Rubin's rule[10] to account for variance both in the within and across the imputed datasets.

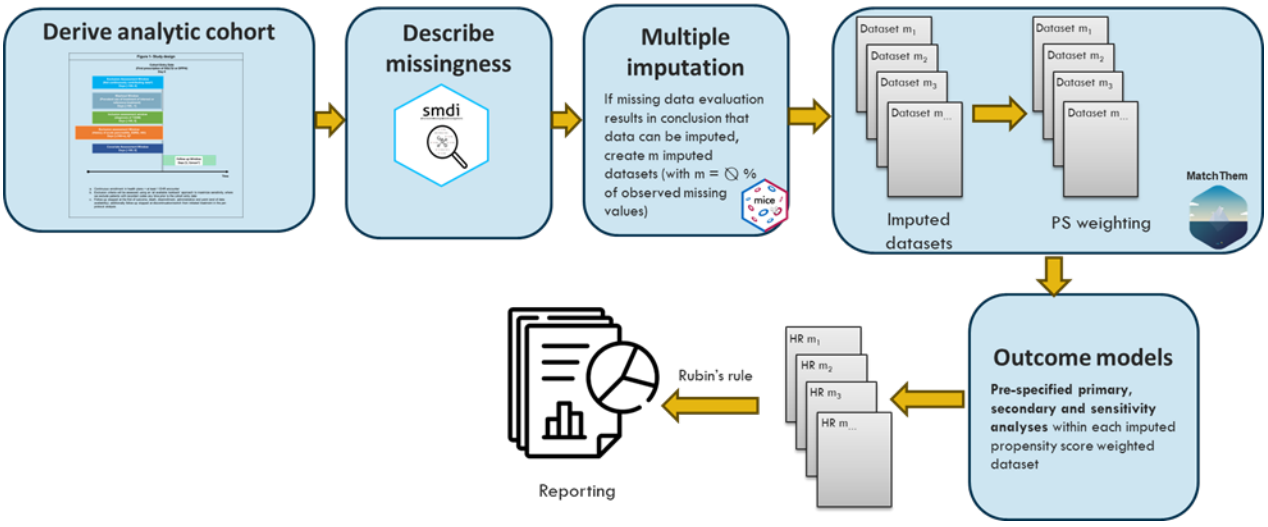

Figure 3. Analytic Workflow.

Table 1. Primary, Secondary, and Subgroup Analysis Specification.

Hypothesis:	SGLT2 inhibitors increases the risk of acute pancreatitis compared to DPP-4 inhibitors
Exposure Contrast:	SGLT2 inhibitor vs. DPP-4 inhibitor
Outcome:	Acute pancreatitis
Analytic Software:	R
Model(s): ***(provide details or code)***	R packages: smdi, mice, MatchThem
Confounding Adjustment Method	***Propensity scores fine stratification***
Missing Data Methods	***Multiple imputations with random forests***
Subgroup Analyses	***List all subgroups***
	1. Sex (Male/Female) 2. Age (<65, >=65) 3. History of risk factors for acute pancreatitis

Table 2. Sensitivity Analyses: Rationale, Strength, and Limitations.

	What is being varied? How?	**Why? (What do you expect to learn?)**	**Strengths of the sensitivity analysis compared to the primary**	**Limitations of the sensitivity analysis compared to the primary**
Baseline window	Increase baseline window to 12 months for EHR measurements	Greater capture of some of the EHR recorded confounding variables	Less degree of missingness in important clinical variables	EHR information recorded in distant past (>180 days before) may have changed and not relevant at the time of treatment initiation
Restricted to high EHR continuity ("EHR loyalty" cohort)	Patients with ≥ 3 EHR encounters in the baseline are included in the analysis [11]	Greater capture of confounders, less potential for missingness in outcome events	Limiting missingness in important clinical variables	Compromised sample size
Control outcome	Use ischemic stroke as a negative control outcome[12]	Net bias analysis	Enables the detection of bias in the primary analysis, assuming shared confounding structure	N/A

2. Results

Table 3. Claims-based patient characteristics of SGLT2i and DPP4i initiators with Type 2 DM, HealthVerity (2018-2020) and TriNetX (2013-2024)

	HealthVerity (January 2018 – December 2020)				TriNetX (January 2013 – February 2024)			
	SGLT2i Initiators		DPP-4i Initiators		SGLT2i Initiators		DPP-4i Initiators	
Patient Characteristics	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**
Unique Patients	30,174	N/A	42,255	N/A	11,943	N/A	12,747	N/A
Demographic Characteristics								
Age (Years)	56.9	11.1	59.6	12.9	55.4	11.4	55.6	11.5
Age Category								
18-24 years	153	0.5	195	0.5	84	0.7	102	0.8
25-40 years	2,349	7.8	2,960	7	1,264	10.6	1,323	10.4
41-64 years	21,839	72.4	26,836	63.5	8,624	72.2	9,138	71.7
≥ 65 years	5,833	19.3	12,264	29	1,971	16.5	2,184	17.1
Sex								
Female	14,634	48.5	23,106	54.7	5,743	48.1	6,521	51.2
Male	15,540	51.5	19,149	45.3	6,200	51.9	6,226	48.8
Race								
American Indian or Alaska Native	0	0	0	0	50	0.4	43	0.3

	HealthVerity (January 2018 – December 2020)				TriNetX (January 2013 – February 2024)			
	SGLT2i Initiators		DPP-4i Initiators		SGLT2i Initiators		DPP-4i Initiators	
Patient Characteristics	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**
Asian	0	0	0	0	667	5.6	736	5.8
Black or African American	0	0	0	0	3,049	25.5	3,060	24
Multi-racial	0	0	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	112	0.9	211	1.7
Unknown	30,174	100	42,255	100	1,082	9.1	1,202	9.4
White	0	0	0	0	6,983	58.5	7,495	58.8
Hispanic Origin								
Yes	0	0	0	0	789	6.6	701	5.5
No	0	0	0	0	7,247	60.7	8,374	65.7
Unknown	30,174	100	42,255	100	3,907	32.7	3,672	28.8
Region								
Northeast	4,309	14.3	7,495	17.7	0	0	0	0
South	9,473	31.4	13,138	31.1	0	0	0	0
Midwest	7,204	23.9	8,900	21.1	0	0	0	0
West	9,185	30.4	12,714	30.1	0	0	0	0
Invalid	0	0	0	0	0	0	0	0
Missing	3	0	8	0	11,943	100	12,747	100

	HealthVerity (January 2018 – December 2020)				TriNetX (January 2013 – February 2024)			
	SGLT2i Initiators		DPP-4i Initiators		SGLT2i Initiators		DPP-4i Initiators	
Patient Characteristics	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**
Year of Cohort Entry								
2013	N/A	N/A	N/A	N/A	12	0.1	386	3
2014	N/A	N/A	N/A	N/A	137	1.1	1,183	9.3
2015	N/A	N/A	N/A	N/A	352	2.9	1,230	9.6
2016	N/A	N/A	N/A	N/A	426	3.6	1,322	10.4
2017	N/A	N/A	N/A	N/A	546	4.6	1,519	11.9
2018	6,701	22.2	12,571	29.8	629	5.3	1,422	11.2
2019	15,470	51.3	21,005	49.7	927	7.8	1,388	10.9
2020	8,003	26.5	8,679	20.5	1,434	12	1,479	11.6
2021	N/A	N/A	N/A	N/A	2,232	18.7	1,246	9.8
2022	N/A	N/A	N/A	N/A	2,872	24	991	7.8
2023	N/A	N/A	N/A	N/A	2,288	19.2	567	4.4
2024	N/A	N/A	N/A	N/A	88	0.7	14	0.1
Health Characteristics								
Claims-Based Frailty Index	0.1	0	0.2	0	0.2	0	0.2	0
Combined Comorbidity Score	1.2	1.8	1.4	2	1.5	2.1	1.2	2

	HealthVerity (January 2018 – December 2020)				TriNetX (January 2013 – February 2024)			
	SGLT2i Initiators		DPP-4i Initiators		SGLT2i Initiators		DPP-4i Initiators	
Patient Characteristics	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**
Prior Metformin Users	22,764	75.4	29,922	70.8	7,894	66.1	7,792	61.1
Current Metformin Users	19,907	66.0	30,588	72.4	6,941	58.1	8,469	66.4
Prior Sulfonylureas Users	9,770	32.4	15,940	37.7	2,885	24.2	3,562	27.9
Current Sulfonylureas Users	8,203	27.2	14,532	34.4	2,427	20.3	3,247	25.5
Prior Insulin Users	7,168	23.8	7,271	17.2	2,607	21.8	1,898	14.9
Current Insulin Users	6,249	20.7	6,457	15.3	2,278	19.1	1737	13.6
Anticoagulants	1,487	4.9	1,986	4.7	932	7.8	677	5.3
Antiarrhythmics	297	1.0	408	1.0	189	1.6	135	1.1
ACE Inhibitors/ ARBs*	20,899	69.3	29,163	69	7,716	64.6	7,484	58.7
Beta Blockers	10,570	35.0	14,594	34.5	4,305	36	3,702	29.0
Calcium Channel Blockers	7,054	23.4	10,836	25.6	3,097	25.9	2,866	22.5
Prior Alphaglucosidase Users	127	0.4	198	0.5	18	0.2	21	0.2

	HealthVerity (January 2018 – December 2020)				TriNetX (January 2013 – February 2024)			
	SGLT2i Initiators		DPP-4i Initiators		SGLT2i Initiators		DPP-4i Initiators	
Patient Characteristics	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**
Current Alphaglucosidase Users	100	0.3	171	0.4	13	0.1	22	0.2
Prior Thiazolidinediones Users	2,122	7	2,384	5.6	479	4	425	3.3
Current Thiazolidinediones Users	1,816	6	2,211	5.2	422	3.5	376	2.9
Prior Amylin analog Users	1	0	1	0	0	0	0	0
Current Amylin Analog Users	1	0	1	0	0	0	0	0
Prior Meglitinides Users	197	0.7	307	0.7	79	0.7	87	0.7
Current Meglitinides Users	146	0.5	260	0.6	59	0.5	86	0.7
Thiazides	8,287	27.5	11,592	27.4	3,131	26.2	3,330	26.1
Diuretics	3,629	12	4,916	11.6	2,193	18.4	1,513	11.9
Digoxin	180	0.6	255	0.6	83	0.7	93	0.7
NSAIDS* without Aspirin	8,889	29.5	13,231	31.3	3,249	27.2	3,296	25.9
Aspirin	2,900	9.6	5,416	12.8	876	7.3	729	5.7

