Glycemic Outcomes of Second-Line Diabetes Drug Choice in a Real-World Population

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Abstract

Hypoglycemia and acute metabolic complications (AMCs; ketoacidosis, hyperosmolarity, and coma) are glycemic outcomes that have high cost and high morbidity; these outcomes must be taken into consideration when choosing initial second-line therapy after metformin. We conducted a retrospective cohort study analyzing national administrative data from adults with type 2 diabetes mellitus who started a second-line diabetes medication (sulfonylureas [SFUs], thiazolidinediones [TZDs], glucagon-like peptide 1 [GLP-1] agonists, dipeptidyl peptidase 4 [DPP-4] inhibitors, basal insulin, or sodium-glucose contransporter 2 [SGLT-2] inhibitors) between April 1, 2011 and September 30, 2015 (N=43,288) and compared rates of hypoglycemia and AMCs. Most patients (24,506 [56.6%]) were prescribed sulfonylurea as second-line treatment, followed by DPP-4 inhibitors (7953 [18.4%]), GLP-1 agonists (3854 [8.9%]), basal insulin (2542 [5.9%]), SGLT-2 inhibitors (2537 [5.9%), and TZDs (1896 [4.4%]). Baseline rates of hypoglycemia varied more than 5-fold across initial second-line antidiabetic medication classes, and rates of AMCs varied 7-fold. Compared with patients taking an SFU, lower adjusted rates of hypoglycemia were associated with taking a DPP-4 inhibitor (63% lower rate; incidence rate ratio [IRR], 0.37; 95% CI, 0.25 to 0.57), SGLT-2 inhibitor (54% lower; IRR, 0.46; 95% CI, 0.22 to 0.94), or TZD (79% lower; IRR, 0.21; 95% CI, 0.08 to 0.56) but not a glucagon-like peptide 1 agonist or basal insulin. For AMCs, only initiation of a DPP-4 inhibitor (43% lower rate; IRR, 0.57; 95% CI, 0.41 to 0.81) was associated with a lower adjusted rate compared with SFU. Use of SGLT-2 inhibitors was not associated with a substantially increased rate of acute metabolic complications compared with SFU. Special attention still needs to be paid to glycemic outcomes when choosing a second-line diabetes therapy following metformin.

Most patients with type 2 diabetes mellitus (DM) eventually require additional medication after initial treatment with metformin, and several of the available choices have the potential to cause adverse glycemic events.[1] With at least 7 classes of medications available as initial second-line therapy, clinicians must balance the effectiveness, cost, and availability of these medication choices with the risk for harms. Clinicians must weigh hypoglycemia risk with the risk of acute metabolic complications (AMCs), which include ketoacidosis, hyperosmolarity, and coma. Rates of hypoglycemia have increased and are of particular concern

among older adults and those with multiple comorbidities.[2] In addition, sodium-glucose cotransporter 2 (SGLT-2) inhibitors specifically have been associated with ketoacidosis.[3] Because these complications confer high short-term mortality,[4,5] even modest differences in risk can have important implications for appropriate medication selection in clinical practice. Not surprisingly, there is interest from national stakeholders to develop quality metrics for monitoring hypoglycemia and AMCs as a means to improve patient safety.

Although clinical trials provide data on hypoglycemia and AMCs under controlled conditions, there is limited information about the

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magnitude of these risks under real-world conditions and on a population scale. The objective of this study was to compare rates of hypoglycemia and AMCs among adult patients taking metformin who subsequently initiate a second antidiabetic medication (sulfonylureas [SFUs] or meglitinides, thiazolidinediones [TZDs], basal insulin, glucagon-like peptide 1 [GLP-1] agonists, dipeptidyl peptidase 4 (DPP-4) inhibitors, and SGLT-2 inhibitors).

