

Yandong Qiang¹, Casie E. Horgan², Andrew B Petrone², Joy Kolonoski², Aaron Hansbury², Christian Hampp¹, Sarah Dutcher², Sruthi Adimadhyam², Sengwee Toh²
¹ Division of Epidemiology, CDER, FDA, Silver Spring, MD

² Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA

ICPE ALL ACCESS September 16-17, 2020

INTRODUCTION

- Observational studies investigating the safety and effectiveness of drugs may use
 - Incident new users to control the potential impact from variation of historical drug exposure in the causal pathway and improve the baseline comparability of the study population
 - May have limited sample size/statistical power^a
 - Prevalent new users to improve statistical power and generalizability
 - May compromise internal validity due to failure to account for differences in characteristics among different types of new users
- The impact of including prevalent new users to evaluate the safety and effectiveness of oral anti-hyperglycemic agents is not well understood

OBJECTIVE

- To identify factors related to SGLT2i dispensing among naïve, incident, and prevalent new users

Design: A retrospective descriptive study

Data Sources:

- Sentinel System-- electronic health care data for primarily commercially-insured patients from 8 data partners

Study Population and inclusion/exclusion:

- Type II diabetes patients of all ages, with
 - At least one dispensing of either one of the SGLT2i (canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin) or DPP4i (alogliptin, linagliptin, saxagliptin, and sitagliptin) between 2013-2018
 - Continuous data in 365 days prior to the date of the first dispensing of interest
- Excluded patients with
 - Diagnosis of Type I diabetes, gestational diabetes, or secondary diabetes mellitus
 - A claim for a nursing home, skilled nursing facility, hospice, or inpatient stay on date of first dispensing

METHODS

Eligible patients were classified as (Baseline user categories):

- Naïve users if they had no dispensing of any non-metformin antihyperglycemic agent (AHA) in the prior 365 days
- Incident new users: no baseline use of both SGLT2i and DPP4i
- Prevalent new users: free of the cohort-defining drugs at baseline

Factors potentially related to AHA dispensing of interest:

- Demographics (age, sex, race)
- Baseline Adapted Diabetes Complications and Severity Index (aDCSI)^{b,c,d} conditions
- Baseline medication use
- Baseline comorbidities

Statistical Analysis:

- Exploratory Data analysis: proportions of users by factors potentially related to AHA dispensing and user categories
- Site-adjusted and multivariable-adjusted logistic regression modeling analysis

RESULTS

Of the 427,307 SGLT2i prevalent users, 27% had baseline DPP4i and 22% were naïve users. Of the 758,232 DPP4i prevalent users, 5% had baseline SGLT2i and 37% were naïve users

SGLT2i initiators were more likely than the DPP4i users to have baseline AHA use in both the prevalent new users and incident new users except for sulfonylureas

Among all user categories, SGLT2i initiators were less likely to have aDCSI related medical conditions than the DPP4i users

Table 1. Baseline characteristics among SGLT2i and DPP4i users by baseline user category, March 1st, 2013 - December 31st, 2018, the Sentinel System

