DIABETIC COMPLICATIONS ASSOCIATED WITH SGLT2 AND DPP4 INHIBITORS: A REAL WORLD APPROACH

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OBJECTIVES

Prior studies have investigated and shown an association between use of sodium glucose cotransporter 2 (SGLT2) inhibitors with serious adverse events (SAEs), including lower limb amputation, acute kidney failure, diabetic keto-acidosis and acute pancreatitis (1, 2). This study aimed to investigate whether there is any difference in the risk for these SAEs when comparing sodium glucose co-transporter 2 (SGLT2) inhibitors, to dipeptidyl peptidase-4 (DPP4) inhibitors in a real world setting.

METHODS

Real world data, composed of electronic medical records, pharmacy records and insurance claims from approximately 190 million U.S. patients were analyzed using TriNetX Analytics. Type 2 diabetes patients were defined with the ICD-10 code, E11 and two unique cohorts were defined for patients treated with SGLT2 inhibitors and DPP4 inhibitors (figure 1). In both cohorts, medication adherence was specified as having a second documentation of either SGLT2 inhibitors or DPP4 inhibitors in the SGLT2 and DPP4 cohorts respectively two years after the initial documentation. Patients who took drugs from the other anti-diabetic classes including thiazolidinediones, sulfonureas or metformin were excluded from the analysis. Those who may have switched from taking SGLT2 inhibitors to DPP4 inhibitors or vice-versa were also excluded from the respective cohorts. The index event was defined as initiation of either SGLT2 or DPP4 inhibitors for type 2 diabetes. Medical diagnosis (ICD-10), lab (LOINC) and procedural (CPT) codes were used to define primary outcomes, which included acidosis (ICD-10 codes: E87.2, and LOINC codes: 9021, 558-4), acute kidney failure (ICD-10 codes: N17, N18, N19), acute pancreatitis (ICD-10 code: K85.9) and lower limb amputation (ICD-10 codes: Z89.4, Z89.5, Z89.6 and CPT codes: 1005524, 1005529, 1005298, 1014590, 28820, 27880, 28810, 1005146, 1014580, 27590, 28825, 1005525, 28805, 27882, 27886), with an observation period between 7 days to 5 years after medication initiation. Risk ratios (RR) with 95% confidence intervals (95% CI) were calculated and propensity score matching used to balance cohorts and adjust for 22 most likely confounders (table 1). Propensity scores were matched 1:1 using a nearest neighbor greedy matching algorithm with a caliper of 0.25 times the standard deviation.

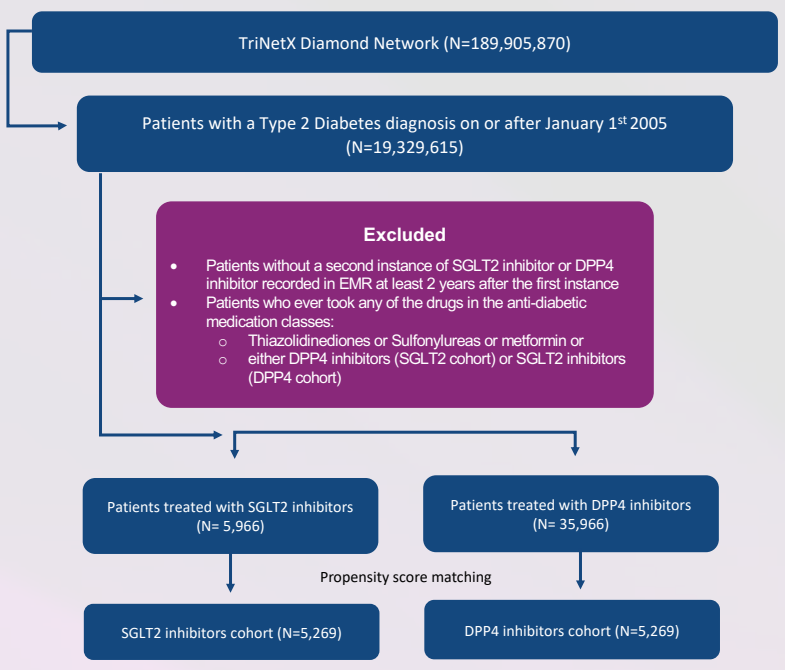

Figure 1. Study population

Table 1. Baseline demographics (before propensity score matching)

	SGLT2 inhibitors (N=5,966)			DPP4 inhibitors (N=35,966)		
		Patient count	% of count		Patient count	% of count
Age (years)						
Age at index (mean + sd)	57.5 + 10.5			69.1 + 12.1		
Sex						
Male		3,086	52		14, 842	41
Female		2,880	48		21,123	59
Ethnicity						
Hispanic or Latino		42	1		334	1
Not Hispanic or Latino		547	9		3,537	10
Unknown		5,377	90		32,095	89
Race						
White		479	8		2,928	8
Black or African American		65	1		560	8
Asian		10	0		37	0
Unknown		5,416	91		32,441	90