PATIENTS AND METHODS

We conducted a retrospective cohort study analyzing national administrative data, including health plan enrollment files, pharmacy claims, medical claims, and laboratory claims from a large commercial health insurer. We included adults with type 2 DM who had (1) at least 6 months of continuous enrollment in a Medicare Advantage or commercial health plan, (2) evidence of only metformin pharmacy claims during their insurance enrollment, and (3) evidence of a new start of a second-line DM medication (SFU, TZD, GLP-1 agonist, DPP-4 inhibitor, basal insulin, or SGLT-2 inhibitor), with an index date between April 1, 2011 and September 30, 2015. Patients were considered to have DM on the basis of their prescription claims for both metformin and a new second-line DM medication (and no additional third agent for 6 months), in addition to one or more medical encounters with a DM-related *International Classification of Diseases, Ninth Revision* (*ICD-9*) code occurring on or before the index date for the new medication drug start, similar to definitions we have utilized previously.[6,7] As done previously, we also excluded patients with *ICD-9* codes for type 1 diabetes, pregnancy, or secondary diabetes. We conducted 2 separate analyses of the outcomes of interest (ie, hypoglycemia and AMCs) for the year after starting the index drug. Hypoglycemic events were defined using the following *ICD-9* diagnosis codes: 251.0, 251.1, 251.2, and 962.3, adapted from Ginde et al.[8] Acute metabolic complications were defined using *ICD-9* codes 250.2X, 250.1X, and 250.3X (250.XX = DM), adapted from our previous work.[4] Covariates included age, race, year of drug initiation, hemoglobin A_{1c} levels, geographic region, health

care professional type, receipt of DM education, hospitalization in the year prior to the new drug, insurance type, previous occurrence of the outcome of interest, and a modified diabetes complications severity index score,[9] which we adapted slightly to remove outcomes of interest to avoid overadjustment (for a full list of codes, see the Supplemental Appendix [available online at http://mcpiqojournal.org]).

We used χ^2 tests to examine bivariate associations between baseline patient characteristics and index medication class. Because of low event rates, multivariable, zero-inflated Poisson regression models were used to assess the association between index medication class and each of the 2 outcomes while adjusting for all covariates listed previously. Sulfonylureas served as the reference group because they are the most commonly prescribed second-line antidiabetic medications.[6] Statistical analyses were conducted using SAS statistical software, version 9.4 (SAS Institute). Because the data were nonidentifiable, the Northwestern University Institutional Review Board judged this study to not be human subjects research.

RESULTS

We included a total of 43,288 patients in this study. Table 1 summarizes patient characteristics stratified by second-line medication class. Statistically significant differences between groups were noted in every category (*P*<.0001). See Supplemental Table 1 for adjusted event rates (available online at http://mcpiqojournal.org). Most patients (24,506 [56.6%]) were prescribed SFU as their second-line agent, followed by DPP-4 inhibitors (7953 [18.4%]), basal insulin (2542 [5.9%]), SGLT-2 inhibitors (2537 [5.9%]), and TZDs (1896 [4.4%]). Baseline rates of hypoglycemia varied more than 5-fold across initial second-line antidiabetic medication classes, and rates of AMCs varied 7-fold. Second-line DM drug choice differed by prescriber type, although the most common prescriber specialty for all drug classes was family practice (34.6% [1333 of 3854] for GLP-1 to 53.5% [1015 of 1896] for TZD). Sulfonylureas were the most commonly selected drug class among all prescriber types except endocrinologists, who most often prescribed GLP-1

TABLE 1. Preexposure Patient, Prescriber, and Health Plan Characteristics Among the 43,288 Study Patients[a,b]

