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## **Contemporary Trends in Prescription of Dipeptidyl Peptidase-4 Inhibitors in the Context of US Food and Drug Administration Warnings of Heart Failure Risk**

**Running Head:** FDA Warnings & DPP-4i Prescription

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## **ABSTRACT**

Dipeptidyl peptidase-4 inhibitors (DPP-4i) are one of the most widely used antihyperglycemic therapeutic classes in type 2 diabetes mellitus management. In April 2016 & August 2017, the US Food and Drug Administration (FDA) introduced sequential labelling requirements regarding heart failure risk related to DPP-4i. We explored longitudinal trends in prescription of DPP-4i before and after these FDA warnings in a multicenter health system. We identified all first-time prescriptions of DPP4i or their combinations across the Partners HealthCare system (Boston, MA) from October 2006 (FDA approval of first DPP-4i) to December 2018. Overall, 11,830 patients were newly prescribed DPP-4i during the study period. Primary care physicians (PCPs; 31.5%) were the most common prescribing specialty. Overall, 8.4%, 20.4%, and 11.6% had heart failure, atherosclerotic cardiovascular disease, and chronic kidney disease, respectively. Median number of background antihyperglycemic therapies was 2 [25th-75th percentiles 1-2], commonly metformin (65.4%) and/or insulin (36.4%). The vast majority of prescriptions were sitagliptin (85.7%), followed by linagliptin (9.5%), saxagliptin (4.7%), and alogliptin (0.2%). Quarterly prescriptions rose gradually from 2006 to mid-2016, and have decreased consistently since then for each of the 4 DPP-4i. Declines in DPP-4i among high-risk groups and those initiated by endocrinologists were most pronounced. In conclusion, while DPP-4i remain a dominant oral antihyperglycemic therapy in clinical practice, new prescriptions have declined recently. These data may reflect relatively swift health system response to broad FDA safety communications regarding heart failure risk, which appeared to impact the entire DPP-4i class, including specific drugs that have not demonstrated any increased risk of heart failure.

**Key Words:** diabetes mellitus; dipeptidyl peptidase-4 inhibitors; heart failure

## **INTRODUCTION**

Dipeptidyl peptidase-4 inhibitors (DPP-4i) comprise a widely used class of oral antihyperglycemic therapies that prevent breakdown of several bioactive peptides, including glucagon-like peptide-1, thereby potentiating their activity. Four DPP-4i (alogliptin, linagliptin, saxagliptin, sitagliptin) are approved by the US Food and Drug Administration (FDA) for glycemic control among patients with type 2 diabetes mellitus. The US FDA introduced labelling requirements regarding potential heart failure risks initially for saxagliptin and alogliptin (1,2) in April 2016, but later expanded requirements for the entire class in August 2017. Subsequent cardiovascular outcomes trials of sitagliptin and linagliptin (3,4), each applying prospectively developed heart failure-specific statistical analysis plans, did not demonstrate excess heart failure risk, though a small mechanistic trial of vildagliptin (5) did suggest adverse effects on left ventricular volumes. We explored longitudinal trends in prescription of DPP-4i before and after these FDA warnings in a multicenter health system.

## **METHODS**

We identified all first-time prescriptions of DPP-4i or their combinations across the Partners HealthCare system encompassing >10 healthcare institutions (Boston, MA) from October 2006 (FDA approval of first DPP-4i) to December 2018. We tracked quarterly DPP-4i prescriptions in aggregate, by prescriber specialty, and among high-risk subgroups, including prevalent heart failure, atherosclerotic cardiovascular disease, and chronic kidney disease. To inform temporal changes in prescriber practices, we ascertained new prescriptions rather than prevalent use. The study was approved by the Partners HealthCare Institutional Review Board. Statistical analyses were performed with STATA 14.1 (College Station, TX).

## RESULTS

From 2006-2018, 11,830 patients were newly prescribed DPP-4i (median age 70 [25<sup>th</sup>-75<sup>th</sup> percentiles 61-78] years, 44.6% women, 74.7% white). Primary care physicians (31.5%) were the most common prescribing specialty. Overall, 8.4%, 20.4%, and 11.6% had heart failure, atherosclerotic cardiovascular disease, and chronic kidney disease, respectively. Median number of background antihyperglycemic therapies was 2 [25<sup>th</sup>-75<sup>th</sup> percentiles 1-2], commonly metformin (65.4%) and/or insulin (36.4%), and infrequently sodium-glucose cotransporter 2 inhibitors (SGLT2i) (1.7%) and/or glucagon-like peptide-1 receptor agonists (GLP-1RA) (2.9%).

