JPHSR Journal of Pharmaceutical Health Services Research

ROYAL PHARMACEUTICAL SOCIETY

Research Paper

JPHS 2020, 11; 395–401

Received April 3, 2020
Accepted June 9, 2020
DOI 10.1111/jphs.12373
ISSN 1759-8885

Health expenditure and health services utilization comparison of patients with type 2 diabetes on sodium–glucose cotransporter-2 inhibitors versus dipeptidyl peptidase-4 inhibitors: evidence from 2015 to 2016 medical expenditure panel survey

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Abstract

Objectives Primary objective of this study was to compare the overall health expenditures of patients with type 2 diabetes on sodium–glucose cotransporter-2 (SGLT2) inhibitors versus dipeptidyl peptidase-4 (DPP4) inhibitors.

Methods Two cohorts of type 2 diabetes patients receiving either SGLT2 inhibitor with metformin or DPP4 inhibitor with metformin were identified from 2015 to 2016 Medical Expenditure Panel Survey (MEPS) data. Propensity score matching was used to balance cohorts based on socio-economic status, insulin utilization status, and the Charlson comorbidity score. Patients in SGLT2 inhibitor cohort were matched with patients in DPP4 inhibitor cohort using 1:2 ratio on the logit of propensity score using caliper width of 0.1 of the standard deviation of the logit of the propensity score. Expenditure variables were analysed using a generalized linear model with log link function and gamma distribution and adjusted for socio-economic variables. Unadjusted means were obtained using bootstrap.

Results After propensity score matching, 240 patients were left in the sample with 80 patients in SGLT2 inhibitor cohort and 160 patients in DPP4 inhibitor cohort. Unadjusted average annual total health expenditure was significantly higher in the SGLT2 inhibitor cohort versus DPP4 inhibitor cohort ($17,325 versus $15,702; P value <0.0001). After adjusting for socio-economic factors, overall health expenditure ($\beta = -0.3516$; $P = 0.0038$) was significantly lower in DPP4 inhibitor cohort compared to SGLT2 inhibitor.

Conclusion SGLT2 inhibitors were associated with significantly higher overall and prescription expenditures compared to DPP4 inhibitors during the study period evaluated. Future studies need to utilize administrative claims data to assess current comparativeness effectiveness trends.

Keywords health expenditures; SGLT2 inhibitors; DPP4 inhibitors; health services research

Introduction

Diabetes is associated with significant morbidity and mortality.[1] About 30 million Americans (~10% of US population) have diabetes, of which about 7 million do not know about their condition.[2] Moreover, 84 million Americans have prediabetes.[2] This represents a significant burden on the healthcare system. Diagnosed diabetes costs the US healthcare system approximately $327 billion which is about 15% of the US healthcare expenditure.[2] Additionally, there has been an increase of about 25% in costs associated with diabetes between 2012 and 2017 due to increase in prevalence, especially amongst the elderly.[2]

There are multiple therapeutic options to help manage diabetes. With the plethora of options, the decision-making process of a healthcare provider becomes a difficult task. Some of the variables that go in the decision-making process include pharmacology of medication, efficacy, safety, cardiovascular risk, adherence, formulary considerations,

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cost, route of administration and contraindications. Despite all these variables, often there is very little to choose from amongst various classes of antidiabetic medications. One such dilemma is the choice between sodium–glucose cotransposter-2 (SGLT2) inhibitors and dipeptidyl peptidase-4 (DPP4) inhibitors.