	HealthVerity (January 2018 – December 2020)				TriNetX (January 2013 – February 2024)			
	SGLT2i Initiators		DPP-4i Initiators		SGLT2i Initiators		DPP-4i Initiators	
Patient Characteristics	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**
Opioids	6,740	22.3	9,278	22	2,659	22.3	3,241	25.4
Statins	21,316	70.6	29,341	69.4	8,123	68	7,828	61.4
Other Lipid Lowering Grugs	3,644	12.1	4,420	10.5	1,182	9.9	1,123	8.8
Anticonvulsants	6,461	21.4	9,721	23.0	2,736	22.9	2,764	21.7
Antidepressants	8,453	28.0	11,496	27.2	3,616	30.3	3,658	28.7
Antiosteoporosis Medications	517	1.7	1,342	3.2	136	1.1	191	1.5
Anxiolytics/ Hypnotics	2,543	8.4	3,562	8.4	1,226	10.3	1,182	9.3
Antipsychotics	1,330	4.4	2,259	5.3	689	5.8	798	6.3
Antiparkinsonian Medications	683	2.3	1,029	2.4	263	2.2	320	2.5
Benzodiazepine	2,884	9.6	3,967	9.4	1,078	9.0	1,301	10.2
Dementia Medications	247	0.8	743	1.8	57	0.5	82	0.6
Proton Pump Inhibitors	6,981	23.1	10,730	25.4	2,923	24.5	3,178	24.9
Sigmoidoscopy/ Colonoscopy	158	0.5	202	0.5	82	0.7	93	0.7
Flu Vaccination	71	0.2	143	0.3	24	0.2	78	0.6

	HealthVerity (January 2018 – December 2020)				TriNetX (January 2013 – February 2024)			
	SGLT2i Initiators		DPP-4i Initiators		SGLT2i Initiators		DPP-4i Initiators	
Patient Characteristics	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**
Mammography	3,846	12.7	5,769	13.7	1,631	13.7	1,746	13.7
Pap Smear	1,649	5.5	2,321	5.5	379	3.2	404	3.2
Pneumococcal Vaccine	7,022	23.3	9,656	22.9	3,074	25.7	2,605	20.4
PSA*/Prostate Exam	1,986	6.6	2,335	5.5	1,025	8.6	713	5.6
Bone Mineral Density (BMD) Test	9	0	27	0.1	1	0	4	0
Blood Chemistry Test	0	0	0	0	0	0	0	0
Hypertension	22,724	75.3	31,973	75.7	9,309	77.9	9,606	75.4
Hyperlipidemia	21,737	72.0	29,063	68.8	8,533	71.4	8,749	68.6
Myocardial Infarction	510	1.7	470	1.1	442	3.7	155	1.2
Obesity	14,436	47.8	18,838	44.6	5,517	46.2	4,761	37.3
Alcohol Abuse Dependence	430	1.4	655	1.6	306	2.6	213	1.7
Stable Angina	1,295	4.3	1,543	3.7	572	4.8	291	2.3
Unstable Angina	570	1.9	562	1.3	310	2.6	142	1.1
Coronary Revascularization	1,769	5.9	1,809	4.3	878	7.4	416	3.3
Coronary Atherosclerosis	4,423	14.7	5,001	11.8	2,099	17.6	1,551	12.2

	HealthVerity (January 2018 – December 2020)				TriNetX (January 2013 – February 2024)			
	SGLT2i Initiators		DPP-4i Initiators		SGLT2i Initiators		DPP-4i Initiators	
Patient Characteristics	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**
Other Chronic IHD*	1,069	3.5	1,051	2.5	577	4.8	416	3.3
History CABG*/PTCA*	1,792	5.9	1,846	4.4	940	7.9	697	5.5
Any Stroke	685	2.3	1,061	2.5	365	3.1	404	3.2
Transient Ischemic Attack	277	0.9	448	1.1	125	1	155	1.2
Late effects of Cerebrovascular Disease	1,649	5.5	2,504	5.9	878	7.4	781	6.1
Peripheral Vascular Disease	1,655	5.5	2,751	6.5	577	4.8	427	3.3
Heart Failure	1,813	6.0	2,498	5.9	1,589	13.3	725	5.7
Atrial Fibrillation	1,260	4.2	1,760	4.2	732	6.1	580	4.6
Other Cardiac Dysrhythmia	2,308	7.6	3,216	7.6	1,457	12.2	1,020	8.0
Cardiomyopathy	807	2.7	932	2.2	780	6.5	330	2.6
Hypertensive Nephropathy	1,000	3.3	2,517	6.0	503	4.2	496	3.9
Acute Kidney Injury	1	0	1	0	8	0.1	105	0.8
Chronic Kidney Disease, Stage 1-2	777	2.6	1,382	3.3	263	2.2	219	1.7

	HealthVerity (January 2018 – December 2020)				TriNetX (January 2013 – February 2024)			
	SGLT2i Initiators		DPP-4i Initiators		SGLT2i Initiators		DPP-4i Initiators	
Patient Characteristics	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**
Chronic Kidney Disease, Stage 3-5	1,084	3.6	3,196	7.6	164	1.4	532	4.2
Anemia	2,875	9.5	5,293	12.5	1,455	12.2	1,235	9.7
Miscellaneous Renal Disease	915	3.0	1,746	4.1	456	3.8	395	3.1
Chronic Obstructive Pulmonary Disease	2,588	8.6	4,180	9.9	1,284	10.8	1,354	10.6
Obstructive Sleep Apnea	4,810	15.9	5,378	12.7	2,088	17.5	1,502	11.8
Asthma	2,508	8.3	3,834	9.1	1,138	9.5	1,099	8.6
Osteoporosis	629	2.1	1,395	3.3	197	1.6	215	1.7
Osteoarthrosis	4,763	15.8	7,339	17.4	1,768	14.8	1,611	12.6
Syncope	560	1.9	875	2.1	300	2.5	307	2.4
Falls	594	2.0	1,062	2.5	301	2.5	343	2.7
NASH*/NAFLD*	2,046	6.8	2,576	6.1	879	7.4	775	6.1
Alzheimer's Disease	57	0.2	224	0.5	18	0.2	37	0.3
Parkinson's Disease	79	0.3	199	0.5	27	0.2	47	0.4
Psychosis	577	1.9	1,113	2.6	290	2.4	308	2.4
Delirium	175	0.6	378	0.9	103	0.9	125	1.0
Depression	5,053	16.7	7,383	17.5	1,971	16.5	1,910	15

	HealthVerity (January 2018 – December 2020)				TriNetX (January 2013 – February 2024)			
	SGLT2i Initiators		DPP-4i Initiators		SGLT2i Initiators		DPP-4i Initiators	
Patient Characteristics	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**
Anxiety	4,343	14.4	5,943	14.1	2,142	17.9	1,848	14.5
Vertebral and Non-Vertebral Fractures	125	0.4	234	0.6	67	0.6	58	0.5
Diabetic Nephropathy	2,805	9.3	5,118	12.1	1,275	10.7	965	7.6
Diabetes with Peripheral Circulatory Disorders	44	0.1	53	0.1	8	0.1	8	0.1
Diabetic Foot	524	1.7	698	1.7	240	2.0	189	1.5
Diabetic Neuropathy	5,844	19.4	8,748	20.7	1,949	16.3	1,714	13.4
Diabetic Retinopathy	3,072	10.2	4,571	10.8	855	7.2	658	5.2
Type 2 Diabetes Mellitus without Mention of Complications	23,235	77.0	32,988	78.1	9,071	76.0	8,275	64.9
Lower limb Amputation	180	0.6	280	0.7	82	0.7	63	0.5
Hypoglycemia	4,339	14.4	6,002	14.2	1,441	12.1	928	7.3
Cancer	2,342	7.8	3,497	8.3	1,040	8.7	1,197	9.4
Valve disorders	364	1.2	476	1.1	275	2.3	138	1.1
Hyperkalemia	277	0.9	535	1.3	0	0	0	0
Hypotension	281	0.9	471	1.1	225	1.9	168	1.3

	HealthVerity (January 2018 – December 2020)				TriNetX (January 2013 – February 2024)			
	SGLT2i Initiators		DPP-4i Initiators		SGLT2i Initiators		DPP-4i Initiators	
Patient Characteristics	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**
Deep Vein Thrombosis/ Pulmonary Embolism	383	1.3	522	1.2	204	1.7	224	1.8
Edema	1,806	6.0	2,651	6.3	884	7.4	778	6.1
History of Autoimmune Diseases	1,557	5.2	2,088	4.9	569	4.8	567	4.4
Gallstones	390	1.3	586	1.4	186	1.6	195	1.5
Fecal Occult Blood Test	171	0.6	255	0.6	39	0.3	31	0.2
Pneumonia	588	1.9	994	2.4	405	3.4	421	3.3
Other dementia types	209	0.7	652	1.5	74	0.6	135	1.1
Type 2 Diabetes mellitus with Unspecified Complications	2,401	8.0	3,509	8.3	755	6.3	726	5.7
Urinary Tract or Fungal Infection History	5,213	17.3	9,283	22.0	1,927	16.1	2,229	17.5
Hyperosmolar Hyperglycemic Nonketotic Syndrome	12	0	19	0	8	0.1	11	0.1
Hyperglycemia	15,460	51.2	19,913	47.1	5,453	45.7	4,796	37.6

	HealthVerity (January 2018 – December 2020)				TriNetX (January 2013 – February 2024)			
	SGLT2i Initiators		DPP-4i Initiators		SGLT2i Initiators		DPP-4i Initiators	
Patient Characteristics	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**
Hypertriglyceridemia	1,248	4.1	1,420	3.4	380	3.2	377	3.0
Pulmonary Hypertension	282	0.9	444	1.1	268	2.2	130	1.0
Tobacco Use	3,636	12.1	4,939	11.7	2,320	19.4	2,191	17.2
Health Service Utilization Intensity Metrics								
Mean Number of Ambulatory Encounters	8.9	9.2	8.5	9.8	8.9	9.5	8.3	8.7
Mean Number of Emergency Room Encounters	0.3	0.9	0.4	1	0.7	1.6	0.7	1.6
Mean Number of Inpatient Hospital Encounters	0.1	0.9	0.2	0.9	0.9	3.5	1	4.2
Mean Number of Non-Acute Institutional Encounters	0.1	0.6	0.1	1.0	0.1	2.0	0.2	2.4
Mean Number of Other Ambulatory Encounters	4.4	19.7	6.5	24.8	6.1	18.1	5.7	17.4
Mean Number of Filled Prescriptions	26	21.2	26.5	22.1	23.8	20.3	22.5	20.9

