FDA U.S. FOOD & DRUG ADMINISTRATION

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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

•Of the 427,307 SGLT2i prevalent users, 27% had baseline DPP4i and 22% were naïve users. •SGLT2i initiators were more likely than the DPP4i users to have baseline AHA use in both Of the 758,232 DPP4i prevalent users, 5% had baseline SGLT2i and 37% were naïve users the prevalent new users and incident new users except for sulfonylureas

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	DPP4i	SGLT2i	DPP4i	SGLT2i	DPP4i									
		(N=427, 307) Mean(SD)/N(%)	(N=756,252) Mean(SD)/N(%)	(N=313,900) Mean(SD)/N (%)	(N=723,703) Mean (SD)/N(%)	(N=95,509) Mean(SD)/N(%)	(N=280,094) Mean(SD)/N(%)	Characteristic		Prevaler	nt New User	Incide	nt New User	Nai	ive User	
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)			Site adjusted	Multivariable adjusted	Site adjusted	Multivariable adjusted	Site adjusted	Multivariable adjusted	
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)			OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Sex	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)	Baseline Anti-Hyperglycemic Agent		Class					
Race*	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)	Metfo	ormin	1.45 (1.44, 1.46)		1.53 (1.52, 1.55)		1.60 (1.57, 1.63)	
	African A	merican	27,033 (6.3)	78,895 (10.4)	19,370 (6.2)	76,680 (10.6)	4,780 (5.1)	26,420 (9.4)	Thiaz	olidinediones	1.39 (1.38, 1.41)	1.17 (1.14, 1.21)	1.30 (1.28, 1.32)	1.17 (1.14, 1.21)		
	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)	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)		
	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)	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)		
aDCSI Score**		1.5 (1.7)	2.1 (2.0)	1.5 (1.7)	2.1 (2.0)	1.1 (1.4)	1.8 (1.9)	Meglit	tinides	1.24 (1.20, 1.27)	1.09 (1.04, 1.14)	1.04 (1.00, 1.07)	1.09 (1.04, 1.14)			
aDCSI A	Abnormality	Conditions							Gluca	gon-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)		
		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)	Short/R	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)		
Cardiovas	ascular	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)	Long a	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)		
		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)	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)		
]	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)	Number	of Classes of Non-motformin	in Anti Humanalwaamia Agant Haad in the Dest 265 Dess her Drier Mattermin Haa at Deseling					
Cerebro	vascular	Some	3,608 (0.8)	8,643 (1.1)	2,554 (0.8)	8,346 (1.2)	700 (0.7)	3,260 (1.2)	Number	r of Classes of Non-mettorinin		gent Used in the Past 50:	5 Days by Prior Metion	rinni Use at Dasenne	F	1
		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)	Mean	With metformin	1.80 (1.79, 1.80)		1.55 (1.54, 1.56)			
Metabol	ic	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)		Without metformin	1.87 (1.86, 1.89)		1.58 (1.56, 1.60)			
		Severe	5,024 (1.2)	9,929 (1.3)	3,591 (1.1)	9,490 (1.3)	759 (0.8)	2,648 (0.9)		0			1.00			
	1	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)		1 without motformin	1.00	1.00		1.00		
Nephrop	pathy	Some	7,175 (1.7)	11,608 (1.5)	5,026 (1.6)	11,233 (1.6)	719 (0.8)	3,059 (1.1)))))))	1 without metrorium						
		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)		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)		
Neurona	thy	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)		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)		
ittenope	ltilly	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)		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)	1.28 (1.25, 1.30)
Dorinhou		No	393,048 (92)	679,328 (89.6)	289,822 (92.3)	647,923 (89.5)	88,080 (94.3)	256,788 (91.5)		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)		
Vascular	r	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)			6 14 (6 02 6 26)	2.08(1.06, 2.20)		2.08(1.06, 2.20)	-	
		Severe	8,367 (2.0)	16,946 (2.2)	6,242 (2.0)	15,985 (2.2)	1,314 s(1.4)	5,095 (1.8)		2-3 with metformin		2.08 (1.90, 2.20)	4.30 (4.22, 4.39)	2.08 (1.90, 2.20)		
]	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)		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)		
Retinopa	athy	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 s(1.6)	6,991 (2.5)								
Baseline	Anti-Hyper	rglycemic Agents Use during th	he 365 Day Prior to the	e First Eligible Dispen	nsing											
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)											
ShortRapid 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)											