There are currently three SGLT2 inhibitors in the market – canagliflozin, dapagliflozin and empagliflozin. They are also available in a combination pill with metformin. These medications typically lower HbA1c levels by about 0.5–1% in about 6 months of therapy.[3–5] There are currently four DPP4 inhibitors in the market – sitagliptin, saxagliptin, linagliptin and alogliptin. Like the SGLT2 inhibitors, these medications are also available in a combination pill with metformin and typically lower HbA1c levels by 0.5–1% in about 6 months of therapy.[6-9]

Both SGLT2 inhibitors and DPP4 inhibitors are similar in their ability to reduce HbA1c levels.[10] From a safety standpoint, both these classes are well tolerated and have favourable weight-gain profile. Additionally, they have a good cardiovascular risk profile, with one of them being indicated for a reduction in risk of cardiovascular death in patients with type 2 diabetes with an established cardiovascular disease.[11–13] Also, both classes of these medications are available in an oral form and usually given once a day to aid in improving adherence. Additionally, they are both priced at comparable price points (both brand name medications with no generic alternatives currently in the market). Given the similarities, the choice between SGLT2 inhibitors and DPP4 inhibitors becomes a very hard one from the patient, provider and payer perspectives.

Comparative effectiveness research between these classes has been limited to clinical trials.[14–16] There is a paucity of real-world head-to-head evidence that compares the effectiveness of these classes of medications in routine clinical practice. Insight into real-world evidence can aid the decision-making process and also help identify populations that will benefit more from one class of medication over the other. Also, prescription expenditure is a big portion of the health expenditure on diabetes.[17] Identifying opportunities to deliver cost-effective care using real-world evidence can help offset some costs associated with the management of diabetes.

The primary objective of this study was to compare overall health expenditures of patients with type 2 diabetes on SGLT2 inhibitors versus DPP4 inhibitors. Secondary objectives were to compare inpatient, outpatient, and prescription expenditure and utilization measures.

Methods

The study utilized a retrospective, cross-sectional design using the 2015–2016 MEPS (Medical Expenditure Panel Survey) data. MEPS is a nationally representative database of survey responses of non-institutionalized civilians administered by the Agency for Healthcare Research and Quality (AHRQ) and the National Center for Health Statistics (NCHS).[18] The database contains information on demographic characteristics, health conditions, health status, health services utilization, charges, payments, access to care, satisfaction with care, health insurance status, income and employment status. The full-year consolidated files were used to obtain demographic, health expenditures and health services utilization information. The medical conditions file was used to identify patients with type 2 diabetes and to impute the Charlson Comorbidity Index score. The prescribed medications file was used to obtain prescription utilization and prescription expenditure information.

Patients on SGLT2 inhibitors and DPP4 inhibitors in combination with metformin were included in the study. They were identified using MULTUM therapeutic class codes, which were determined using the Multum Lexicon database from Cerner Multum, Inc. Therapeutic class codes used to identify SGLT2 inhibitors and DPP4 inhibitors were *458* and *371*. Antidiabetic agents (MULTUM therapeutic class codes – *99, 309, 314*) were also included and then filtered to identify any patients on SGLT2 inhibitors or DPP4 inhibitors. Combination of DPP4 inhibitors/SGLT2 inhibitors with metformin was included in the study. Also, the identified patients were examined to determine that they were using SGLT2 inhibitors or DPP4 inhibitors for type 2 diabetes which was the only indication for these medications.

Statistical analysis

After identifying the patients in both the cohorts, baseline demographics were compared and descriptive statistics were calculated. Propensity score matching was conducted between the two cohorts to address concerns regarding selection bias in a non-experimental, non-randomized and retrospective observational study like the current one to achieve similar baseline characteristics in both the cohorts. Propensity score matching yields a like-for-like patient in both cohorts based on predefined characteristics. The characteristics used in propensity score calculation include age, gender, race, ethnicity, income, employment status, education, insurance type, Charlson Comorbidity Index (CCI) and insulin utilization. The Charlson Comorbidity Index score has been used commonly in retrospective analysis to match two cohorts of patients with diabetes.[19,20] The Charlson Comorbidity Index score is a tool to classify prognosis based on comorbid conditions. Factors included in the computation of the score are: age, myocardial infarction, congestive heart failure, peripheral heart disease, cerebrovascular disease, dementia, COPD, peptic ulcer disease, liver disease, diabetes, hemiplegia, renal disease, tumour, leukaemia, lymphoma and AIDS (not HIV).[21] Based on the above description of the factors, this score accounts for the susceptibility of patients with diabetes to cardiovascular and renal risks. The cohorts were matched using a 1:2 ratio (SGLT2:DPP4) using calipers of width equal to 0.1 of the standard deviation of the logit of the propensity score.