	HealthVerity (January 2018 – December 2020)				TriNetX (January 2013 – February 2024)			
	SGLT2i Initiators		DPP-4i Initiators		SGLT2i Initiators		DPP-4i Initiators	
Patient Characteristics	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**
Mean Number of Generics Dispensed	10.3	5.7	10.6	5.9	10.2	5.8	9.5	5.8
Count of Antidiabetic Medications	1.4	0.8	1.3	0.8	1.2	0.8	1.1	0.8

*ACE: angiotensin converting enzyme; ARBs: angiotensin receptor blockers; NSAIDS: non-steroidal anti-inflammatory drugs; PSA: prostate specific antigen; IHD: ischemic heart disease; CABG/PTCA: coronary artery bypass graft/percutaneous transluminal angioplasty; NASH/NAFLD: non-alcoholic steatohepatitis /non-alcoholic fatty liver disease

Table 3 summarizes the claims-based patient characteristics (number/mean and percent/standard deviation) of SGLT2i and DPP-4i initiators with evidence of Type 2 DM for HealthVerity and TriNetX.

For HealthVerity, there were 30,174 and 42,255 unique patients in the SGLT2i and DPP-4i initiator groups respectively from January 2018 through December 2020. The mean age was 56.9±11.1 in the SGLT2i initiator group and 59.6±12.9 in the DPP-4i initiator cohort with majority of the patients in each of the cohorts falling within the age category of 41-64 years (72.4%; 63.5% respectively). The mean Claims-Based Frailty Index (CFI) and Combined Comorbidity Index (CCI) values were comparable across the two cohorts (CFI= 0.1±0.0 and CCI=1.2±1.8 for the SGLT2i group; CFI=0.2±0.0 and CCI=1.4±2.0 for the DPP-4i group). Metformin was the most common comedication in both groups (66%, 72.4%). Hypertension (75.3%; 75.7%) and hyperlipidemia (72%; 68.8%) were the most common comorbidities for both groups. The proportion of patients in both the groups with myocardial infarction (1.7%, 1.1%), stable angina (4.3%, 3.7%), and heart failure (6%, 5.9%) were overall low and similarly distributed between the two groups. The mean count of antidiabetic drug classes was 1.4±0.8 in the SGLT2i group and 1.3±0.8 in the DPP-4i group. For health services utilization characteristics, the mean number of generics dispensed were 10.3±5.7 for the SGLT2i group and 10.6±5.9 for the DPP-4i group.

For TriNetX, there were 11,943 and 12,747 unique patients in the SGLT2i and DPP-4i initiator groups respectively from January 2013 through February 2024. The mean age was 55.4±11.4 in the SGLT2i initiator group and 55.6±11.5 in the DPP-4i initiator cohort with majority of the patients in each of the cohorts falling within the age category of 41-64 years (72.2%; 71.7% respectively). Patients in each of the groups were predominantly white (58.5%, 58.8%). The mean Claims-Based Frailty Index (CFI) and Combined Comorbidity Index (CCI) values were comparable across the two cohorts (CFI= 0.2±0.0 and CCI=1.5±2.1 for the SGLT2i group; CFI=0.2±0.0 and CCI=1.2±2.0 for the DPP-4i group). Metformin was the most common comedication in both groups (58.1%, 66.4%). Hypertension (77.9%; 75.4%) and hyperlipidemia (71.4%; 68.6%) were the most common comorbidities for both groups. The proportion of patients

with cardiovascular comorbidities was generally higher in the SGLT2i groups; myocardial infarction (3.7%, 1.2%), stable angina (4.8%, 2.3%), and heart failure (13.3%, 5.7%), likely reflecting increasing use of SGLT2i in this patient population after knowledge of their cardiovascular benefits accumulated. The mean count of antidiabetic drug classes was 1.2±0.8 in the SGLT2i group and 1.1±0.8 in the DPP-4i group. The mean number of generics dispensed were 10.2±5.8 for the SGLT2i group and 9.5±5.8 for the DPP-4i group.

Table 4. EHR-Based Patient Characteristics of SGLT2i Initiators with Type 2 Diabetes Mellitus; HealthVerity (2018 – 2020) and TriNetX (2013 – 2024).

	HealthVerity (Jan 2018 - Dec 2020)				**TriNetX (Jan 2010 - Feb 2024)**			
	SGLT2i Initiators		**DPP-4i Initiators**		**SGLT2i Initiators**		**DPP-4i Initiators**	
Patient Characteristics	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**
Unique Patients	30,174	N/A	42,255	N/A	11,943	N/A	12,747	N/A
Laboratory Characteristics								
Hemoglobin A1c								
Test record in PERCENT	8,874	29.4	11,518	27.3	5,802	48.6	6,560	51.5
Mean, standard deviation	8.7	1.9	8.6	1.9	8.6	2	8.5	1.9
No test record	21,300	70.6	30,737	72.7	6,141	51.4	6,187	48.5
Serum Creatinine								
Test record in MG/DL	7,298	24.2	10,020	23.7	6,364	53.3	7,377	57.9
Mean, standard deviation	0.9	0.5	0.9	0.5	0.9	0.3	0.9	0.4
No test record	22,876	75.8	32,235	76.3	5,579	46.7	5,370	42.1
Triglycerides								

	HealthVerity (Jan 2018 - Dec 2020)				TriNetX (Jan 2010 - Feb 2024)			
	SGLT2i Initiators		DPP-4i Initiators		SGLT2i Initiators		DPP-4i Initiators	
Patient Characteristics	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**
Test record in MG/DL	5,955	19.7	8,109	19.2	4,152	34.8	4,877	38.3
Mean, standard deviation	176	90.6	171.4	87.4	174.2	93.6	174.3	92.7
No test record	24,219	80.3	34,146	80.8	7,791	65.2	7,870	61.7
Microalbuminuria Test								
No test record	30,174	100%	42,255	100%	11,943	100%	12,747	100%
Vitals/Lifestyle factors								
Body Mass Index (BMI)								
Recorded in kg/m2	18,326	60.7	26,239	62.1	5,950	49.8	6,055	47.5
Mean, standard deviation	32.4	5.5	31.6	5.7	34.8	8	34.5	7.9
Not recorded	11,848	39.3	16,016	37.9	5,993	50.2	6,692	52.5
Diastolic Blood Pressure (DBP)								
DBP recorded in mmHg	24,896	82.5	34,932	82.7	7,884	66	7,830	61.4
Mean, standard deviation	79	10.2	78.3	10.3	79.8	12.2	79.5	11.6
No test record	5,278	17.5	7,323	17.3	4,059	34	4,917	38.6

	HealthVerity (Jan 2018 - Dec 2020)				TriNetX (Jan 2010 - Feb 2024)			
	SGLT2i Initiators		DPP-4i Initiators		SGLT2i Initiators		DPP-4i Initiators	
Patient Characteristics	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**	**Number/ Mean**	**Percent/ Standard Deviation**
Systolic Blood Pressure (SBP)								
SBP recorded in mmHg	24,896	82.5	34,933	82.7	7,834	65.6	7,752	60.8
Mean, standard deviation	131.3	16.5	131.3	16.8	134.6	19.6	134.2	19
No test record	5,278	17.5	7,323	17.3	4,109	34.4	4,995	39.2
Tobacco Use								
Recorded as Yes	4,384	14.5	5,663	13.4	1,535	12.9	1,608	12.6
Recorded as No	7,588	25.1	11,807	27.9	0	0	0	0
Not recorded	18,202	60.3	24,785	58.7	10,408	87.1	11,139	87.4
EHR Encounters								
Total Number of * Encounters	3.4	2.8	3.5	2.9	3.9	4.7	3.9	4.8

*EHR: Electronic Health Records

Table 4 summarizes the EHR-based patient characteristics (number/mean and percent/standard deviation) of SGLT2i and DPP-4i initiators with evidence of Type 2 DM for HealthVerity and TriNetX. ***Figures 4 and 5*** show the proportion of EHR-based variables missing, stratified by treatment group, for HealthVerity and TriNetX. **For HealthVerity**, we observed significant gaps in the recording of lab tests which were missing for 70-80% of patients. In contrast, systolic and diastolic blood pressure readings showed relatively less missing data, with approximately 80% of patients having these measurements recorded. **For TriNetX**, we observed similar trends as HealthVerity; however, most of the labs such as HbA1c, triglycerides and creatinine had relatively less proportion of missingness. **In HealthVerity**, for a total of 29.4% SGLT2i initiators and 27.3% DPP-4i initiators, HbA1c results were available (mean HbA1c: 8.7$\pm$1.9, 8.6$\pm$1.9). Serum creatinine and triglyceride levels were recorded for around 20-25% of the patients (mean serum creatinine: 0.9$\pm$0.5,

0.9±0.5; mean triglycerides: 176±90.6; 171.4±87.4). BMI was recorded for > 60% of the patients in both groups (mean BMI: 32.4±5.5, 31.6±5.7). Blood pressure was recorded for >80% of the patients in both groups (mean systolic: 131.3±16.5, 131.3±16.8; mean diastolic: 79±10.2; 78.3±10.3). Total number of EHR encounters were comparable across both groups (mean EHR encounters: 3.4±2.8, 3.5±2.9). **In TriNetX**, HbA1c results were available for around 50% of the patients in both groups (mean HbA1c: 8.6±2.0, 8.5±1.9). Serum creatinine and triglyceride levels were recorded for around 35-60% of the patients (mean serum creatinine: 0.9±0.3, 0.9±0.4; mean triglycerides: 174.2±93.6; 174.3±92.7). BMI was recorded for around half of the patients in both groups (mean BMI: 34.8±8.0, 34.5±7.9). Blood pressure was recorded for >60% of the patients in both groups (mean systolic: 134.6±19.6, 134.2±19.0; mean diastolic: 79.8±12.2; 79.5±11.6). Total number of EHR encounters were comparable across both groups (mean EHR encounters: 3.9±4.7, 3.9±4.8).