Variable	DPP-4 (n=7953)	GLP-1 (n=3854)	Basal insulin (n=2542)	SGLT-2 (n=2537)	SFU (n=24,506)	TZD (n=1896)
Hypoglycemia rate per 1000 person-years[c]	6.6	35.2	10.8	11.3	7.0	7.8
Metabolic complication rate per 1000 person-years[c]	15.6	8.4	44.7	6.4	11.4	14.1
Sex (%)[d]						
Female	3296 (41.4)	2330 (60.5)	1144 (45)	1052 (41.5)	9626 (39.3)	679 (35.8)
Male	4657 (58.6)	1524 (39.5)	1398 (55)	1485 (58.5)	14880 (60.7)	1217 (64.2)
Age (y)[d]						
18-34	130 (1.6)	191 (5.0)	76 (3.0)	81 (3.2)	466 (1.9)	23 (1.2)
35-44	726 (9.1)	625 (16.2)	282 (11.0)	367 (14.5)	2235 (9.1)	155 (8.2)
45-54	1990 (25.0)	1243 (32.2)	680 (26.8)	867 (34.2)	6087 (24.8)	445 (23.5)
55-64	3053 (38.4)	1341 (34.8)	899 (35.4)	1008 (39.8)	8403 (34.3)	623 (32.9)
65-74	1520 (19.1)	394 (10.2)	415 (16.3)	198 (7.8)	4877 (19.9)	424 (22.4)
≥75	534 (6.7)	60 (1.6)	190 (7.5)	16 (0.6)	2438 (10.0)	226 (11.9)
Race/ethnicity[d]						
Black	769 (9.7)	369 (9.6)	326 (12.8)	257 (10.1)	2519 (10.3)	120 (6.3)
Hispanic	1152 (14.5)	429 (11.1)	399 (15.7)	329 (13.0)	4210 (17.2)	389 (20.5)
Unknown	968 (12.1)	260 (6.8)	214 (8.4)	189 (7.5)	2593 (10.5)	237 (12.5)
White	5064 (63.7)	2796 (72.6)	1603 (63.1)	1762 (69.5)	15,186 (62.0)	1150 (60.7)
HbA$_{1c}$ (%)[d]						
Not available[e]	4784 (60.2)	2428 (63)	1850 (72.8)	1270 (50.1)	16,814 (68.6)	1265 (66.7)
<8	1240 (15.6)	843 (21.9)	139 (5.5)	552 (21.7)	2402 (9.8)	290 (15.3)
8-10	1325 (16.6)	382 (9.9)	181 (7.1)	451 (17.8)	3193 (13.0)	224 (11.8)
≥10	604 (7.6)	201 (5.2)	372 (14.6)	264 (10.4)	2098 (8.6)	117 (6.2)
DCSI score[d,f]						
0	4855 (61.1)	2555 (66.3)	1538 (60.5)	1615 (63.6)	15,495 (63.2)	1212 (64.0)
1	1379 (17.3)	706 (18.3)	418 (16.5)	462 (18.2)	3997 (16.3)	320 (16.8)
2-3	1287 (16.2)	496 (12.9)	435 (17.1)	369 (14.5)	3789 (15.5)	280 (14.8)
≥4	432 (5.4)	98 (2.5)	150 (5.9)	92 (3.6)	1225 (5)	84 (4.4)
Diabetes education[d]	236 (3.0)	267 (6.9)	104 (4.1)	77 (3.0)	605 (2.5)	46 (2.4)
Insurance[d]						
Commercial	7020 (88.3)	3700 (96)	2151 (84.6)	2509 (98.9)	19,980 (81.5)	1503 (79.3)
Medicare	933 (11.7)	154 (4)	391 (15.4)	28 (1.1)	4526 (18.5)	393 (20.7)
Plan type[d]						
EPO	641 (8.1)	359 (9.3)	242 (9.5)	258 (10.2)	1919 (7.83)	143 (7.54)
HMO	2161 (27.2)	638 (17.0)	733 (28.9)	329 (13.0)	7624 (31.1)	643 (33.9)
Indemnity	84 (1.1)	15 (0.4)	32 (1.3)	16 (0.6)	297 (1.2)	21 (1.1)
Other	359 (4.5)	179 (4.6)	72 (2.8)	78 (3.1)	723 (3.0)	50 (2.6)
POS	4542 (57.1)	2574 (66.8)	1409 (55.4)	1812 (71.4)	13,412 (54.7)	987 (52.1)
PPO	166 (2.1)	89 (2.3)	54 (2.1)	44 (1.7)	532 (2.2)	52 (2.7)

TABLE 1. Continued

Variable	DPP-4 (n=7953)	GLP-1 (n=3854)	Basal insulin (n=2542)	SGLT-2 (n=2537)	SFU (n=24,506)	TZD (n=1896)
Prescriber type[d]						
Endocrinologist	543 (6.8)	797 (20.7)	152 (6.0)	226 (8.9)	765 (3.1)	53 (2.8)
Family practice	3353 (42.2)	1333 (34.6)	1122 (44.1)	1135 (44.7)	11,449 (46.7)	1015 (53.5)
General/internal medicine	2761 (34.7)	980 (25.4)	752 (29.6)	680 (26.8)	8097 (33.0)	527 (27.8)
Nurse/PA	574 (7.2)	401 (10.4)	195 (7.7)	274 (10.8)	1632 (6.7)	117 (6.2)
Other/missing	722 (9.1)	343 (9.0)	321 (12.6)	222 (8.8)	2566 (10.5)	184 (9.7)

[a]DCSI, Diabetes Complications Severity Index; DPP-4, dipeptidyl peptidase 4 inhibitors; EPO, exclusive provider organization; GLP-1, glucagon-like peptide 1 agonists; HbA$_{1c}$, hemoglobin A$_{1c}$; HMO, health maintenance organization; PA, physician assistant; POS, point of service; PPO, preferred provider organization; SFU, sulfonylureas or meglitinides; SGLT-2, sodium-glucose cotransporter 2 inhibitors; TZD, thiazolidinediones.

[b]Data are presented as No. (percentage) of patients unless indicated otherwise.

[c]Event rates observed prior to index date (date of first pharmacy fill of second-line medication).

[d]$P<.0001$.