Expenditure variables and their association with the medication class were analysed using a generalized linear model with a log link function and gamma distribution. The analysis adjusted for age, gender, race, ethnicity, insurance, employment, education, income, insulin utilization status and the Charlson Comorbidity Index score. Means were

calculated using bootstrapping to account for the skewed distribution of expenditure variables.[22,23] According to MEPS, total healthcare expenditure is the sum of all payments for care provided during the year which include out-of-pocket payments, payments by private, public (Medicare and Medicaid) and any other sources.[18] Inpatient expenditure was a sum of facility expenses and provider expenses that are incurred during either a hospitalization and/or an emergency room visit. Outpatient expenditure was a sum of facility expenses and provider expenses incurred during a visit to a healthcare provider in an outpatient setting (physicians, chiropractors, nurse practitioners, optometrist, physician assistant, physical therapy or occupational therapy).

Utilization variables (inpatient visits, outpatient visits, number of prescriptions) were compared using Student's *t*-test between the two cohorts. Inpatient visits included both the number of emergency room visits and hospital discharges. Outpatient visits included the number of office-based visits in an outpatient setting in a year. The number of prescriptions included the number of prescriptions obtained in a year. All statistical analyses were performed on SAS 9.3 (SAS Institute, Cary, NC), and a level of statistical significance was set at $\alpha = 0.05$ for all analyses.

Results

Three hundred and seventy-nine patients were identified to be using either SGLT2 inhibitor or DPP4 inhibitor in combination with metformin. None of the patients had a diagnosis of Type 1 diabetes. Of the 379 patients, 89 and 290 patients were in the SGLT2 inhibitor and DPP4 inhibitor cohort respectively. (Figure 1) Following 1:2 propensity score matching, there were 80 patients in the SGLT2 inhibitor cohort and 160 patients in the DPP4 inhibitor cohort.

Baseline characteristics (Table 1) were similar in both the cohorts after propensity score matching. From pre-matching data in Table 1, it can be observed that a significantly higher proportion of middle-aged (41–64 years) individuals were on SGLT2 inhibitors compared to DPP4 inhibitors. On the contrary, a significantly higher proportion of elderly (≥65 years) were on DPP4 inhibitors compared to SGLT2 inhibitors. A significantly higher proportion of patients on SGLT2 inhibitors were enrolled in commercial plans unlike DPP4 inhibitors where a significantly higher proportion of patients were enrolled in government-sponsored insurance.

Comparing the expenditures (results in Table 2) in the two cohorts revealed that patients on SGLT2 inhibitors ($17,325; 95% CI $17,131–$17,519) incurred significantly higher overall health expenditures compared to those on DPP4 inhibitors ($15,702; 95% CI $15,607–$15,797, $P < 0.0001$). Outpatient expenditures were significantly higher amongst patients on SGLT2 inhibitors ($3,596; 95% CI $3,552–$3,640) compared to those on DPP4 inhibitors ($3,067; 95% CI $3,042–$3,093, $P < 0.0001$). Prescription expenditures were significantly higher amongst those on SGLT2 inhibitors ($9,313; 95% CI $9,236–$9,390) versus those on DPP4 inhibitors ($9,003; 95% CI $8,968–$9,038, $P = 0.0087$). However, inpatient expenditures were significantly higher amongst those on DPP4 inhibitors ($2,836; 95% CI $2,799–$2,873) versus those on SGLT2 inhibitors ($2,527; 95% CI $2,493–$2,561, $P < 0.0001$).

