Among Commercially Insured Members with Diabetes Mellitus (DM), Choice and Persistence of Drug Therapy: Dipeptidyl Peptidase-4 Inhibitors (DPP-4i) Versus Glucagon-like Peptide-1 Agonists (GLP-1) or Sodium-Glucose Cotransporter-2 Inhibitors (SGLT-2i)

PRIME THERAPEUTICS®

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Background

- Diabetes mellitus (DM) is a complex metabolic disorder associated with:
  - Microvascular complications, such as retinopathy, nephropathy, and neuropathy, and
  - Macrovascular complications, such as atherosclerotic cardiovascular disease (ASCVD).
- ASCVD is the leading cause of death in DM.[1] In commercially insured populations, ASCVD and conditions typically caused by ASCVD, also account for the largest category of excess medical claims expense associated with DM.[2]
- Clinical trials have established that pharmacologic control of chronic hyperglycemia reduces microvascular complications.[3]
  - Three newer classes of antihyperglycemics, DPP-4i, GLP-1, and SGLT-2i, now account for almost 95 percent of commercial pharmacy benefit expense for non-insulin diabetes agents.[4]
  - The approved drugs have been shown to have efficacy in improving glycemic control. However, their effectiveness in long-term outcome improvement requires long-term drug therapy persistence.
- Evidence that control of hyperglycemia reduces macrovascular complications has not been clearly shown, though a modest benefit was shown after a prolonged follow-up period.[5]
- Recent clinical trials have found that at least two GLP-1, two SGLT-2i, but no DPP-4i agents improve long-term cardiovascular outcomes in DM patients with ASCVD, presumably by mechanisms independent of glycemic control.[6,7,8,9] A meta-analysis of clinical trial results for patients with and without ASCVD concluded that use of SGLT-2i or GLP-1 was associated with lower mortality than DPP-4i or placebo, and use of DPP-4i was not associated with lower mortality than placebo or no therapy.[10]
- The U.S. Food and Drug Administration (FDA) approved established ASCVD as a new indication for the SGLT-2i empagliflozin in December 2016 and the GLP-1 liraglutide in August 2017. Preferential use of one of these agents, or the SGLT-2 canagliflozin, is now part of the American Diabetes Association guideline recommendations for individuals with established ASCVD.[11]

Objective

Among members with DM newly initiating either a DPP-4i, GLP-1 or SGLT-2i, to determine:

1) if there are differences at the class level in observed persistence with therapy, and
2) if the fraction with established ASCVD initiating a DPP-4i decreased following appearance of evidence supporting preferred use of a GLP-1 or SGLT-2i.

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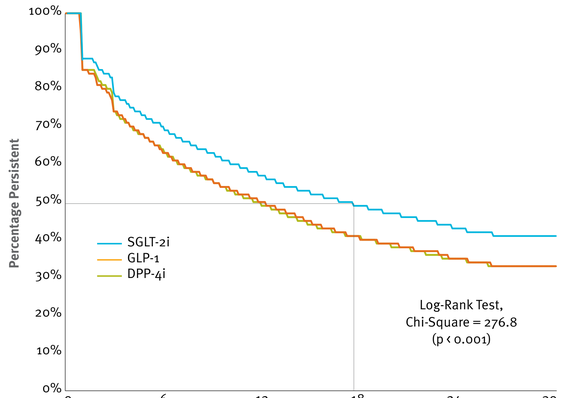
Methods