[e]Laboratory values are not routinely available in health plan administrative data sources unless submitted by the laboratory vendor as part of their contract with the health payer; because of the potential for a relationship between baseline HbA$_{1c}$ and both hypoglycemia and AMCs, we included an HbA$_{1c}$ result if available, in addition to the DCSI and other surrogate markers for baseline diabetes severity for all patients.

[f]Adapted composite score (index severity score 0-3) of 6 complications: retinopathy, nephropathy, neuropathy, cerebrovascular, cardiovascular, peripheral vascular disease.

agonists. Interestingly, encounters for diabetes education were infrequent (2.4% [46 of 1896] for TZD to 6.9% [267 of 3854] for GLP-1 across groups), similar to previous reports.[10]

Table 2 summarizes adjusted incidence rate ratios (IRRs) for both outcomes, hypoglycemia and AMCs. Compared with patients taking an SFU, lower adjusted rates of hypoglycemia were associated with taking a DPP-4 inhibitor (63% lower rate; IRR, 0.37 [95% CI, 0.25 to 0.57]), SGLT-2 inhibitor (54% lower; IRR, 0.46 [95% CI, 0.22 to 0.94]), or TZD (79% lower; IRR, 0.21 [95% CI, 0.08 to 0.56]) but not a GLP-1 agonist or basal insulin. For AMCs, only initiation of a DPP-4 inhibitor (43% lower rate; IRR, 0.57 [95% CI, 0.41 to 0.81]) was associated with a lower adjusted rate compared with SFU. Taking an SGLT-2 inhibitor was not associated with a significantly increased rate of AMCs compared with SFU ($P=.35$).

History of previous hypoglycemia or AMC, increasing diabetes complications severity index score, or any hospitalization in the previous year were associated with increased rates of both hypoglycemia and AMC events, independent of medication class. Higher rates of hypoglycemia were associated with an endocrinologist or "other/missing" health care professional prescribing the index drug. Higher AMC rates were associated with a history of diabetes education and enrollment in a non—managed care, fee-for-service (indemnity) health plan. Age, prescription fill year, and baseline hemoglobin A$_{1c}$ level were nonsignificant in either model.

DISCUSSION

Analyzing data from over 43,000 adults with type 2 diabetes who initiated a second-line DM medication following metformin monotherapy, we found low event rates for adverse glycemic outcomes resulting in health care visits. Substantially different rates of hypoglycemia and/or AMCs were observed when patients initiated second-line therapy with alternative DM medication classes, relative to SFUs, which currently remain the most common initial second-line choice after metformin. Compared with SFUs, the initiation of SGLT-2 inhibitors, DPP-4 inhibitors, or TZDs was associated with lower rates of hypoglycemia, whereas initiation of a GLP-1 agonist or basal insulin resulted in comparable rates of hypoglycemia. Because GLP-1 agonists are generally considered to pose a lower risk for hypoglycemia, it was surprising that event rates in real-world practice were not substantially lower than those for SFUs. Prior studies have found that additional hypoglycemia risk is noted when initiating dual therapy with combined new DM agents (ie, metformin plus a new additional agent), which are not thought to present added risk when prescribed separately from metformin[11]; however, our data show clear differences among DM drug classes initiated after metformin.

TABLE 2. Adjusted Incidence Rate Ratios for Hypoglycemia and Acute Metabolic Complications[a]

Variable	Hypoglycemia, IRR (95% CI)	Acute metabolic complications, IRR (95% CI)
Index second-line medication class (referent group, SFU)		
DPP-4	0.37 (0.25-0.57)[b]	0.57 (0.41-0.81)[c]
GLP-1	0.99 (0.70-1.43)	0.75 (0.42-1.34)
Basal insulin	1.36 (0.87-2.11)	1.23 (0.85-1.77)
SGLT-2	0.46 (0.22-0.94)[d]	1.36 (0.71-2.60)
TZD	0.21 (0.08-0.56)[c]	0.83 (0.48-1.43)
Covariates		
History of outcome event	1.50 (1.36-1.67)[b]	1.6 (1.47-1.74)[b]
Race/ethnicity (referent group, White)		
Black	0.87 (0.59-1.29)	0.99 (0.69-1.42)
Hispanic	1.16 (0.83-1.62)	1.59 (1.36-2.24)[c]
Unknown	1.03 (0.70-1.51)	0.93 (0.60-1.43)
DCSI score (referent group, 0)[e]		
1	0.83 (0.56-1.22)	1.40 (1.00-1.95)
2-3	1.61 (1.17-2.21)[c]	2.13 (1.55-2.93)[b]
≥4	1.89 (1.26-2.84)[c]	1.86 (1.26-2.73)[c]
Diabetes education	0.68 (0.87-15.11)	2.10 (1.11-3.97)[d]
Prior hospital admission	2.09 (1.53-2.86)[b]	2.65 (2.00-3.49)[b]
Insurance plan type (referent group, PPO)		
EPO	1.49 (0.66-3.36)	1.76 (0.60-5.19)
HMO	1.44 (0.67-3.11)	1.83 (0.64-5.21)
Indemnity	1.85 (0.61-5.64)	4.49 (1.42-14.18)[c]
Other	3.50 (1.56-7.83)[c]	1.28 (0.35-4.61)
POS	2.23 (1.1-4.51)[d]	2.27 (0.83-6.22)
Prescriber type (referent group, Family Practice)		
Endocrinologist	1.85 (1.22-2.81)[c]	0.62 (0.32-1.21)
Internal medicine	0.92 (0.70-1.21)	1.02 (0.78-1.33)
Nurse/PA	1.40 (0.88-2.21)	0.98 (0.55-1.74)
Other/missing	1.69 (1.23-2.32)[b]	0.74 (0.52-1.07)

