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Primary Occurrence of Cardiovascular Events After Adding Sodium-Glucose Cotransporter-2 Inhibitors or Glucagon-like Peptide-1 Receptor Agonists Compared With Dipeptidyl Peptidase-4 Inhibitors: A Cohort Study in Veterans With Diabetes

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Abstract

Background—The effectiveness of glucagon-like peptide 1 receptor agonists (GLP1RA) and sodium–glucose cotransporter 2 inhibitors (SGLT2i) in preventing major adverse cardiac events (MACE) is uncertain for those without pre-existing cardiovascular disease.

Objective—To test the hypothesis that MACE incidence was lower with addition of GLP1RA or SGLT2i compared to dipeptidyl peptidase 4 inhibitors (DPP4i) for primary prevention to baseline therapy.

Design—Retrospective cohort study of US veterans from 2001-2019.

Setting—Veterans 18 years and older receiving care in Veterans Health Administration, with data linkage to Medicare, Medicaid and National Death Index.

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Patient Episodes—Addition of GLP1RA; SGLT2i; or DPP4i by veterans who were currently using metformin, sulfonylurea or insulin alone or in combination. Episodes were stratified by history of prior cardiovascular disease.

Measurements—Study outcomes were MACE (acute myocardial infarction, stroke, or cardiovascular death) and heart failure (HF) hospitalization. Cox models compared the outcome between medication groups using pairwise comparisons in a weighted cohort adjusted for covariates.

Results—The cohort included 28,759 GLP1RA vs 28,628 DPP4i and 21,200 SGLT2i vs 21,170 DPP4i weighted pairs. Median age was 67 years and diabetes duration was 8.5 years. GLP1RA was associated with lower MACE and HF vs DPP4i (adjusted Hazard Ratio [aHR] 0.82 [0.72, 0.94]); yielding an adjusted risk difference [aRD] of 3.2 events (1.1, 5.0) per 1,000 person years. SGLT2i was not associated with MACE and HF (aHR 0.91 (0.78, 1.08); aRD 1.28 (−1.12, 3.32) compared with DPP4i.

Limitations—Residual confounding; Use of DPP4i, GLP1RA, SGLT2i as first line therapies were not examined

Conclusions—GLP1RA addition was associated with primary reductions of MACE and HF hospitalization compared with DPP4i use; SGLT2 addition was not associated with primary MACE prevention.

INTRODUCTION

Diabetes is common and confers a high risk for cardiovascular disease (CVD) which remains the leading cause of death (1-4). It is less clear whether CVD onset can be prevented by newer antidiabetic medications (5-10). Since 2008, regulatory guidance for licensure of new antidiabetic medications requires evaluation of both HbA1c and major adverse cardiovascular events (MACE) [myocardial infarction, stroke and cardiovascular death] as study endpoints (11).

There have been multiple pivotal trials of glucagon-like peptide 1 receptor agonists (GLP1RA) or sodium-glucose cotransporter 2 inhibitors (SGLT2i) vs placebo that evaluate MACE outcomes (12-18). These trials individually, along with meta-analyses, demonstrated benefit in MACE risk among those with pre-existing CVD (secondary prevention) (19-21). However, these trials collected little data or were inadequately powered for patients without CVD (primary prevention). Additionally, the dipeptidyl peptidase 4 inhibitors (DPP4i) are regarded as cardio-neutral and they continue to be widely used (5-7,10,22-24 25-27).

Our aim was to test the hypothesis that among patients with diabetes, fatal and nonfatal cardiovascular endpoints was lower with adding either GLP1RA or SGLT2i compared to DPP4i for primary prevention. We conducted confirmatory analyses among the full cohort including those with CVD to evaluate secondary prevention.