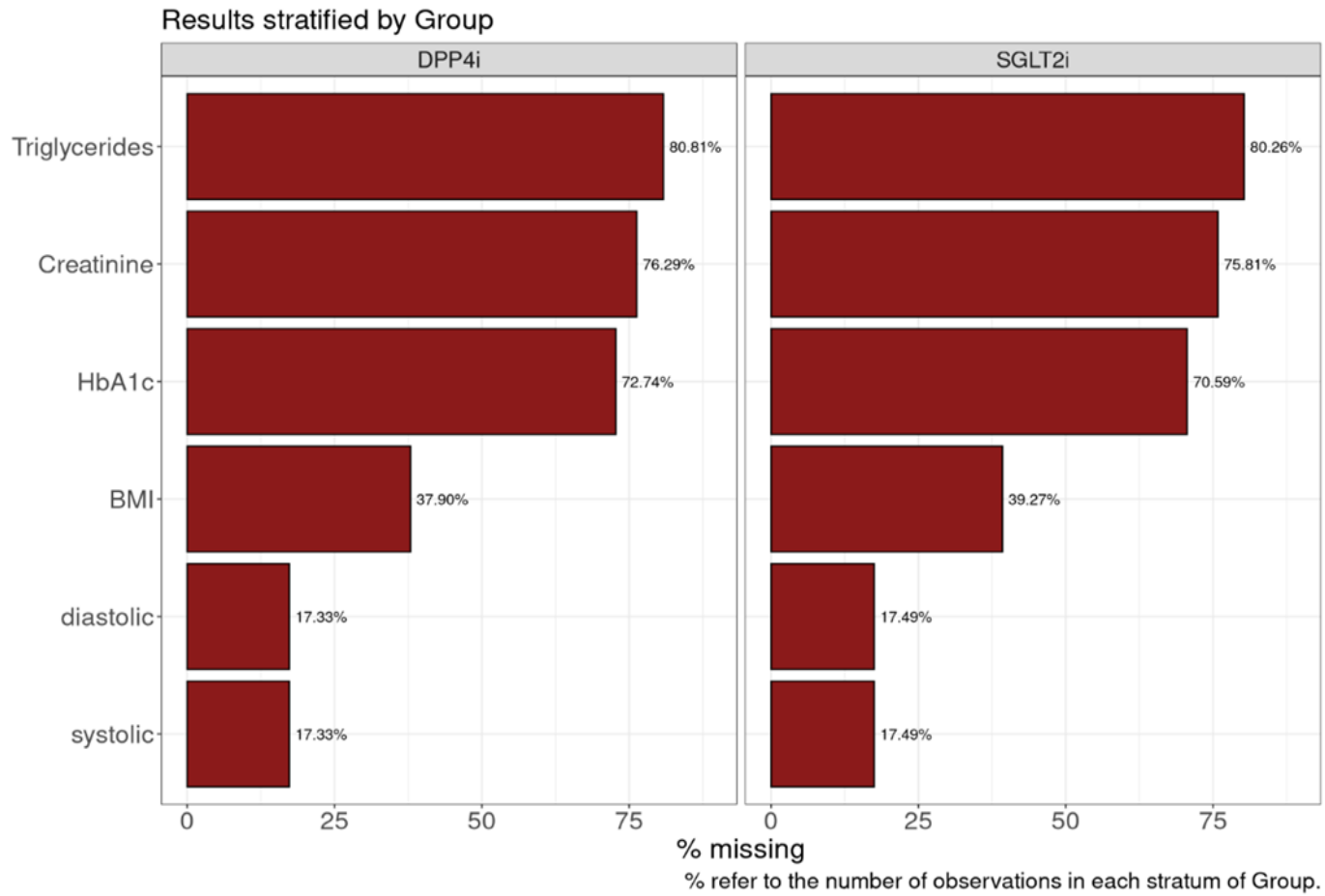

Figure 4. Proportion of Missing EHR-Based Variables Stratified by Treatment Group (HealthVerity).

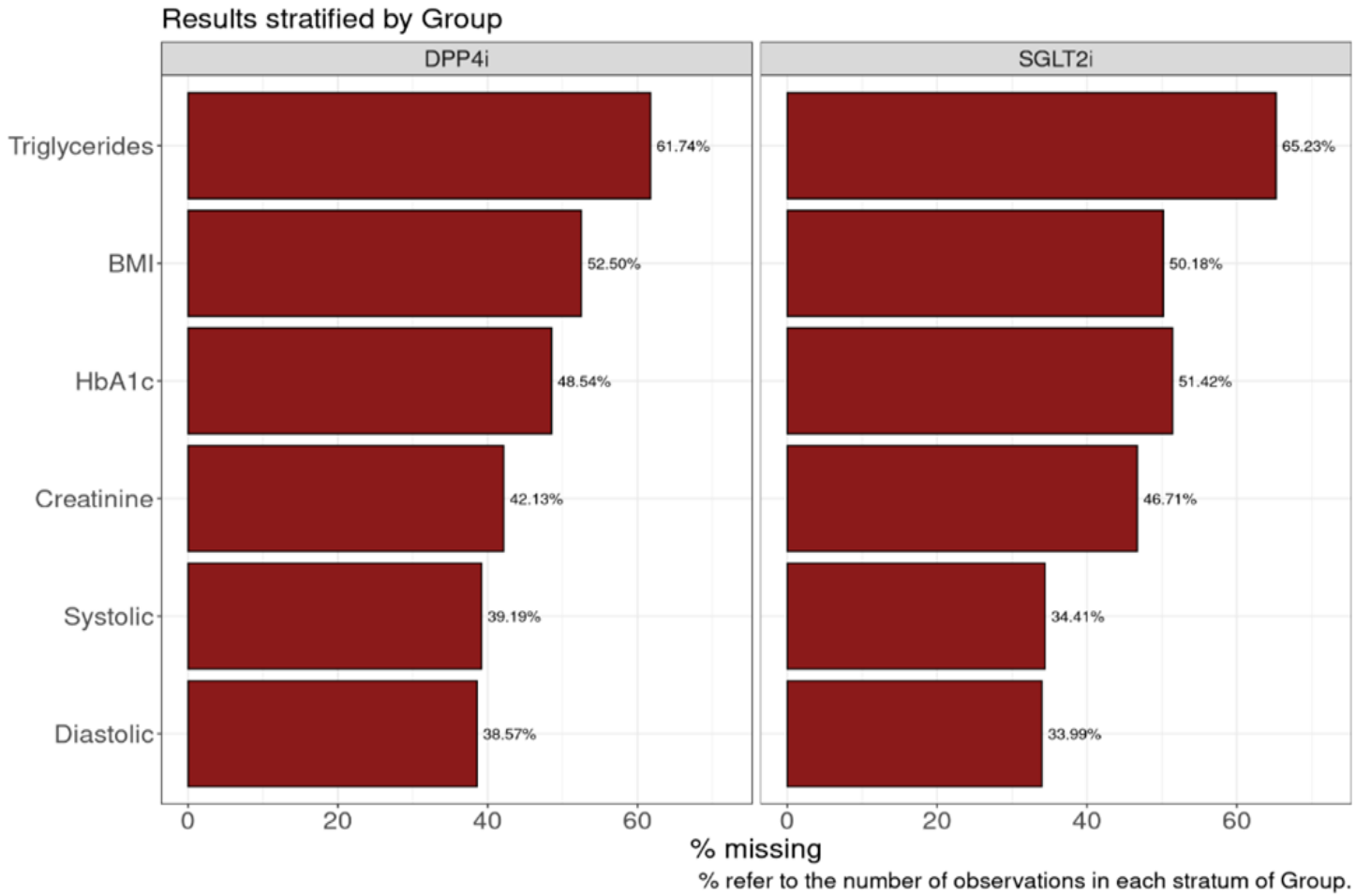

Figure 5. Proportion of Missing EHR-Based Variables Stratified by Treatment Group (TriNetX).