CONCLUSIONS

- Baseline characteristic imbalances between SGLT2i and DPP4 initiators varied between naïve, incident, and prevalent new users
- Factors related to the choice of SGLT2i over DPP4i differ substantially between naïve users and the other users. Among incident new users and prevalent new users, the prior non metformin AHA use played an important role in the choice of SGLT2i over DPP4i
- Proper design and analytic approaches addressing these imbalances and important factors require consideration in epidemiologic studies including prevalent new users

Factors related to sodium glucose cotransporter 2 inhibitor (SGLT2i) and dipeptidyl peptidase 4 inhibitor (DPP4i) dispensing among naïve, incident, and prevalent new users

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Design: A retrospective descriptive study

Data Sources:

- Sentinel System-- electronic health care data for primarily comme 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 (canaglif) empagliflozin, and ertugliflozin) or DPP4i (alogliptin, linaglipt sitagliptin) between 2013-2018
 - Continuous data in 365 days prior to the date of the first disp
- Excluded patients with
 - Diagnosis of Type I diabetes, gestational diabetes, or second
 - A claim for a nursing home, skilled nursing facility, hospice, first dispensing

RESULTS

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

- 2018.2013.

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MET	HODS						
	Eligible patients were classified as (Base						
ercially-insured patients from	 Naïve users if they had no dispensing the prior 365 days 						
	 Incident new users: no baseline use of 						
	 Prevalent new users: free of the coho 						
	Factors potentially related to AHA dispe						
lozin, dapagliflozin, tin, saxagliptin, and	 Demographics (age, sex, race) 						
	Baseline Adapted Diabetes Complication						
pensing of interest	 Baseline medication use 						
	 Baseline comorbidities 						
lary diabetes mellitus	Statistical Analysis:						
or inpatient stay on date of	 Exploratory Data analysis: proportion dispensing and user categories 						

medical conditions than the DPP4i users

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

		Preval	ent New User	Incid	ent New User	Naïve User			
Characteristic		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									
	No	1.00	1.00	1.00	1.00	1.00	1.00		
Cardiovascular	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)		
	No	1.00	1.00	1.00	1.00	1.00	1.00		
Cerebrovascular	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)		
Matabalia	No	1.00	1.00	1.00	1.00	1.00	1.00		
Metabolic	Severe	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)		
	No	1.00	1.00	1.00	1.00	1.00	1.00		
Nephropathy	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)		
Nouropathy	No	1.00	1.00	1.00	1.00	1.00	1.00		
neuropauly	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)		
Doninhanal	No	1.00	1.00	1.00	1.00	1.00	1.00		
Veccular	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)		
vasculai	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)		
	No	1.00	1.00	1.00	1.00	1.00	1.00		
Retinopathy	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, 0.62)		0.51(0.49, 0.53)			
5+		0.55 (0.54, 0.56)		0.51 (0.50, 0.52)		0.40 (0.38, 0.41)			
Complication Counts									
Mean		0.89 (0.88, 0.89)		0.87 (0.87, 0.87)		0.81 (0.80, 0.81)			
0		1.00		1.00		1.00			
1		0.94 (0.93, 0.95)		0.93 (0.92, 0.94)		0.84 (0.83, 0.86)			
2		0.81 (0.80, 0.82)		$0.78 \ (0.77, \ 0.79)$		0.66 (0.64, 0.67)			
3		0.69 (0.68, 0.70)		0.66 (0.65, 0.67)		0.53 (0.51, 0.55)			
4		0.62 (0.61, 0.63)		0.58 (0.56, 0.59)		0.43 (0.41, 0.46)			
5+		0.53 (0.52, 0.55)		0.49 (0.47, 0.50)		0.31 (0.28, 0.35)			
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REFERENCES

FDA. Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data, available at https://www.fda.gov/downloads/drugs/guidances/ucm243537.pdf, retrieved on July 17,

Chang HY, Weiner JP, Richards TM, et al, Validating the adapted Diabetes Complications Severity Index in claims data. Am J Manag Care. 2012;18(11):721-726. c. Young BA, Lin E, Von Korff, et al, Diabetes complication severity index and risk of mortality,

hospitalization, and healthcare utilization. Am J Manag Care. 2008;14(1):15-23 Wicke FS, Glushan A, Schubert I, et al, Performance of the adapted diabetes complications severity index translated to ICD-10. Am J Manag Care. 2019;25(2):e45-e49





eline user categories):

g of any non-metformin antihyperglycemic agent (AHA) in

of both SGLT2i and DPP4i ort-defining drugs at baseline ensing of interest:

tions and Severity Index (aDCSI) ^{b,c.d} conditions

ns of users by factors potentially related to AHA

Site-adjusted and multivariable-adjusted logistic regression modeling analysis

•Among all user categories, SGLT2i initiators were less likely to have aDCSI related

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DISCLAIMER

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