Characteristics	Prevalent New Users		Incident New Users		Naïve Users	
	SGLT2i (N=427,307)	DPP4i (N=758,232)	SGLT2i (N=313,900)	DPP4i (N=723,705)	SGLT2i (N=93,369)	DPP4i (N=280,694)
Age (years)	62.9 (10.1)	68.5 (11.1)	62.1b(10.0)	68.7 (11.1)	60.9 (10.2)	67.8 (11.4)
Sex ^c						
Female	200,087 (46.8)	401,486 (53.0)	145,825 (46.5)	383,568 (53.0)	43,363 (46.4)	149,625 (53.3)
Male	227,211 (53.2)	356,729 (47.0)	168,068 (53.5)	340,120 (47.0)	50,005 (53.6)	131,062 (46.7)
Race ^c						
Caucasian	211,822 (49.6)	447,376 (59.0)	151,521 (48.3)	429,834 (59.4)	40,546 (43.4)	161,943 (57.7)
African American	27,033 (6.3)	78,895 (10.4)	19,370 (6.2)	76,680 (10.6)	4,780 (5.1)	26,420 (9.4)
Hispanic	11,165 (2.6)	29,504 (3.9)	7,250 (2.3)	28,498 (3.9)	1,711 (1.8)	9,015 (3.2)
Asian	10,043 (2.4)	26,185 (3.5)	5,646 (1.8)	25,266 (3.5)	1,672 (1.8)	9,223 (3.3)
aDCSI Score ^c	1.5 (1.7)	2.1 (2.0)	1.5 (1.7)	2.1 (2.0)	1.1 (1.4)	1.8 (1.9)
aDCSI Abnormality Conditions						
Cardiovascular	No 276,356 (64.7)	423,655 (55.9)	205,942 (65.6)	401,537 (55.5)	65,887 (70.6)	165,196 (58.9)
Some	84,651 (19.8)	163,801 (21.6)	60,272 (19.2)	156,965 (21.7)	15,451 (16.5)	55,885 (19.9)
Severe	66,300 (15.5)	170,776 (22.5)	47,686 (15.2)	165,203 (22.8)	12,031 (12.9)	59,613 (21.2)
Cerebrovascular	No 387,834 (90.8)	654,263 (86.3)	286,308 (91.2)	623,214 (86.1)	86,203 (92.3)	244,380 (87.1)
Some	3,608 (0.8)	8,643 (1.1)	2,554 (0.8)	8,346 (1.2)	700 (0.7)	3,260 (1.2)
Severe	35,865 (8.4)	95,326 (12.6)	25,038 (8.0)	92,145 (12.7)	6,466 (6.9)	33,054 (11.8)
Metabolic	No 422,283 (98.8)	748,303 (98.7)	310,309 (98.9)	714,215 (98.7)	92,610 (99.2)	278,046 (99.1)
Severe	5,024 (1.2)	9,929 (1.3)	3,591 (1.1)	9,490 (1.3)	759 (0.8)	2,648 (0.9)
Nephropathy	No 365,088 (85.4)	542,632 (71.6)	271,934 (86.6)	514,215 (71.1)	85,180 (91.2)	214,020 (76.2)
Some	7,175 (1.7)	11,608 (1.5)	5,026 (1.6)	11,233 (1.6)	719 (0.8)	3,059 (1.1)
Severe	55,044 (12.9)	203,992 (26.9)	36,940 (11.8)	198,257 (27.4)	7,470 (8.0)	63,615 (22.7)
Neuropathy	No 308,793 (72.3)	544,863 (71.9)	228,329 (72.7)	520,465 (71.9)	76,076 (81.5)	218,409 (77.8)
Some	118,514 (27.7)	213,369 (28.1)	85,571 (27.3)	203,240 (28.1)	17,293 (18.5)	62,285 (22.2)
Peripheral Vascular	No 393,048 (92)	679,328 (89.6)	289,822 (92.3)	647,923 (89.5)	88,080 (94.3)	256,788 (91.5)
Some	25,892 (6.1)	61,958 (8.2)	17,836 (5.7)	59,797 (8.3)	3,975 (4.3)	18,811 (6.7)
Severe	8,367 (2.0)	16,946 (2.2)	6,242 (2.0)	15,985 (2.2)	1,314 (1.4)	5,095 (1.8)
Retinopathy	No 363,619 (85.1)	636,804 (84.0)	268,761 (85.6)	607,572 (84.0)	85,247 (91.3)	248,535 (88.5)
Some	53,255 (12.5)	95,953 (12.7)	37,698 (12.0)	91,479 (12.6)	6,591 (7.1)	25,168 (9.0)
Severe	10,433 (2.4)	25,475 (3.4)	7,441 (2.4)	24,654 (3.4)	1,531 (1.6)	6,991 (2.5)
Baseline Anti-Hyperglycemic Agents Use during the 365 Day Prior to the First Eligible Dispensing						
Metformin	342,143 (80.1)	549,514 (72.5)	253,643 (80.8)	521,866 (72.1)	76,553 (82.0)	205,857 (73.3)
Thiazolidinediones	45,438 (10.6)	60,722 (8.0)	30,714 (9.8)	57,162 (7.9)	---	---
Sulfonylureas	193,228 (45.2)	348,111 (45.9)	130,591 (41.6)	331,944 (45.9)	---	---
Alpha Glucosidase Inhibitors	3,524 (0.8)	4,627 (0.6)	2,004 (0.6)	4,338 (0.6)	---	---
Meglitinides	8,552 (2.0)	13,528 (1.8)	5,153 (1.6)	12,812 (1.8)	---	---
Glucagon-like peptide-1 agonists	75,467 (17.7)	32,912 (4.3)	62,421 (19.9)	27,820 (3.8)	---	---
Short/Rapid Acting Insulins	50,052 (11.7)	53,979 (7.1)	41,636 (13.3)	51,082 (7.1)	---	---
Long/ and Short Acting Insulin Combinations	13,507 (3.2)	16,874 (2.2)	11,047 (3.5)	15,981 (2.2)	---	---