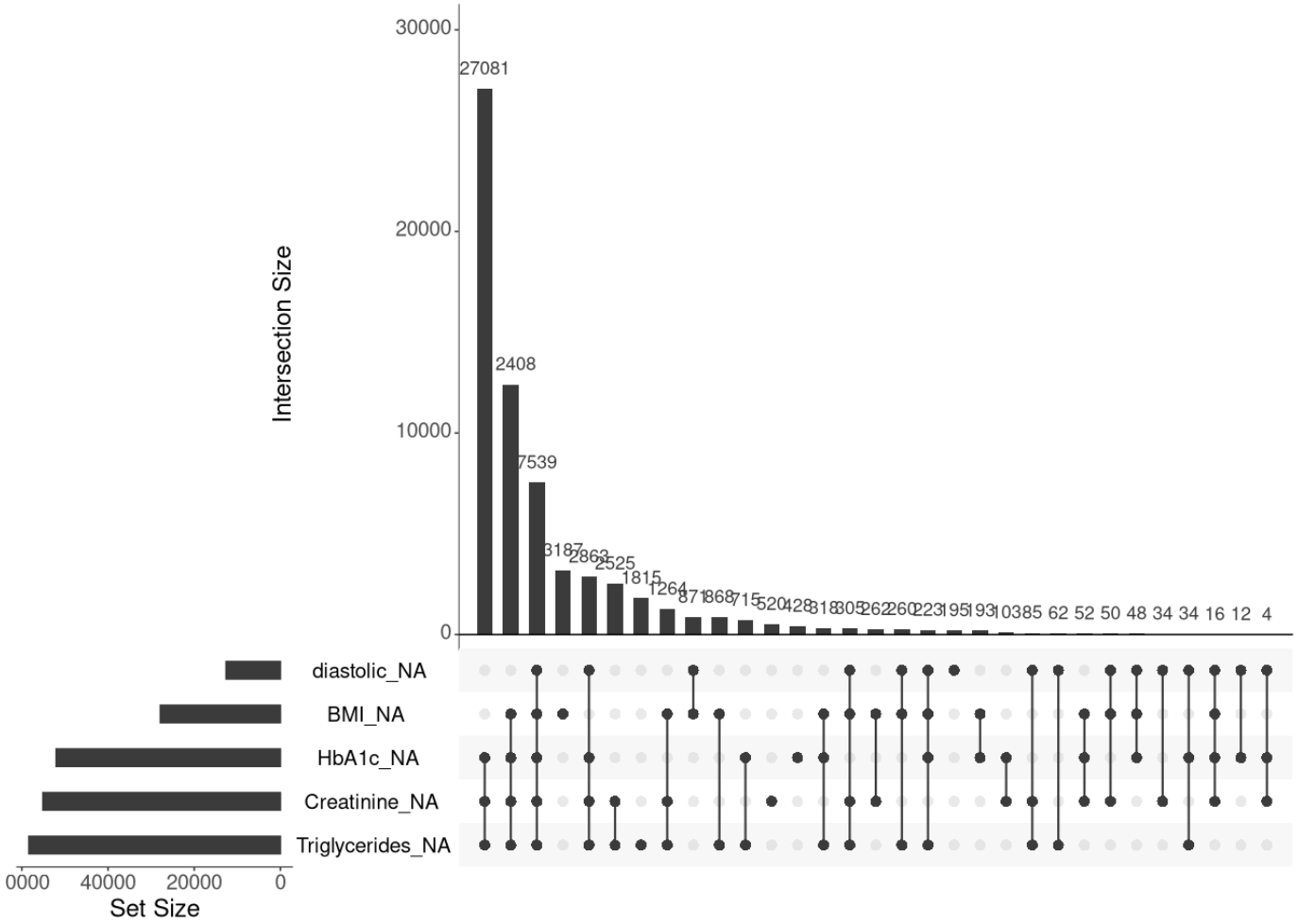

Figure 6A. Missingness Patterns, HealthVerity.

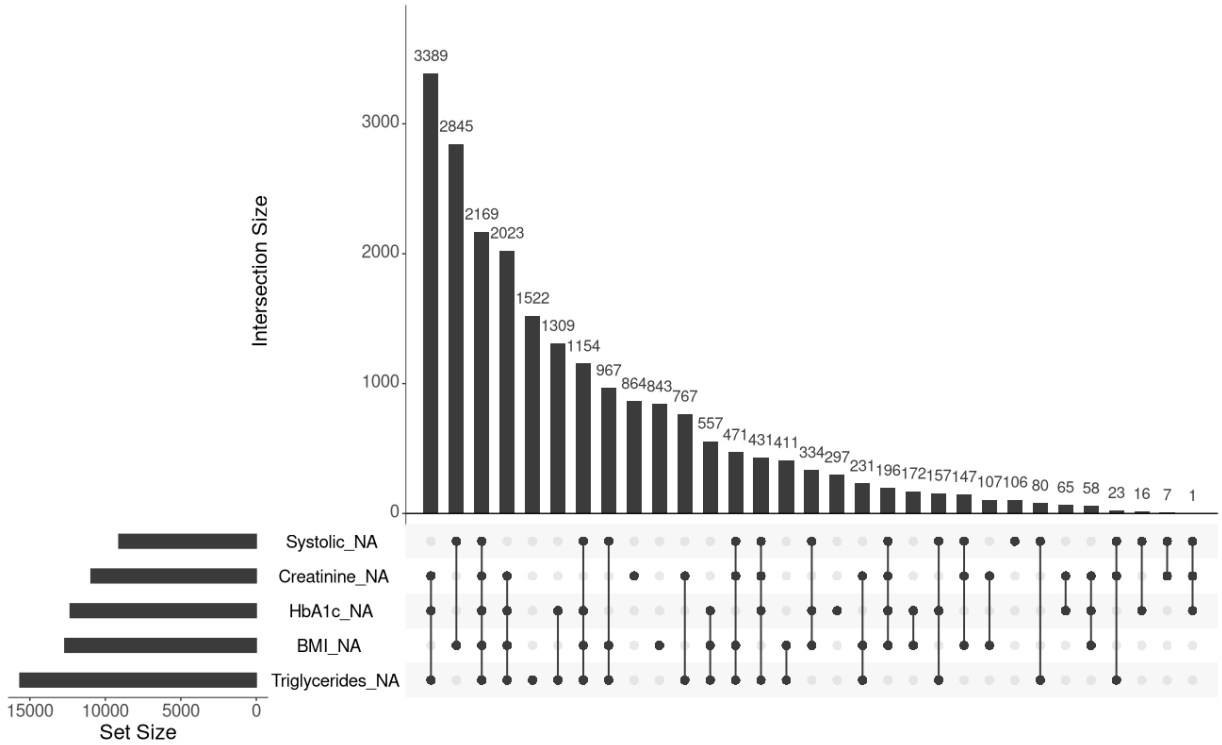

Figure 6B. Missingness Patterns, TriNetX.

Figures 6A and 6B demonstrates the overall missingness patterns of the EHR-based variables at baseline. The set size displays the count of missing observations for each individual variable whereas the intersection size displays the count of intersecting missing observations across all EHR-based variables. Generally, we saw that frequently, several patients have more than one EHR-based variable missing. For example, out of the 21,719 patients with at least one unobserved value for either of the variables in TriNetX, 2,169 (around 10%) patients were observed with missing values for all EHR-based variables and 3,389 (15.6%) patients with missing values for creatinine, HbA1c and triglycerides. These trends suggest a monotonic missingness pattern, as patients with missing data for these key variables are likely to exhibit consistent gaps in other EHR-based measurements.

Table 5. Missingness Diagnostics for the EHR-Based Variables; HealthVerity and TriNetX.

Confounder	*ASMD (Median, Min/Max) in other confounders between subjects with and without missing data	Area under the curve for a random forest model predicting missingness	Log HR** (unadjusted) for the association between missingness indicator and the outcome	Log HR (adjusted) for the association between missingness indicator and the outcome
HealthVerity				
Body Mass Index	0.015 (0.00, 0.33)	0.57	-0.08 (-0.35, 0.18)	-0.12 (-0.39, 0.15)
Systolic Blood Pressure	0.015 (0.00, 0.79)	0.51	-0.40 (-0.79, 0.00)	-0.33 (-0.69, 0.06)
HbA1c	0.043 (0.00, 0.62)	0.61	0.17 (-0.12, 0.46)	0.07 (-0.24, 0.38)
Creatinine	0.035 (0.00. 0.67)	0.57	-0.03 (-0.33, 0.26)	-0.11 (-0.42, 0.21)
Triglyceride	0.047 (0.00, 0.63)	0.54	0.08 (-0.25, 0.41)	-0.03 (-0.37, 0.32)
TriNetX				
Body Mass Index	0.028 (0.00, 0.46)	0.66	-0.02 (-0.35, 0.32)	-0.02 (-0.35, 0.32)
Systolic Blood Pressure	0.029 (0.00, 0.90)	0.71	0.23 (-0.10, 0.57)	0.30 (-0.10, 0.69)
HbA1c	0.033 (0.00, 0.49)	0.70	0.27 (-0.07, 0.60)	0.05 (-0.31, 0.42)
Creatinine	0.033 (0.00, 0.51)	0.65	-0.05 (-0.38, 0.29)	-0.06 (-0.42, 0.29)
Triglyceride	0.045 (0.00, 0.27)	0.62	0.13 (-0.22, 0.48)	-0.12 (-0.49, 0.25)

*ASMD: Absolute Standardized Mean Distribution; **HR: Hazard Ratio

Table 5 shows the missingness diagnostics for the EHR-based variables for HealthVerity and TriNetX. Overall, in both datasets, there were some differences observed in measured variables between those with and without missing data for EHR-based variables as seen by absolute standardized mean distribution, with medians of around 0.02-0.5 with some variables showing large differences suggested by maximum values of up to 0.9. Next, for prediction models, we observed relatively high area under the curve (AUCs) for each of these

variables, especially in TriNetX. High AUCs suggest that missing at random (MAR) conditional on measured information may be a likely missingness mechanism. Finally, we evaluated associations between missingness indicator in each of these EHR variables and the outcome (acute pancreatitis). These results indicated that when adjusting for other measured variables, no significant association exists between missingness indicator and the outcome. This observation provides some reassurance against missing not at random (MNAR) mechanism. Overall, we concluded that MAR may be a reasonable assumption regarding missingness mechanism for these variables and therefore, multiple imputations are likely to provide best bias-variance trade-off.

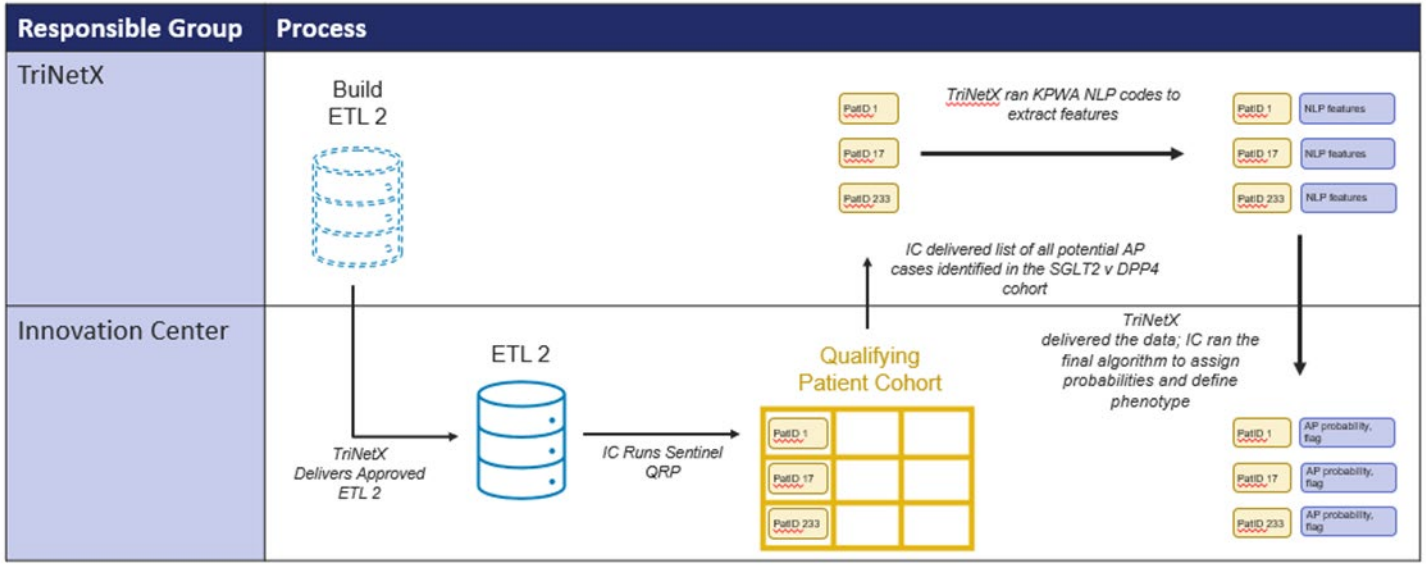

Figure 7. Visual Summary of Acute Pancreatitis (AP) Phenotyping Algorithm, TriNetX.