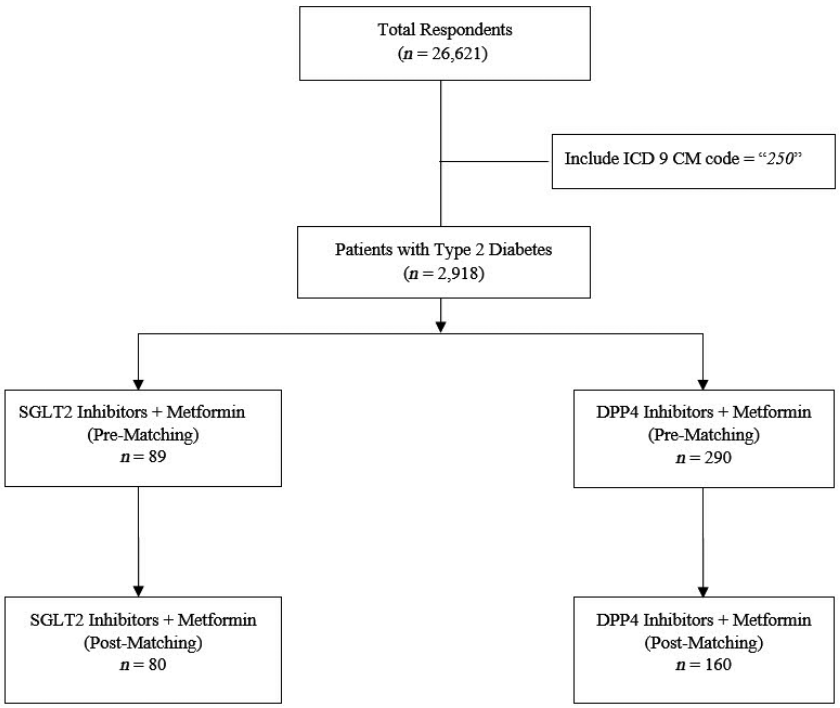

Figure 1 Flow chart of cohort identification.

Table 1 Demographic characteristics pre-matching and post-matching

	Pre-matching			Post-matching		
	SGLT2	**DPP4**	***P* value**	**SGLT2**	**DPP4**	***P* value**
n	89	290		80	160	
Age						
19–40	5 (5.62%)	12 (4.23%)	0.0060	5 (6.25%)	8 (5.00%)	0.3399
41–64	59 (66.29%)	144 (49.65%)	0.0060	50 (62.50%)	92 (57.50%)	0.3399
≥65	25 (28.09%)	134 (46.13%)	0.0060	25 (31.25%)	60 (37.50%)	0.3399
Gender						
Female	49 (55.06%)	149 (51.38%)	0.5435	40 (52.50%)	80 (50.00%)	0.7148
Insurance						
Public	24 (26.97%)	139 (47.93%)	0.0051	23 (28.75%)	60 (37.50%)	0.1791
Private	62 (69.66%)	140 (48.28%)	0.0051	54 (67.50%)	93 (58.13%)	0.1791
Uninsured	3 (3.37%)	11 (3.79%)	0.0051	3 (3.75%)	7 (4.38%)	0.1791
Education						
≤High school	59 (66.29%)	210 (72.41%)	0.3306	54 (67.50%)	107 (66.87%)	0.7030
Some college	12 (13.48%)	36 (12.41%)	0.3306	10 (12.50%)	20 (12.50%)	0.7030
≥Bachelors	18 (20.22%)	44 (15.17%)	0.3306	16 (20.00%)	33 (20.63%)	0.7030
Income						
< $20,000	38 (42.70%)	150 (51.72%)	0.1362	35 (43.75%)	76 (47.50%)	0.5828
$20,000 - $49,999	30 (33.71%)	84 (28.97%)	0.1362	25 (31.25%)	54 (33.75%)	0.5828
$50,000 - $100,000	15 (16.85%)	45 (15.52%)	0.1362	14 (17.50%)	23 (14.38%)	0.5828
>$100,000	6 (6.74%)	11 (3.79%)	0.1362	6 (7.50%)	7 (4.38%)	0.5828
Race						
White	60 (67.42%)	196 (67.59%)	0.8712	54 (67.50%)	105 (65.63%)	0.6576
African American	18 (20.22%)	60 (20.69%)	0.8712	16 (20.00%)	36 (22.50%)	0.6576
Other minorities	11 (12.36%)	34 (11.72%)	0.8712	10 (12.50%)	19 (11.88%)	0.6576
Ethnicity						
Hispanic	17 (19.10%)	86 (29.66%)	0.0503	17 (21.25%)	32 (20.00%)	0.8208
Employed						
Employed	42 (47.19%)	109 (37.59%)	0.1054	40 (50.00%)	70 (43.75%)	0.3596
Insulin utilization						
Yes	38 (42.69%)	70 (24.14%)	0.0002	31 (38.75%)	55 (34.38%)	0.4998
CCI (mean)	2.72	2.64	0.6083	2.64	2.68	0.8000