The vast majority of prescriptions were sitagliptin (85.7%), followed by linagliptin (9.5%), saxagliptin (4.7%), and alogliptin (0.2%). Quarterly prescriptions rose gradually from 2006 to mid-2016, and have decreased consistently since then for each of the 4 DPP-4i (**Figure 1A**). Declines in prescriptions by endocrinologists and other medical specialties were most pronounced (**Figure 1B**). Among high-risk groups, declines in new prescriptions started earlier in mid-2015 (**Figure 1C**).

## DISCUSSION

We describe contemporary patterns of use of DPP-4i in a multicenter academic health system over 14 years. Sitagliptin, which was first FDA-approved DPP-4i, remained the most commonly prescribed agent within the class. DPP-4i use continued to increase, even among high-risk groups, after initial publication of potential heart failure risk with saxagliptin in October 2013. New prescription of DPP-4i declined starting in mid-2016, which coincides with

the first FDA communication regarding heart failure risk (6). Temporal declines appeared consistent for specific DPP-4i therapies with or without potential heart failure risk signals.

Recent declines in DPP-4i may also reflect concurrent increases in SGLT2i or GLP-1RA (7,8), 2 classes of therapies with known cardiovascular and renal benefits. We observed marked declines in new prescription of DPP-4i among patients with cardiovascular or renal disease. Upfront selection or switching from DPP-4i to 1 of these classes in appropriately selected high-risk patients represents an opportunity for care optimization.

This retrospective analysis is subject to certain limitations. Although we tracked initial prescriptions, we were unable to determine discontinuations or adherence given limitations of the database. Similarly, while we were unable to assess temporal changes in volume of encounters, increasing use of other antihyperglycemic therapies during a similar timeframe (7,8) suggests that a lower number of evaluated patients with diabetes mellitus is unlikely to explain recent trends in DPP-4i use. High-risk subgroups were identified using administrative coding, which may introduce misclassification. DPP-4i initiation outside the integrated health system would not have been captured.

While DPP-4i remain a dominant oral antihyperglycemic therapy in clinical practice, new prescriptions have declined recently. These data may reflect relatively swift health system response to broad FDA safety communications regarding heart failure risk, which appeared to impact the entire DPP-4i class, including specific drugs that have not demonstrated any increased risk of heart failure.