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METHODS

Study design and Data sources

We assembled a cohort of Veterans Health Administration (VHA) patients with diabetes and a first prescription for an antidiabetic medication between 1/1/2001 and 12/31/2016. Additional cohort follow-up data were obtained through 12/31/2019. VHA data included: demographic, diagnostic, and procedure information from inpatient and outpatient encounters, laboratory results and vital signs from clinical sources. Pharmacy data included medication dispensed, date filled, days supplied, and number of pills/injections dispensed. For Medicare or Medicaid enrollees, we obtained enrollment, claims files, and prescription (Part D) data. We obtained dates and cause of death from vital status and the National Death Index files. The institutional review board of VHA Tennessee Valley Healthcare System approved this study with a waiver of consent. Our retrospective comparative effectiveness study design emulates a controlled trial for each of the comparisons of interest (Supplemental methods).

Diabetes population and episode index date

The source population comprised veterans aged 18 years and older who were regular VHA users, i.e., had an encounter or prescription fill at least once every 365 days for two or more years before cohort entry. We identified patients who newly filled a first antidiabetic prescription (metformin, insulin, or sulfonylurea) without any antidiabetic fill in the 180 days prior. We then identified episodes from this cohort defined by a new fill of one of the following medication classes: GLP1RA; SGLT2i or DPP4i.

The index date and start of follow-up was the day of GLP1RA; SGLT2i or DPP4i prescription fill. A new episode of use was defined as a new prescription for one of the medications in the study classes (see Exposures, Supplemental Table 1) without use of that medication class in the prior 180 days. We created a wash out period before the index date by restricting use of any other new medication class in the 90 days prior to the index date (Figure 1). This allowed for an evaluation of the new medication without contamination or withdrawal by a different medication class under investigation. For example, a patient who began a new SGLT2i episode would qualify for inclusion as a new episode if there were no fills of SGLT2i in the prior 180 days (new user) and no active days supply of DPP4i or GLP1RA in the prior 90 days. Patients who were on metformin, insulin or sulfonylurea co-therapies (or combinations) in the 180 days before the index date were included. Patients who used all three medications (metformin+ sulfonylurea+ insulin) or another drug class (such as acarbose or thiazolidinedione) were excluded. Patients on dialysis, organ transplantation, or hospice care within the 2 years prior to the index date were excluded.

All episodes were then stratified by CVD status. Prior CVD was defined as any of the following conditions: myocardial infarction; obstructive coronary disease; peripheral artery disease or revascularization; carotid revascularization and history of stroke or transient ischemic attack in the 720 days prior to the index date.

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Exposures

Study exposures included persistent use of: exenatide, liraglutide, semaglutide, dulaglutide, lixisenatide, albiglutide (GLP1RA); empagliflozin, dapagliflozin, canagliflozin (SGLT2i); or alogliptin, linagliptin, saxagliptin, sitagliptin (DPP4i). The index date and start of follow-up was the medication fill date and continued through an outcome or non-persistence of that drug class, defined as 90 days without that drug class or the addition or crossover to a different medication class under investigation. Switching within medication class was allowed. A patient who ended follow-up could re-enter the cohort as a new episode if all entry criteria were satisfied.

Outcomes

The composite outcome was the time to MACE or HF hospitalization. The outcome date was hospital admission date for acute myocardial infarction, ischemic or hemorrhagic stroke, acute heart failure, or cardiovascular death date. The primary discharge diagnosis or underlying cause of death identified each event. We also evaluated each component separately.

We defined acute myocardial infarction by discharge codes 410.x, or I21.x. Stroke hospitalizations included ischemic stroke (433.x1, 434 [excluding 434.x0], 436, or I63.30; I63.40; I63.50; I66.09; I66.19; I66.29; I66.9; I66.9; I67.848; I67.89), intracerebral hemorrhage (431 or I61.x), and subarachnoid hemorrhage (430 or I60.x). When compared to medical record review, these codes demonstrate high positive predictive values (90% acute myocardial infarction; 81% stroke)(28).