Table 2. Site-adjusted and multivariable-adjusted odds ratios and 95% confidence intervals between baseline AHA use and initiation of SGLT2i vs DPP4i by user category, March 1st, 2013 - December 31st, 2018, the Sentinel System

Characteristic	Prevalent New User		Incident New User		Naïve User	
	Site adjusted	Multivariable adjusted	Site adjusted	Multivariable adjusted	Site adjusted	Multivariable adjusted
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Baseline Anti-Hyperglycemic Agent Class						
Metformin	1.45 (1.44, 1.46)	--	1.53 (1.52, 1.55)	--	1.60 (1.57, 1.63)	--
Thiazolidinediones	1.39 (1.38, 1.41)	1.17 (1.14, 1.21)	1.30 (1.28, 1.32)	1.17 (1.14, 1.21)	--	--
Sulfonylureas	1.02 (1.02, 1.03)	0.81 (0.79, 0.83)	0.89 (0.88, 0.90)	0.81 (0.79, 0.83)	--	--
Alpha Glucosidase Inhibitors	1.50 (1.43, 1.56)	1.16 (1.09, 1.24)	1.20 (1.13, 1.26)	1.16 (1.09, 1.24)	--	--
Meglitinides	1.24 (1.20, 1.27)	1.09 (1.04, 1.14)	1.04 (1.00, 1.07)	1.09 (1.04, 1.14)	--	--
Glucagon-like peptide-1 agonists	4.40 (4.34, 4.46)	3.83 (3.73, 3.94)	5.76 (5.68, 5.85)	3.83 (3.73, 3.94)	--	--
Short/Rapid Acting Insulins	1.87 (1.85, 1.90)	1.49 (1.45, 1.54)	2.23 (2.20, 2.27)	1.49 (1.45, 1.53)	--	--
Long and Short Acting Insulin	1.56 (1.53, 1.60)	1.53 (1.47, 1.58)	1.80 (1.75, 1.84)	1.52 (1.47, 1.58)	--	--
Long/Intermediate Acting Insulins	1.89 (1.88, 1.91)	1.37 (1.33, 1.40)	2.16 (2.14, 2.18)	1.37 (1.33, 1.40)	--	--
Number of Classes of Non-metformin Anti-Hyperglycemic Agent Used in the Past 365 Days by Prior Metformin Use at Baseline						
Mean	With metformin	1.80 (1.79, 1.80)	---	1.55 (1.54, 1.56)	---	---
	Without metformin	1.87 (1.86, 1.89)	---	1.58 (1.56, 1.60)	---	---
Count	0	1.00	1.00	1.00	1.00	---
	1 without metformin	1.50 (1.46, 1.53)	1.27 (1.23, 1.32)	1.18 (1.15, 1.21)	1.27 (1.23, 1.32)	---
	2-3 without metformin	4.11 (4.02, 4.21)	1.60 (1.51, 1.70)	2.69 (2.63, 2.76)	1.60 (1.51, 1.70)	---
	4+ without metformin	9.90 (9.35, 10.48)	1.40 (1.22, 1.60)	5.11 (4.71, 5.55)	1.39 (1.22, 1.59)	---
	0 with metformin	1.60 (1.57, 1.63)	1.28 (1.25, 1.31)	1.59 (1.56, 1.62)	1.28 (1.25, 1.30)	1.60 (1.57, 1.63)
	1 with metformin	2.27 (2.23, 2.32)	1.68 (1.62, 1.73)	1.91 (1.88, 1.95)	1.68 (1.62, 1.73)	---
	2-3 with metformin	6.14 (6.02, 6.26)	2.08 (1.96, 2.20)	4.30 (4.22, 4.39)	2.08 (1.96, 2.20)	---
	4+ with metformin	12.35 (11.87, 12.84)	1.87 (1.67, 2.09)	8.98 (8.52, 9.47)	1.87 (1.67, 2.09)	---

Table 3. Site-adjusted and multivariable-adjusted odds ratios and 95% confidence intervals between baseline aDCSI conditions and initiation of SGLT2i vs DPP4i by user category, March 1st, 2013 - December 31st, 2018, the Sentinel System