[a]DPP-4, dipeptidyl peptidase 4 inhibitors; EPO, exclusive provider organization; GLP-1, glucagon-like peptide 1 agonists; HMO, health maintenance organization; IRR, incident rate ratio; PA, physician assistant; POS, point of service; PPO, preferred provider organization; SGLT-2, sodium-glucose cotransporter 2 inhibitors; TZD, thiazolidinediones.

[b]$P \leq .0001$.

[c]$P \leq .01$.

[d]$P < .05$.

[e]Adapted composite score (index severity score 0-3) of 6 complications: retinopathy, nephropathy, neuropathy, cerebrovascular, cardiovascular, peripheral vascular disease.[9]

Dipeptidyl peptidase 4 inhibitors were associated with fewer AMCs than SFU, whereas prior hospital admission, increased diabetes-related complications, and previous diabetes education were all substantially associated with severe AMCs (ketoacidosis, hyperosmolarity, coma). Interestingly, although the study population comprised patients starting a second-line DM agent, some had underlying comorbidities, including diabetes-related complications, which may have contributed to these poor DM-related outcomes. Sodium-glucose contransporter 2 inhibitors, which in some previous studies have been linked to an increased risk for euglycemic and hyperglycemic diabetic ketoacidosis,[12,13] had no difference in overall metabolic complications in our study, which included episodes of diabetic ketoacidosis in the outcome definition. However, because event rates were generally low and the confidence interval for the IRR comparing SGLT-2

inhibitors to SFUs was wide, this finding requires confirmation.

This was an observational study and has some notable limitations. Even after adjustment for differences in demographic and clinical covariates, it is possible that patients initiating insulin or SFUs may still be at higher risk for AMC events, unrelated to the medication, resulting in residual confounding. For this reason, confirmatory studies are needed for some unanticipated associations, such as the lower rate of AMCs among patients initiating DPP-4 inhibitors. Diabetes education, meant to improve self-efficacy, is designed to minimize AMCs or severe hypoglycemic events, but our analysis revealed low rates of diabetes education and an association with higher rates of adverse glycemic outcomes, suggesting that patients who receive these services are at a higher risk for AMCs, regardless of the second-line medication choice. Diabetes education has been previously reported to be similarly low in other studies.[10,14] However, variable reimbursement for these services and inconsistent use of billing codes (see Supplemental Appendix) may result in estimates of diabetes education services derived from claims data that are lower than actual practice. In addition, there could be residual confounding, specifically confounding by indication, present in our analysis despite adjusting for confounders. This issue is a known limitation of the observational study design, and we have included covariates available in claims data that can account for glycemic control, health care provider, and insurance plan type.

CONCLUSION

Results from this study are important given a paucity of prior real-world evidence on the association of second-line medication choice with subsequent hypoglycemia and AMC events among patients with type 2 DM. Despite recent expansion in the numbers of second-line DM medication alternatives, hyperglycemia and hypoglycemia remain critical issues in DM management. Although infrequent, these episodes are extremely costly and could be deemed partially iatrogenic given that risks for these outcomes are driven partly by choices in medication prescribing. Moreover, because the rates of glycemic complications associated with different second-line agents varied with patient comorbidities in our study, our analysis also underscores the importance of clinical guidelines and quality metrics that allow health care professionals and patients autonomy in selecting the most appropriate medication option based on circumstances unique to each individual.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://mcpiqojournal.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

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