For TriNetX, ***Figure 7*** demonstrates a visual process of the acute pancreatitis phenotyping algorithm. After implementing Sentinel's Query Request Package with additional programming, a subset of the final cohort or "qualifying patient cohort" (i.e, potential AP cases identified), and the AP algorithm were delivered to TriNetX for NLP-extraction. After implementation of the algorithm, TriNetX delivered the NLP-derived variables back to the Sentinel Innovation Center for running the final algorithm with information from structured EHR data. Please refer to the AP model application guide attached as an appendix for a detailed list of model components.

For HealthVerity, the phenotyping algorithm process was different from TriNetX due to the limitations surrounding unstructured data. Firstly, out of the total ten M patients in HealthVerity, only 6% had > one note. Another major limitation was that these notes were all from ambulatory office visits. We were unable to derive NLP features from the HealthVerity clinical notes as NLP features for an AP model are predominantly extracted from radiology reports which were unavailable. Hence, we built the phenotype without the NLP features i.e., using features only from the structured data and lab data.

Table 6. Crude Incidence Rates (IR) of Acute Pancreatitis in SGLT2i and DPP-4i Initiators; HealthVerity and TriNetX.

			Intent to Treat Follow-Up	Per protocol follow-up
HealthVerity (January 2018 - December 2020)	**SGLT2i Initiators (n=30,174)**	**Number of Events / PY**	88/33,889	40/16,374
		IR / 1,000 PY	2.6 (2.1-3.2)	2.4 (1.7-3.3)
	DPP-4i Initiators (n=42,255)	**Number of Events / PY**	148/51,561	67/24,608
		IR / 1,000 PY	2.9 (2.4-3.4)	2.7 (2.1-3.5)
TriNetX (January 2013 - February 2024)	**SGLT2i Initiators (n=11,943)**	**Number of Events/ PY**	44/22,756	15/7,891
		IR / 1,000 PY	1.9 (1.4-2.6)	1.9 (1.1-3.1)
	DPP-4i Initiators (n=12,747)	**Number of Events/ PY**	94/36,783	26/10,499
		IR / 1000 PY	2.6 (2.1-3.1)	2.5 (1.6-3.6)

Table 6 shows a comparison of crude incidence rates (IRs) of AP in new users of SGLT2i and DPP-4i in HealthVerity and TriNetX. The total event count in HealthVerity was 236 and 138; while TriNetX was 107 and 41 for ITT and per-protocol schemes respectively. Overall, we observed event rates in the range of two to three per 1,000 person-years across both databases in the two follow-up schemes.

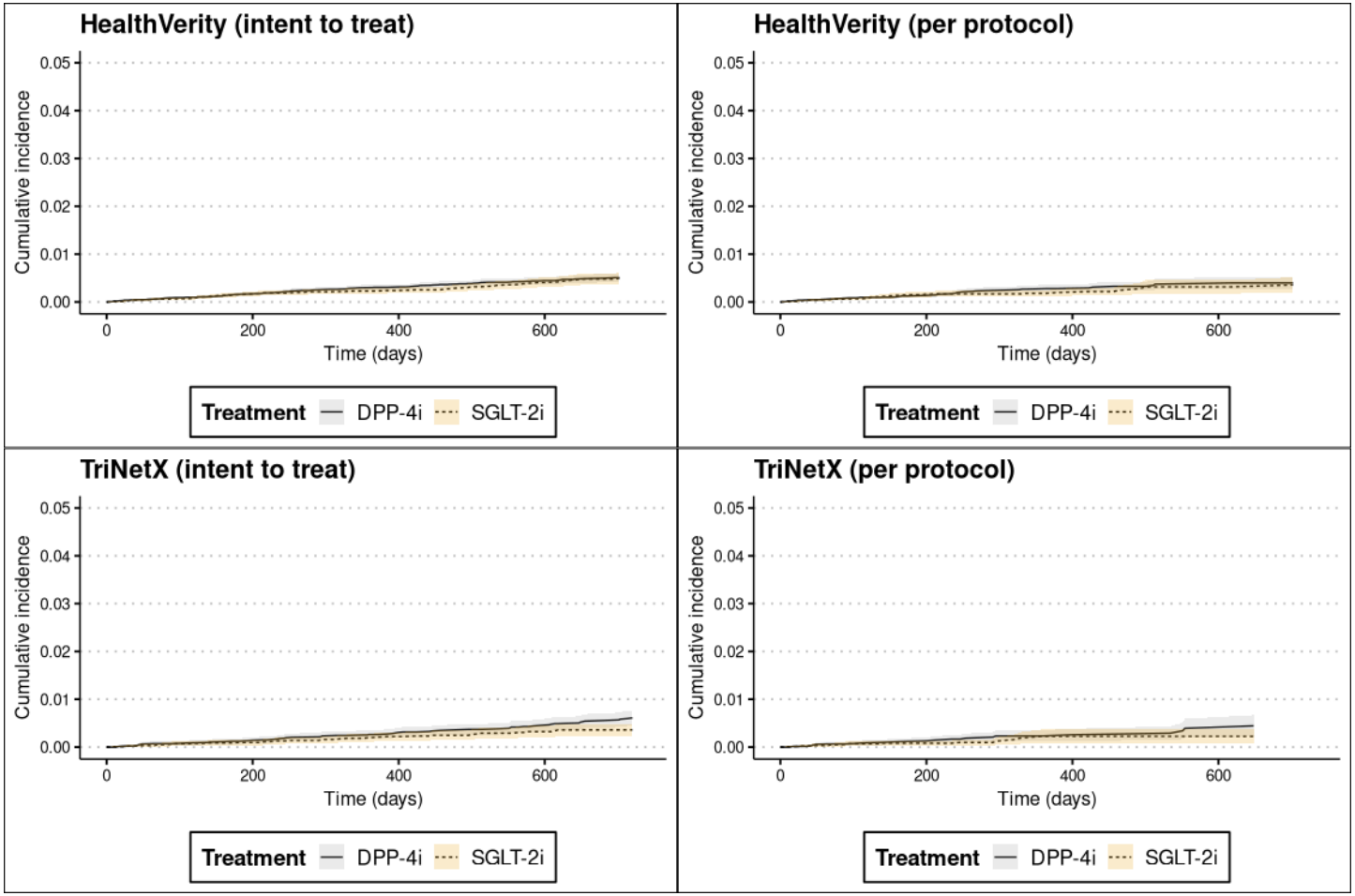

Figure 8. Cumulative Incidence Plots Comparing SGLT2i and DPP-4i Initiators with Type 2 Diabetes Mellitus in Relation to Acute Pancreatitis; HealthVerity and TriNetX.

Figure 8 compares the cumulative incidence (CI) of acute pancreatitis in new users of SGLT2i versus DPP4i with Type 2 DM, including both ITT and PP analyses in HealthVerity and TriNetX. Overall, the plots suggested that the cumulative incidence of acute pancreatitis was comparable between the two treatment groups for both ITT and PP approach in HealthVerity and TriNetX.

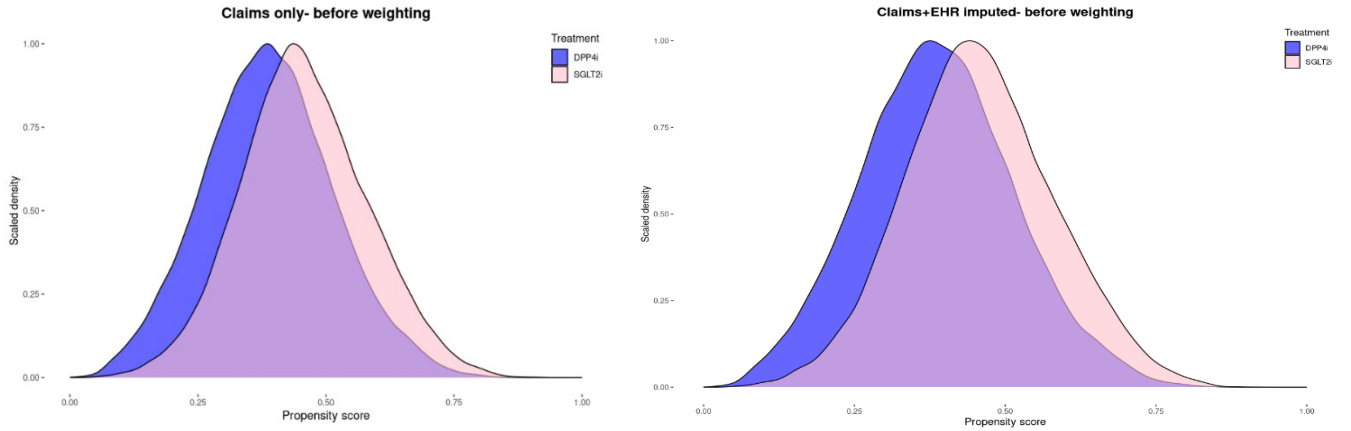

Figure 9A. Overlap of Propensity Scores (PS) for SGLT2i and DPP-4i Initiators; HealthVerity.