- From integrated medical and pharmacy claims for 15 million commercially insured members, we identified all continuously eligible members from January 2014 to March 2018. DM members were defined as those with ≥ 2 medical claims for physician evaluation that had an ICD-9 or ICD-10 diagnosis code for DM.
- All members were selected whose first claim (index date) since January 2014 for a DPP-4i, GLP-1 or SGLT-2i was between Jan. 1, 2016 and March 31, 2018, and who did not have a preceding claim for any other antihyperglyemic agent other than metformin.
- Persistence was assessed by Kaplan-Meier analysis and defined as days from index date to the first claim plus the days supply of the claim when this was followed by a gap of 60 or more days. Members with no 60-day gap were right-censored.
  - We included members initiating DPP-4i, GLP-1 or SGLT-2i therapy with a combination drug containing metformin.
  - We excluded the small number of members initiating two of DPP-4i, GLP-1 or SGLT-2i on the same date, due to either a claim for a combination drug or claims for separate prescriptions.
- ASCVD was defined as an inpatient claim with an ICD-9 or ICD-10 diagnosis code for acute myocardial infarction or ischemic stroke, or any claim with a diagnosis code for unstable angina or a HCPCS or ICD-9 or ICD-10 procedure code for coronary revascularization during the 24 months before index date.
- The percentage of members with ASCVD treated first with a DPP-4i versus GLP-1 or SGLT-2i was determined by three-month intervals from January 2016 through March 2018.

Figure. Kaplan-Meier Derived Persistency of Drug Therapy: DPP-4i versus GLP-1 and SGLT-2i among 44,021 Commercial Members with First Antihyperglycemic Claim, Other than for Metformin



Number at risk*:						
SGLT-2i	17,019	10,292	6,432	3,652	1,549	0
GLP-1	13,154	6,905	4,043	2,057	805	0
DPP-4i	14,028	7,627	4,474	2,446	1,016	0

Discontinuation was defined as a > 60-day gap in therapy between a drug claim plus its days supply and the next claim. For example, if a claim of a DPP-4 was incurred on Jan. 1, 2016 with 30 days supply, then discontinuation would be identified if the member had no subsequent claim by April 1, 2016 (Jan. 1, 2016 + 30 days supply + 60-day gap).

Inclusion: The 44,021 members in this graph were commercially insured, continuously enrolled from January 2014 through March 2018, and less than 65 years of age as of March 31, 2018. The index date was the first claim for a DPP-4i, GLP-1 or SGLT-2i, limited to members whose first claim was incurred on or after Jan. 1, 2016 and preceded by a claim for no antihyperglycemic agents other than metformin. Analysis was at this class level, allowing switching within the class.

Censoring occurred when a member had a drug supply or less than a 60-day gap in therapy as of March 31, 2018. Censored cases contribute to the estimate of duration of therapy but do not cause the persistence curve to drop.

*Number at risk: Members who did not discontinue therapy and were not censored up to and including the time point shown on the graph are at risk of discontinuing therapy or being censored in the future.

Results

- Of 3.64 million continuously enrolled members, 220,919 (6.1%) had a diagnosis of DM of whom 14,028 (6.3%) first initiated a DPP-4i, 13,154 (6.0%) a GLP-1, and 17,019 (7.7%) an SGLT-2i between January 2016 and March 2018, with no preceding claims for antihyperglycemics, other than metformin.
  - There were 95 (0.04%) additional members who initiated therapy with initial claim(s) for two or three of these classes on the same date.
  - Of 44,296 newly initiating DPP-4i, GLP-1, or SGLT-2i therapy, 32,425 (73.2%) had a preceding claim for single-agent metformin while 11,871 (26.8%) had no preceding claim for any antihyperglycemic agent.
- Persistence of SGLT-2i therapy was significantly longer than GLP-1 or DPP-4i, which were not significantly different (see Figure).
  - Log-Rank Test: Chi-Square = 276.8 (p < 0.001)
  - Twelve months after index date, 56.9% of SGLT-2i, 50.0% of GLP-1 and 49.3% of DPP-4i had not discontinued.
- 2,961 of 44,296 (6.7%) members with a first claim for a DPP-4i, GLP-1 or SGLT-2i had claims evidence of ASCVD in the preceding 24 months. The percentage newly initiating with a DPP-4i remained constant: 95 of 313 (30.4%) January–March 2016 compared to 93 of 312 (29.8%) January–March 2018 (see Table).