Table 2. Propensity score matching characteristics

Code(s)	Diagnosis or Medication
E08-E13	Diabetes Mellitus
E70-E88	Metabolic Disorders
I10-I15	Hypertensive Diseases
E00-E89	Endocrine, nutritional and metabolic diseases
N17-N19	Acute kidney failure and chronic kidney disease
N25-N29	Other disorders of kidney and ureter
S80-S89	Injuries to the knee and lower leg
S90-S99	Injuries to the ankle and foot
CV000	Cardiovascular Medications
HS501	Insulin
HS509	Hypoglycemic agents,other
60548	Exenatide
HS503	Antihypoglycemics
CV805	Angiotensin ii inhibitor
CV800	Ace inhibitors
CV350	Antilipemic agents
3407	Digoxin
MS102	Nonsalicylate nsais,antirheumatic
CN100	Analgesics
HS850	Thyroid modifiers
HS100	Androgens/anabolics
HS050	Adrenal corticosteroids

Table 3. Risks and risk ratios (SGLT2 inhibitors vs DPP4 inhibitors)

	SGLT2 inhibitors	DPP4 inhibitors		
Outcome	Risk (%)	Risk (%)	Risk Ratio	95% CI
Acidosis	4.04	7.93	0.51	(0.43,0.60)
Amputation	1.40	2.51	0.56	(0.42,0.74)
Acute Kidney Failure	12.10	42.40	0.26	(0.26,0.31)
Acute Pancreatitis	0.63	0.42	1.50	(0.88,2.57)

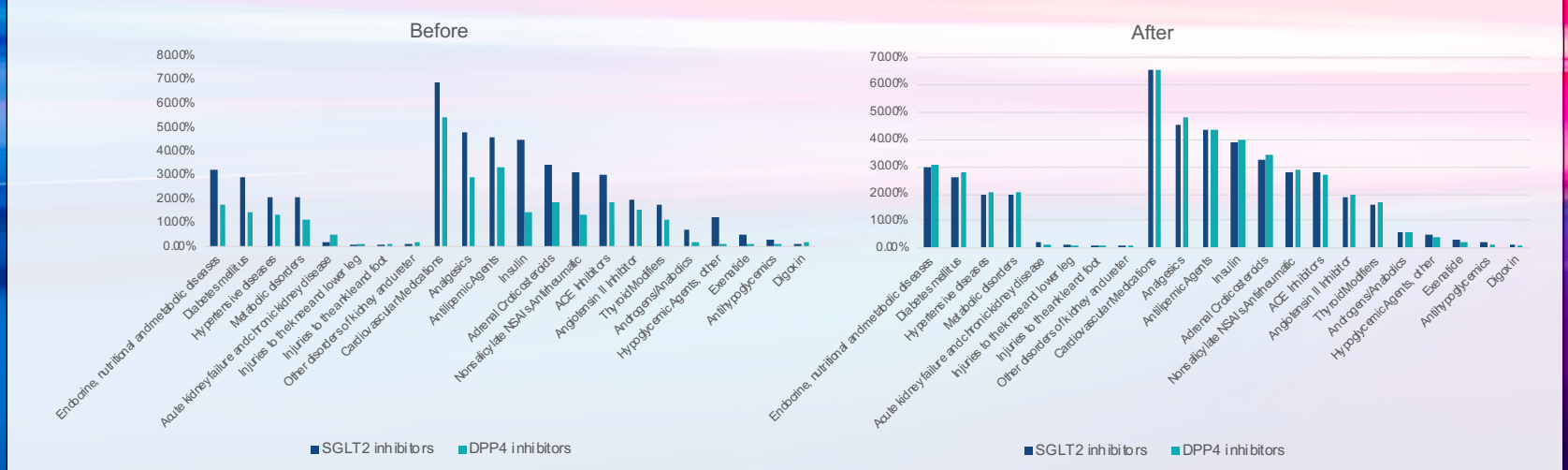

Figure 2. Baseline co-morbidities and medications (before and after propensity score matching)

RESULTS

In the balanced cohort of 10,538 patients, use of SGLT2 inhibitors, compared to DPP4 inhibitors was associated with a lower risk for acidosis RR (95% CI) 0.51 (0.43,0.60), amputation RR (95% CI) 0.56 (0.42,0.74), acute kidney failure RR (95% CI) 0.26 (0.26,0.31), but not with acute pancreatitis RR (95% CI) 1.5 (0.88,2.57) (table 3).

CONCLUSIONS

In this real world analysis, use of SGLT2 inhibitors was associated with a lower risk for acidosis, acute kidney failure and lower limb amputation, but not acute pancreatitis as compared with DPP4 inhibitors.

1.Ueda et al. Sodium glucose cotransporter 2 inhibitors and risk of serious adverse events: nationwide register based cohort study . 2018; 363: k4365

2. Chang et al. Association Between Sodium-Glucose Cotransporter 2 Inhibitors and Lower Extremity Amputation Among Patients With Type 2 Diabetes JAMA Internal Medicine. 2018; 178:9