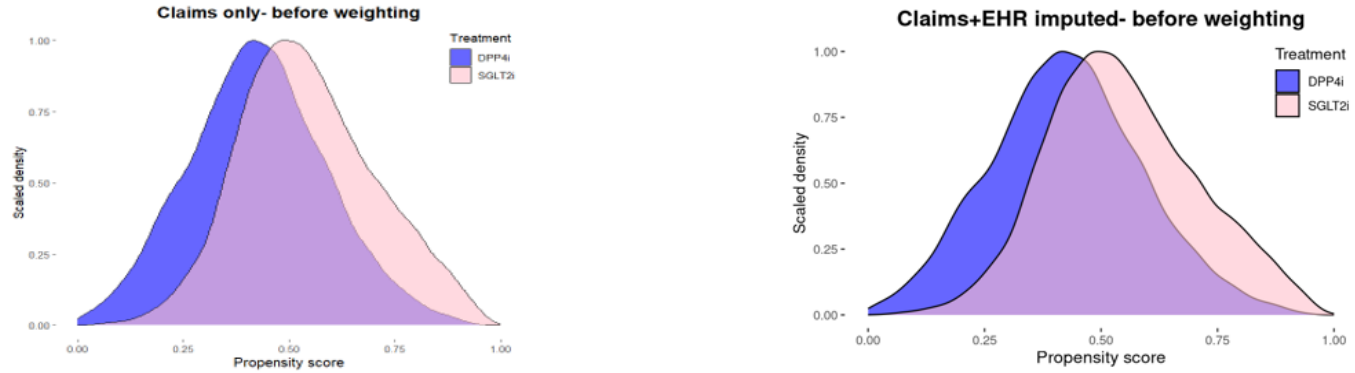

Figure 9B. Overlap of Propensity Scores (PS) for SGLT2i and DPP-4i Initiators; TriNetX.

Figures 9A and 9B show the distribution of propensity scores across new users of SGLT2i and DPP-4i in HealthVerity and TriNetX before weighting claims-based confounders only (left) and claims±EHR-based confounders. Overall, both the plots show substantial overlap in PS distribution implying clinical equipoise and reasonable comparability in the study cohort between two treatment groups with no indication of positivity violation, which is a key assumption needed for causal inference.

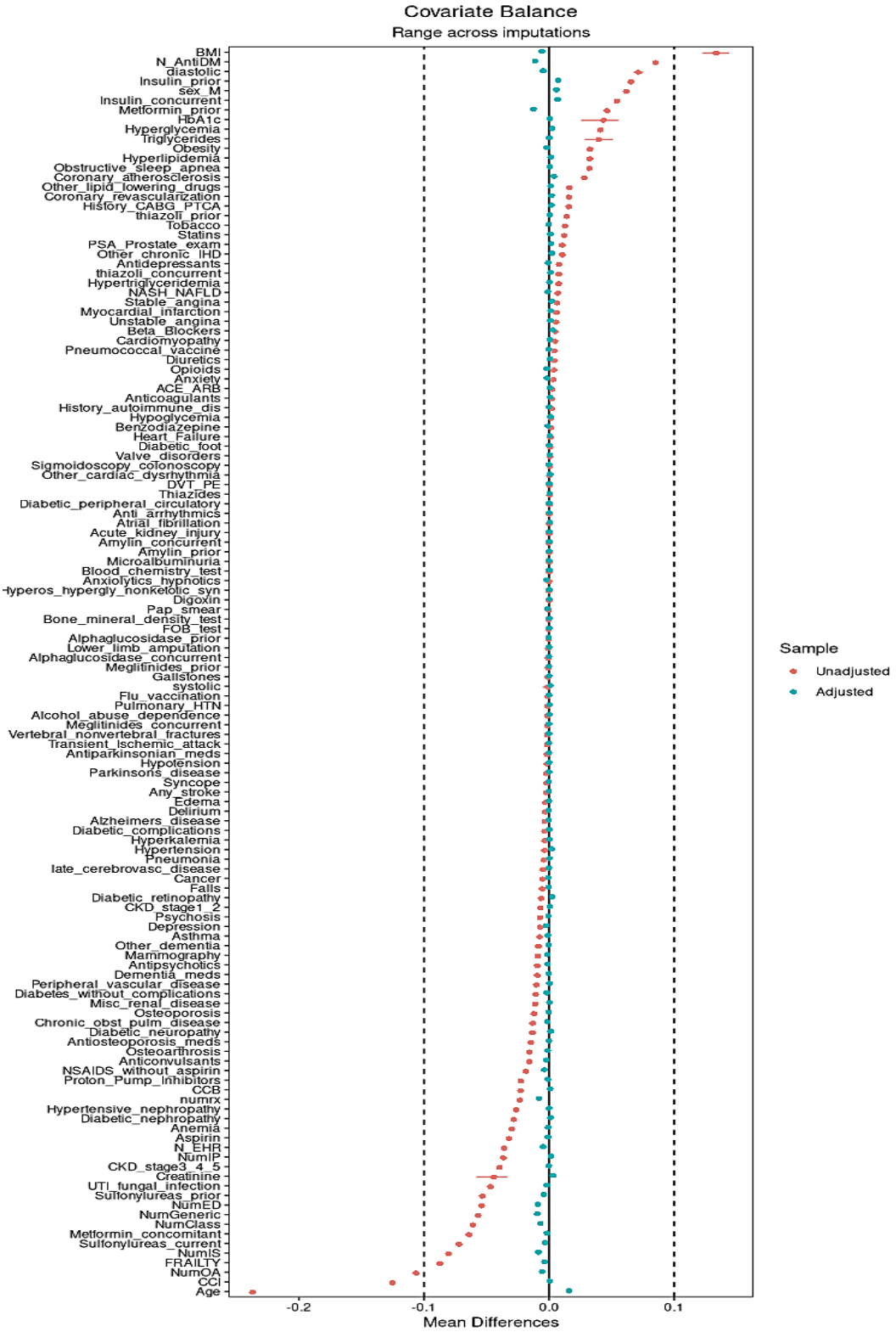

Figure 10. Balance Range in Variables Across Multiple Imputations, HealthVerity.

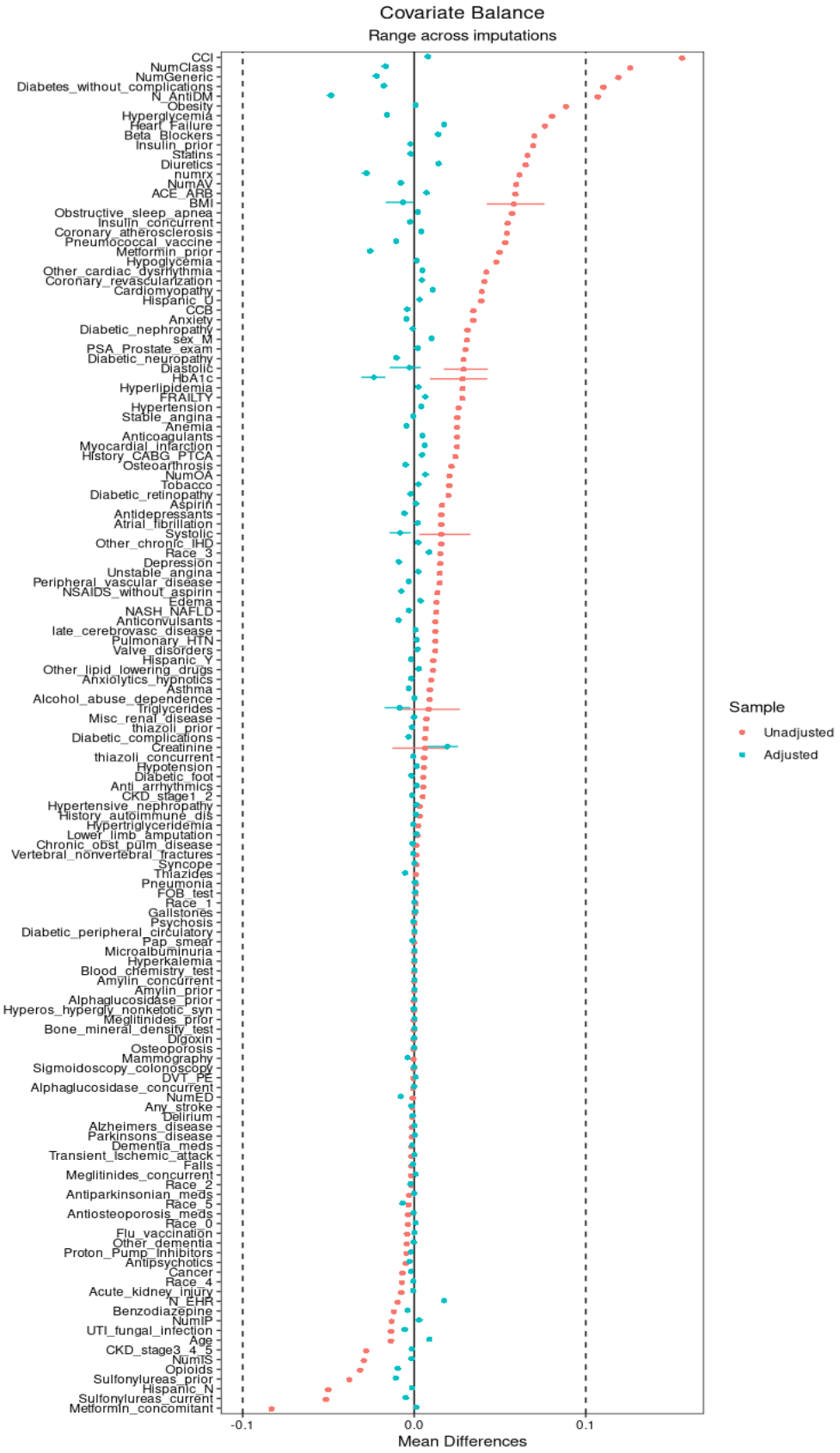

Figure 11. Balance Range in Variables Across Multiple Imputations, TriNetX .

Figures 10 and 11 shows range of balance, expressed as mean difference, achieved in all variables across 20 imputations for both datasets. Before PS weighting, a few variables in each dataset exhibited some imbalances including BMI, age, and CCI in HealthVerity, while CCI and number of medications total and specific to diabetes for TriNetX. In general, however, most of the variables demonstrated little imbalance between two treatment groups as demonstrated by mean differences close to 0. Our PS weighting procedure was extremely effective at achieving balance as demonstrated by the range of post-weighting mean differences close to zero across all 20 imputations**.**

Table 7. Hazard Ratios for Acute Pancreatitis (AP) in New Users of SGLT2i Compared to DPP-4i, Intent-to-Treat and Per Protocol Approach; HealthVerity and TriNetX.