Table. Members with a First Claim for a DPP-4i, GLP-1 or SGLT-2i who had Claims Evidence of ASCVD in the Preceding 24 Months: Percentages Starting Therapy by Class and Three-Month Incurred Intervals

N members with ASCVD history newly initiating therapy	Incurred date of first claim									
	2016				2017				2018	Total
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	
Total members	313	365	327	289	332	347	331	345	312	2,961
SGLT-2i	114	118	112	88	125	125	109	120	100	1,011
GLP-1	93	119	107	86	95	113	112	121	104	950
DPP-4i	95	116	98	104	104	100	102	93	93	905
DPP-4i+SGLT-2i	4	4	4	10	5	3	3	4	8	45
GLP-1+SGLT-2i	4	5	4	1	3	6	3	5	6	37
DPP-4+GLP-1	3	2	2	–	–	–	2	2	–	11
DPP-4+GLP-1+SGLT-2i	–	1	–	–	–	–	–	–	1	2
% SGLT-2i	36.4%	32.3%	34.3%	30.4%	37.7%	36.0%	32.9%	34.8%	32.1%	34.1%
% GLP-1	29.7%	32.6%	32.7%	29.8%	28.6%	32.6%	33.8%	35.1%	33.3%	32.1%
% DPP-4i	30.4%	31.8%	30.0%	36.0%	31.3%	28.8%	30.8%	27.0%	29.8%	30.6%
% DPP-4i+SGLT-2i	1.3%	1.1%	1.2%	3.5%	1.5%	0.9%	0.9%	1.2%	2.6%	1.5%
% GLP-1+SGLT-2i	1.3%	1.4%	1.2%	0.3%	0.9%	1.7%	0.9%	1.4%	1.9%	1.2%
% DPP-4i+GLP-1	1.0%	0.5%	0.6%	0.0%	0.0%	0.0%	0.6%	0.6%	0.0%	0.4%
% DPP-4i+GLP-1+SGLT-2i	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.1%

ASCVD = atherosclerotic cardiovascular disease; ASCVD history = medical claim coded for ASCVD within 24 months of first claim; first claim = first claim for DPP-4i, GLP-1 or SGLT-2i, incurred on or after Jan. 1, 2016 and preceded by no claims for an antihyperglycemic agent other than metformin; Q = calendar quarter; DPP-4i = dipeptidyl peptidase-4 inhibitor; GLP-1 = glucagon-like peptide-1 agonists; SGLT-2i = sodium-glucose cotransporter-2 inhibitor.
The small number of members initiating two of DPP-4i, GLP-1 or SGLT-2i on the same date either had a claim for a combination drug or claims for separate prescriptions.

Conclusions

- In this commercially insured population, persistence of therapy with all three of these diabetes mellitus (DM) drug classes was suboptimal, with about half of members discontinuing within one year.
- The percentage of DM members with ASCVD starting DPP-4i before a GLP-1 or SGLT-2i did not decline despite publication of clinical trial results, FDA approved labeling use of GLP-1 or SGLT-2i for this indication, and professional guideline recommendation for use of GLP-1 or SGLT-2i in this subset of patients when lifestyle management plus metformin does not achieve or maintain A1C goal.

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Limitations

- This study groups drugs by class (DPP-4i, GLP-1 and SGLT-2i) and was not designed to make comparisons between individual drugs within or between these classes.
- The results are not adjusted for any differences between the members in the comparison groups that might have confounded the effect of the drug class choice.
- To make time interval samples more comparable, claims evidence of ASCVD was defined based on claims history in the 24 months preceding first DPP-4i, GLP-1 or SGLT-2i. This identifies a smaller percentage of newly initiating members as having a history of ASCVD than using all the claims history available for these members. In addition, it is likely that the percentage of members with a clinical history of established ASCVD was higher still. This study, therefore, is not intended to provide an estimate of the fraction of commercial members who meet the criterion of established ASCVD at the time of DM drug therapy intensification.
- These results are from a large sample of commercially insured members and may not be generalizable to other populations.

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