CCI, Charlson Comorbidity Index.

The number of prescriptions obtained in a year was significantly higher amongst patients on an SGLT2 inhibitor compared to DPP4 inhibitor (55.86 versus 45.49; $P = 0.0483$). Inpatient and outpatient utilization measures were similar in both the cohorts. (Table 3).

After adjusting for the socio-economic variables, both total health expenditures ($\beta = -0.3516$; $P = 0.0038$) and prescription expenditures ($\beta = -0.3873$; $P = 0.0016$) were significantly lower in the DPP4 cohort compared to SGLT2 cohort (Table 4). Total health expenditures ($\beta = 0.4270$;

Table 2 Unadjusted health expenditure comparison

	SGLT2	**DPP4**	***P* value**
Total health expenditure	$17,325 (95% CI: $17,131–$17,519)	$15,702 (95% CI: $15,607–$15,797)	<0.0001
Outpatient expenditure	$3,596 (95% CI: $3,552–$3,640)	$3,067 (95% CI: $3,042–$3,092)	<0.0001
Inpatient expenditure	$2,527 (95% CI: $2,493–$2,561)	$2,836 (95% CI: $2,799–$2,873)	<0.0001
Prescription expenditure	$,9313 (95% CI: $9,236–$9,390)	$9,003 (95% CI: $8,968–$9,038)	0.0087

Table 3 Health services utilization comparison

	SGLT2	**DPP4**	***P* value**
Outpatient visits	12.40 (95% CI: 12.34–12.46)	12.28 (95% CI: 12.20–12.36)	0.3072
Inpatient visits	0.6053 (95% CI: 0.5978–0.6129)	0.6099 (95% CI: 0.6043–0.6155)	<0.3454
Prescriptions/year	55.86 (95% CI: 55.60–56.12)	45.49 (95% CI: 45.32–45.66)	0.0483

Table 4 Factors associated with total health expenditures and prescription expenditures

	Total health expenditures		Prescription expenditure	
	Coefficient	***P* value**	**Coefficient**	***P* value**
Intercept	9.1930	<0.0001	8.6609	<0.0001
Cohort				
SGLT2	Reference	–	Reference	–
DPP4	−0.3516	0.0038	−0.3873	0.0016
Age				
19–40	Reference	–	Reference	–
41–64	0.1291	0.6091	0.0432	0.8649
≥65	0.0503	0.8552	−0.2135	0.4384
Gender				
Male	Reference	–	Reference	–
Female	0.1051	0.3841	0.1632	0.1699
Insurance				
Private	Reference	–	Reference	–
Public	0.1139	0.4854	0.5173	0.0030
Uninsured	−1.2876	<0.0001	−1.2596	<0.0001
Education				
≥Bachelors	Reference	–	Reference	–
Some college	−0.0156	0.9396	−0.1912	0.3486
≤High school	0.4960	0.0508	0.7158	0.0063
Income				
>$100,000	Reference	–	Reference	–
$50,000–$100,000	−0.0681	0.8078	0.0694	0.8064
$20,000–$49,999	0.1247	0.6387	0.0911	0.7322
<$20,000	0.3426	0.2322	0.0727	0.7990
Race				
White	Reference	–	Reference	–
African American	−0.1997	0.1588	−0.4695	0.0012
Other minorities	−0.2609	0.1482	−0.5569	0.0018
Ethnicity				
Hispanic	Reference	–	Reference	–
Non-Hispanic	0.4270	0.0049	0.5464	0.0005
Employment status				
Employed	Reference	–	Reference	–
Unemployed	0.2005	0.2198	0.0182	0.9136
Insulin utilization				
Yes	Reference	–	Reference	–
No	−0.5370	<0.0001	−0.2411	0.0722
CCI	0.2704	<0.0001	0.2373	0.0007