Characteristic	Prevalent New User		Incident New User		Naïve User		
	Site adjusted	Multivariable adjusted	Site adjusted	Multivariable adjusted	Site adjusted	Multivariable adjusted	
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	
Conditions							
Cardiovascular	No	1.00	1.00	1.00	1.00	1.00	
	Some	0.94 (0.93, 0.95)	1.00 (0.98, 1.02)	0.92 (0.91, 0.93)	1.00 (0.98, 1.02)	0.88 (0.86, 0.90)	1.02 (0.99, 1.05)
	Severe	0.72 (0.71, 0.73)	1.00 (0.97, 1.02)	0.71 (0.70, 0.72)	1.00 (0.97, 1.02)	0.67 (0.65, 0.69)	0.97 (0.93, 1.01)
Cerebrovascular	No	1.00	1.00	1.00	1.00	1.00	
	Some	0.81 (0.77, 0.84)	0.97 (0.91, 1.04)	0.78 (0.75, 0.82)	0.97 (0.91, 1.04)	0.74 (0.68, 0.81)	0.91 (0.80, 1.02)
	Severe	0.74 (0.73, 0.75)	1.05 (1.02, 1.07)	0.71 (0.70, 0.73)	1.05 (1.02, 1.07)	0.70 (0.68, 0.72)	1.05 (1.01, 1.09)
Metabolic	No	1.00	1.00	1.00	1.00	1.00	
	Some	0.95 (0.91, 0.98)	0.97 (0.93, 1.01)	0.93 (0.89, 0.97)	0.97 (0.93, 1.01)	0.91 (0.84, 0.99)	1.02 (0.93, 1.11)
	Severe	0.92 (0.91, 0.92)	1.00 (0.97, 1.02)	0.92 (0.91, 0.92)	1.00 (0.97, 1.02)	0.88 (0.86, 0.90)	1.02 (0.99, 1.05)
Nephropathy	No	1.00	1.00	1.00	1.00	1.00	
	Some	0.94 (0.91, 0.97)	0.98 (0.94, 1.02)	0.87 (0.84, 0.90)	0.98 (0.94, 1.02)	0.62 (0.57, 0.68)	0.92 (0.84, 1.00)
	Severe	0.46 (0.46, 0.47)	0.52 (0.51, 0.52)	0.42 (0.41, 0.42)	0.52 (0.51, 0.52)	0.36 (0.35, 0.37)	0.51 (0.49, 0.52)
Neuropathy	No	1.00	1.00	1.00	1.00	1.00	
	Some	1.11 (1.10, 1.12)	1.08 (1.06, 1.09)	1.12 (1.11, 1.13)	1.08 (1.07, 1.09)	0.95 (0.93, 0.97)	1.07 (1.05, 1.10)
	Severe	0.97 (0.95, 1.00)	0.97 (0.93, 1.02)	1.02 (0.99, 1.05)	0.97 (0.93, 1.02)	0.91 (0.85, 0.97)	1.02 (0.93, 1.11)
Peripheral Vascular	No	1.00	1.00	1.00	1.00	1.00	
	Some	0.85 (0.83, 0.86)	0.99 (0.97, 1.01)	0.81 (0.79, 0.82)	0.99 (0.97, 1.01)	0.78 (0.75, 0.81)	1.00 (0.96, 1.04)
	Severe	0.97 (0.95, 1.00)	0.97 (0.93, 1.02)	1.02 (0.99, 1.05)	0.97 (0.93, 1.02)	0.91 (0.85, 0.97)	1.02 (0.93, 1.11)
Retinopathy	No	1.00	1.00	1.00	1.00	1.00	
	Some	1.07 (1.06, 1.09)	1.03 (1.01, 1.04)	1.05 (1.04, 1.06)	1.03 (1.01, 1.04)	0.88 (0.86, 0.91)	1.02 (0.99, 1.05)
	Severe	0.81 (0.79, 0.83)	0.90 (0.88, 0.93)	0.79 (0.77, 0.81)	0.90 (0.87, 0.93)	0.76 (0.71, 0.80)	0.95 (0.89, 1.01)
Score							
Mean	0.90 (0.90, 0.90)	---	0.89 (0.88, 0.89)	---	0.85 (0.85, 0.85)	---	
0	1.00	---	1.00	---	1.00	---	
1	1.09 (1.08, 1.11)	---	1.09 (1.07, 1.10)	---	0.98 (0.96, 1.00)	---	
2	0.85 (0.84, 0.86)	---	0.83 (0.82, 0.84)	---	0.73 (0.71, 0.74)	---	
3	0.82 (0.80, 0.83)	---	0.79 (0.78, 0.80)	---	0.67 (0.65, 0.69)	---	
4	0.65 (0.64, 0.66)	---	0.61 (0.60, 0.6				