	HealthVerity HR (95% CI)	TriNetX HR (95% CI)	Pooled HR (95% CI)
Intent-to-Treat Follow-up			
Crude	0.90 (0.69-1.18)	0.71 (0.49-1.02)	0.83 (0.67-1.03)
***Claims Only Confounders in the Propensity Score**	0.92 (0.70-1.22)	0.72 (0.48-1.07)	0.85 (0.67-1.07)
***Claims ± EHR Confounders in the Propensity Score**	0.92 (0.69-1.22)	0.71 (0.47-1.07)	0.85 (0.67-1.07)
Per-Protocol Follow-up			
Crude	0.89 (0.60-1.31)	0.73 (0.39-1.39)	0.84 (0.61-1.18)
***Claims Only Confounders in the Propensity Score**	0.88 (0.58-1.33)	0.72 (0.34-1.49)	0.84 (0.59-1.20)
***Claims ± EHR Confounders in the Propensity Score**	0.88 (0.58-1.34)	0.73 (0.34-1.56)	0.84 (0.58-1.22)

Claims only model had >130 variables, Claims ± EHR model added 6 additional variables and used multiple imputation.

Table 7 provides the crude and adjusted (claims only and claims±EHR) hazard ratios (HRs) for acute pancreatitis in SGLT2i initiators compared to DPP-4i initiators with Type 2 DM in HealthVerity and TriNetX. Overall, we observed no statistically significant difference between SGLT2i and DPP-4i initiators regarding the risk of acute pancreatitis across the two follow-up schemes and two data sources. We noted that confounding adjustment, first using only the >130 claims-based covariates in each dataset, and then using six additional EHR-based variables, did not move the estimates for hazard ratios meaningfully.

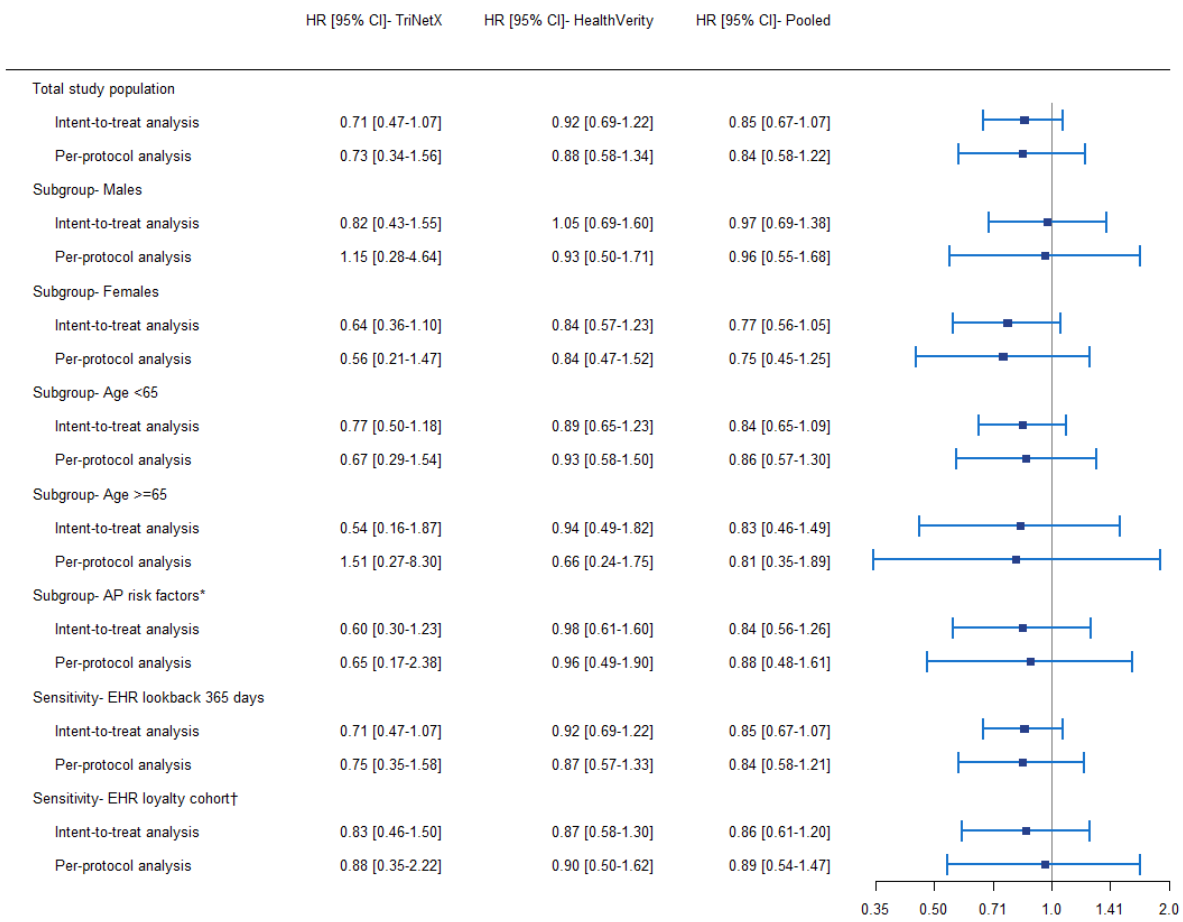

Figure 12. Hazard Ratios for Acute Pancreatitis in New Users of SGLT2i Compared to DPP-4i in subgroup and sensitivity analyses, Intent-to-Treat and Per Protocol Approach; HealthVerity and TriNetX.

* AP risk factors included gallstones, tobacco use, and alcohol abuse.
† EHR loyalty cohort included patients with ≥3 EHR encounters during the baseline period

Figure 12 shows results from the subgroup and sensitivity analyses. For all subgroups considered (age <65 and ≥65, males, females, and with history of AP risk factors), we found results consistent with the overall population. In the two sensitivity analyses where we attempted to reduce missingness proportions for EHR based covariates by increasing the lookback period and by only restricting to those with ≥3 EHR encounters, we noted that the capture increased for all confounders (Figure 13). The results from these two analyses were also consistent with the primary analysis.

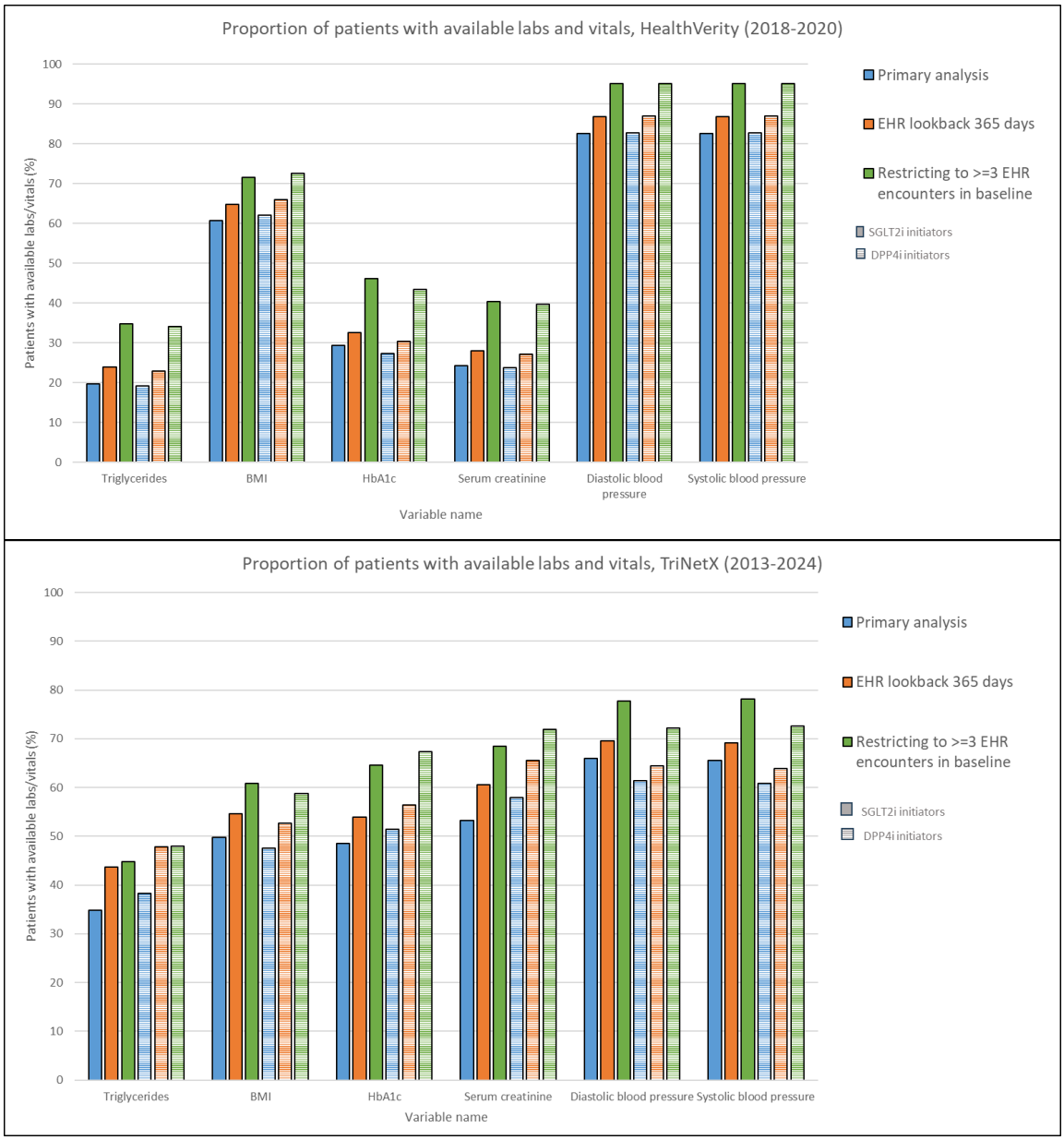

Figure 13. Proportion of Patients with Available Laboratory Test Results and Vital Statistics in the Primary and Sensitivity Analyses; HealthVerity and TriNetX.

3. Learnings/Conclusion

In conclusion, this demonstration project in FDA Sentinel's RWE-DE commercial network serves as a proof-of-concept for future protocol-based assessments in Sentinel. Specifically, this project highlights the value of EHR data for capturing clinical information not available in administrative claims data. Analytic pipelines and packages contributed by prior methods projects supported by the FDA Sentinel Initiative provide key building blocks to achieve scalable and timely execution of complex analyses using claims-EHR linked assets.

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