CCI, Charlson Comorbidity Index

$P = 0.0049$) and prescription expenditures ($\beta = 0.5464$; $P = 0.0005$) were significantly higher amongst non-Hispanics compared to their Hispanic counterparts taking either DPP4 inhibitors or SGLT2 inhibitors. Total health expenditures ($\beta = -1.2876$; $P < 0.0001$) and prescription expenditures were ($\beta = -1.2596$; $P < 0.0001$) were significantly lower amongst uninsured compared to the commercially insured patients in the study. The Higher Charlson Comorbidity Index scores were associated with higher total health expenditures ($\beta = 0.2704$; $P < 0.0001$) and higher prescription expenditures ($\beta = 0.2373$; $P = 0.0007$). Total health expenditures were significantly lower amongst those who did not use insulin ($\beta = -0.5370$; $P < 0.0001$) compared to those who did. Prescription expenditures were significantly lower amongst patients who are African American ($\beta = -0.4695$; $P = 0.0012$) and other minorities ($\beta = -0.5569$; $P = 0.0018$) compared to patients who are White. Prescription expenditures were significantly higher amongst patients with public insurance ($\beta = 0.5173$; $P = 0.0030$) compared to patients with private insurance in the study sample.

Discussion

The favourable safety profile, efficacy profile and the availability in oral dosage forms make both SGLT2 inhibitors and DPP4 inhibitors extremely worthwhile options in the management of type 2 diabetes. Choosing between these two classes of medications becomes a difficult proposition.

Results of the current study suggest that overall health, outpatient and prescription expenditures are higher amongst patients on SGLT2 inhibitors versus those on DPP4

inhibitors. Although there are no head-to-head real-world observational studies comparing these two classes of medications and their impact on health expenditures and health services utilization; an observational study did compare canagliflozin with DPP4 inhibitors. A study conducted by Grabner et al. found that health expenditures (all-cause and diabetes-related) and prescription costs (all-cause and diabetes-related) were significantly higher amongst patient with type 2 diabetes on canagliflozin compared to those on DPP4 inhibitors.[24] This difference could be attributed to the fact that SGLT2 inhibitors are often initiated in patients with poorly controlled HbA1c levels, which has been reported in the literature.[24,25] In addition, the pre-matching CCI scores indicate that patients in the SGLT2 cohort had slightly higher scores than those in the DPP4 cohort, albeit not statistically significant, suggesting that patients in the SGLT2 group might be poorly controlled.

While the current study suggests that SGLT2 inhibitors are associated with higher overall health expenditures, it must be noted that this study utilized 2015 utilization data. Grabner et al utilized claims data between 2011 and 2013 and Buysman et al utilized data from 2013.[24,25] The FDA approved the first SGLT2 inhibitor (canagliflozin) in 2013. The first DPP4 inhibitor (sitagliptin) was approved in 2006 in the United States. In addition, the AACE guidelines in 2013 recommended the use of SGLT2 inhibitors with caution given the limited evidence.[26] It was not until the year 2015, when AACE recommended the use of SGLT2 inhibitors.[27] Hence, the results of this study need to account for the guidelines at that point of time prior to making any inferences. The study results may not accurately reflect outcomes associated with current prescribing patterns. Currently, SGLT2 inhibitors are not only indicated to improve glycaemic control in patients with type 2 diabetes, but also to reduce risk of major adverse cardiovascular events and to reduce risk of end-stage kidney disease.[11–13] In light of the evidence, current guidelines recommend using SGLT2 inhibitors as second line, especially amongst those with established atherosclerotic cardiovascular disease (ASCVD) risk or chronic kidney disease.[28]