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None

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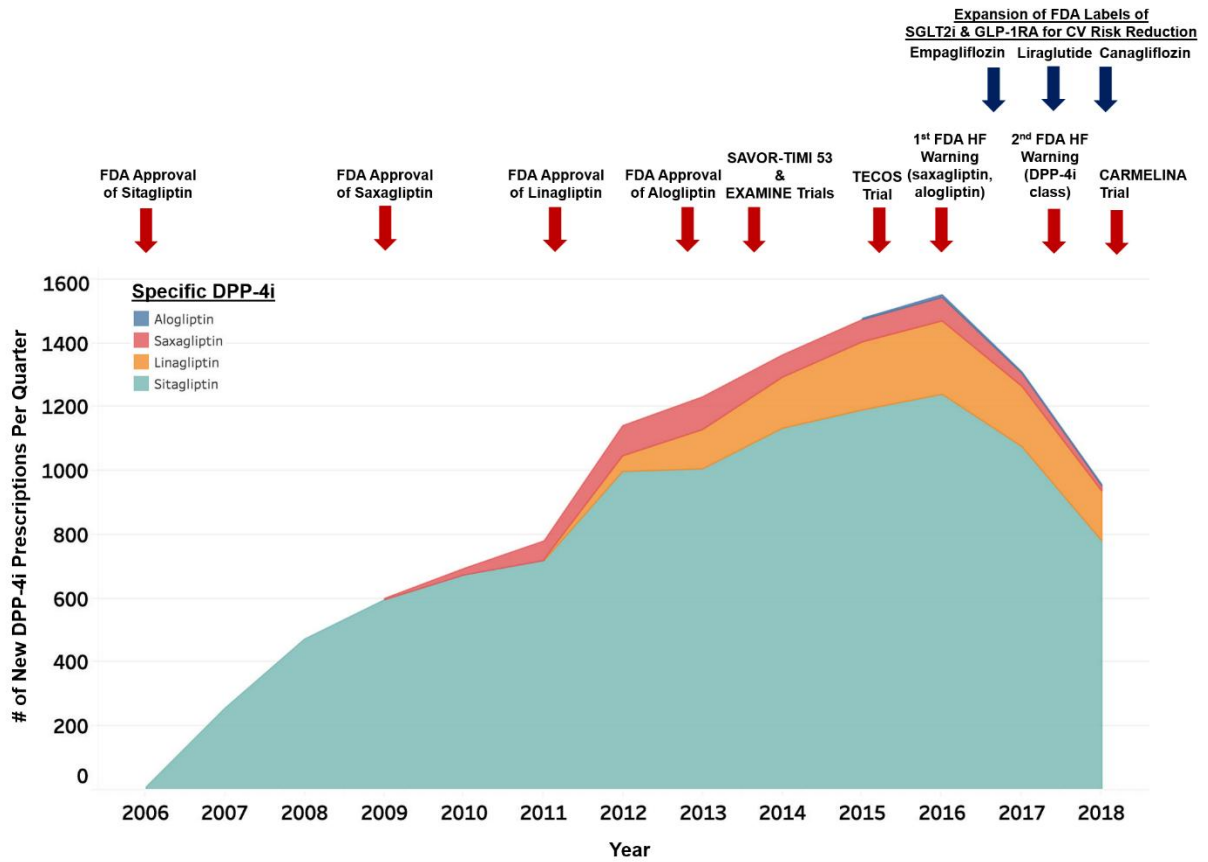
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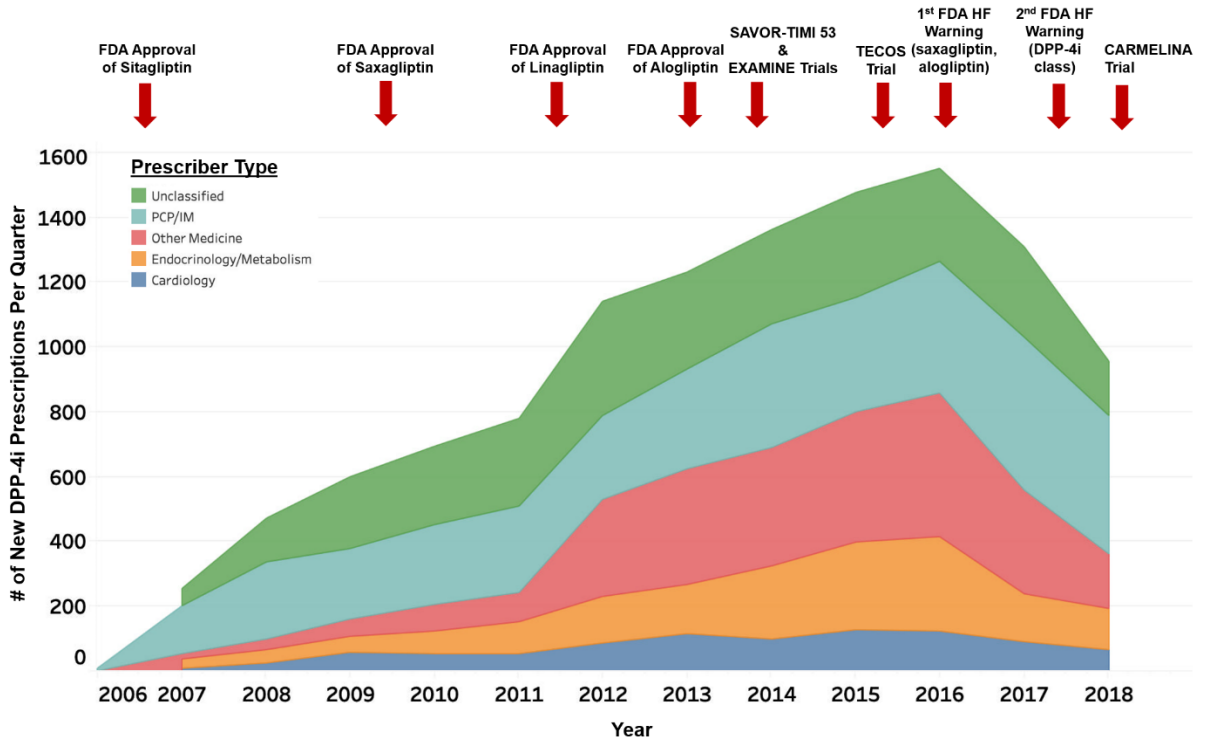


# FIGURE LEGEND

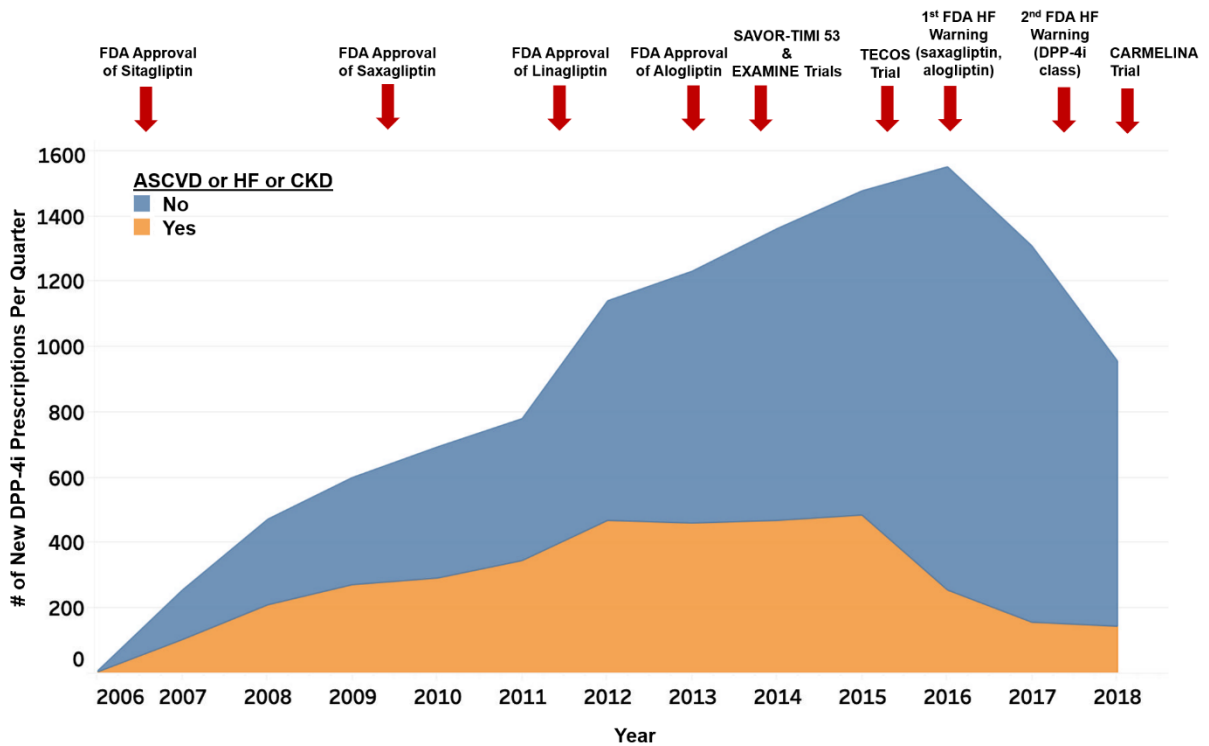
Panel A



Panel B



Panel C



**Figure.** New dipeptidyl peptidase-4 inhibitors (DPP-4i) quarterly prescriptions by specific drug within class (**Panel A**), prescriber type (**Panel B**), and among high-risk subgroups (**Panel C**). Red arrows indicate key US Food and Drug Administration (FDA) regulatory approvals, warnings, or publication of landmark cardiovascular outcomes trials.

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; CARMELINA = The Cardiovascular and Renal Microvascular Outcome Study With Linagliptin; CKD = chronic kidney disease; CV = cardiovascular; EXAMINE = Examination of Cardiovascular Outcomes with Alogliptin vs Standard of Care; FDA = Food and Drug Administration; GLP-1RA = glucagon-like peptide-1 receptor agonists; HF = heart failure; SAVOR-TIMI 53 = Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53; IM = internal medicine; PCP = primary care physician; SGLT2i = sodium-glucose cotransporter 2 inhibitors; TECOS = Trial Evaluating Cardiovascular Outcomes with Sitagliptin.