The current study observed utilization and expenditure outcomes for a relatively short period. As mentioned earlier, some SGLT2 inhibitors are indicated for reducing risk of cardiovascular death and others show positive cardiovascular outcomes.[11–13] Observing health expenditures and health services utilization over a longer period may provide insights on the cardiovascular benefits of SGLT2 inhibitors. Cardiovascular risk reduction is an important component of managing diabetes. Cardiovascular complications are the primary cause of deaths amongst diabetes, and reduction in HbA1c levels has minor effect on cardiovascular risk profile.[29,30] Hence, identifying other strategies to reduce cardiovascular risk adds value to the management of diabetes. Although, this study indicates that healthcare costs are higher in patients receiving SGLT2 inhibitors, it must be recognized that this was during a time when not much was known about cardiovascular benefits of SGLT2 inhibitors. While the total healthcare costs are higher, cardiovascular outcomes may be meaningful and worth the additional cost over a longer observation period. Hence, conducting similar observational studies with longer follow-up may provide insight into the real-world performance of SGLT2 inhibitors in reducing the risk of cardiovascular events and possibly being associated with lower overall healthcare costs.

Socio-economic disparities exist in the management of diabetes. This study also explores the association of socio-economic variables with health expenditures. The results obtained in this study with respect to lower expenditures in African Americans (compared to Whites), other minorities (compared to Whites), Hispanics (compared to non-Hispanics), uninsured (compared to commercially insured) and commercially insured (compared to public insurance) are consistent with a study conducted by Ozieh et al.[31] Also, disparities exist in access to antidiabetic medications. In a study by McCoy et al, they had found that younger, healthier, non-Black patients were more likely to start on a SGLT2 inhibitor.[32] This is a disturbing trend that can eventually impact not only health outcomes of socially disadvantaged groups, but also lead to higher healthcare costs and inappropriate use of health services like emergency departments. Exploring interventions that reduce disparities may help in reducing the differences observed in health expenditures and health outcomes.

Limitations

MEPS is a self-reported survey response data set, which is associated with recall bias, missing responses and social desirability bias. However, the survey administrators verify the responses for accuracy, given that the respondents may not exhibit high levels of health literacy. In addition, clinical information (HbA1c, lipid levels, blood pressure levels) are unavailable to establish a diabetes-specific baseline level for the two cohorts. While the use of CCI allows us to match the two groups of patients holistically, availability of clinical information (HbA1c) could have aided in ascertaining diabetes-specific risk profile of the patients in the two cohorts. Use of other disease-specific comorbidity measures like Diabetes Complications Severity Index (DCSI) would have been more appropriate.[33] However, DCSI requires a higher level of specificity with respect to ICD-9-CM codes which is not captured in the MEPS data set. MEPS data set limits reporting of ICD-9-CM codes to three characters. To address this limitation, matching was also conducted based on the utilization of insulin. Also, the survey response data from 2015 to 2016 may not mimic current prescribing patterns. However, this was the most recent data available through MEPS when this study was conducted.

Conclusion

SGLT2 inhibitors were associated with significantly higher overall and prescription expenditures compared to DPP4 inhibitors during the study period evaluated. However, future comparative effectiveness research needs to be conducted with more relevant data like administrative claims data that reflect current prescribing patterns and its impact on health expenditures and health services utilization. As guidelines evolve,

future research needs to evaluate adherence to evidence-based patient-centred guidelines and associated outcomes. Additionally, this study adds to the already extensive literature on the need to address disparities in care for patients with diabetes.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Ethics statement

This analysis used secondary data from the Medical Expenditure Panel Survey, as such all ethics approvals and consent to participate were waived.

Authors' contributions

Concept and design (PMP, VV); acquisition of data (PMP); analysis and interpretation of data (PMP, VV); drafting of the manuscript (PMP, VV); statistical analysis (PMP, VV).

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