HF hospitalization included a primary diagnosis of HF, cardiomyopathy, or hypertensive heart disease with HF (425.X; 428.X; 404.01, 404.03, 404.11, 404.13, 398.91, 402.01, 402.11, 402.91, 404.91, 404.93, I50.2*; I50.3*; I50.9; I42.9; I13.0; I13.2; I09.81; I11.0). HF hospitalization could also be captured with a diagnosis-related group code (127 or 291-293) (29,30). To understand HF hospitalization type, we utilized the natural language processing echocardiogram algorithm developed by Patterson et. al (precision measured for ejection fraction between 0.97 and 1.0) (31). Only echocardiograms conducted within VHA were available to determine HF type based on ejection fraction (reduced <40%; mid-range 40-49%; and preserved ≥50%). The echocardiogram used was the study closest to admission day and up to seven days after admission. If no echocardiogram was obtained, we evaluated echocardiograms up to one year before and closest to admission. If no echocardiogram information was available (no numeric ejection fraction or Medicare claim hospitalization), then HF hospitalization type was considered unknown.

Cardiovascular deaths were identified from death certificates with an underlying cause of death compatible with cardiac death, fatal myocardial infarction, stroke or cardiomyopathy (I00-I78 excluding I30.X [diseases of the pericardium]) or unattended sudden cardiac death (R98, R99, R960, R961). This definition included the Centers for Disease Control and Prevention definition of cardiac death and a validated strategy for identifying sudden cardiac deaths (32).

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Covariates

Study covariates were measured up to 720 days before the index date and included: age, sex, race, year, and a surrogate for diabetes duration (years from cohort entry to index date). We accounted for diabetes co-therapies (metformin, sulfonylurea, insulin), and Veterans Integrated Service Network. Each network is a geographic designation for VHA and represents an estimation of geographic variation of diabetes prevalence and care. Physiologic variables were defined as the most recent measure in the two years before index date and included: body mass index, blood pressure, HbA1c, low density lipoprotein, hemoglobin, proteinuria, echocardiogram ejection fraction and creatinine. Creatinine was used to calculate estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration 2021 equation without race adjustment (33,34). Healthcare utilization included: hospitalization, nursing home, number of outpatient visits or medications, Medicare or Medicaid insurance use. We collected data on smoking, co-morbidities and selected medications defined in Supplemental Table 2. We utilized self-reported categorical race from VHA and Medicare in models (35).

Statistical Analyses

The primary analysis used Cox Proportional Hazard models to compare time to MACE and HF events between medication groups using pairwise comparisons in a propensity score weighted cohort in patients without prior CVD. The unit of analysis was the episode of medication use. Censoring criteria included: study end date (December 31, 2019); non persistence (90 days without medication); crossover/addition of diabetes drug in a different class (e.g. SGLT2i user who starts GLP1RA) and the 181st day of no VHA contact (inpatient, outpatient, or pharmacy use).

The propensity score modeled the probability of GLP1RA versus DPP4i or SGLT2i versus DPP4i given baseline covariates noted above and an indicator for imputed covariates. Missing covariates were handled using thirty iterations of chained imputations (36). We used matching weights to balance the distribution of observed baseline values between exposure groups (Supplemental Methods and Supplemental Figures 1-3) (37-39). DPP4i was the reference in each weighted cohort and models adjusted for covariates. For each pairwise comparison, statistical significance for the two-sided p value was set at 0.05 using robust standard errors to account for patients who contributed multiple episodes of medication use. The proportional hazards assumptions were verified through examination of Schoenfeld residuals over time and follow up was truncated at 3.5 years due to sparse data yielding uncertainty in the proportional hazards assumptions (40). The inverse non-parametric Kaplan Meier estimates of the survival function were used to generate the cumulative incidence curves for the time to event in the weighted cohorts with confidence intervals using 5,000 bootstraps (41).

Secondary, Sensitivity, Subgroup analyses, and effect of an unmeasured confounder

We conducted a secondary analysis that compared the incidence of outcomes between SGLT2i and GLP1RA among those without CVD and for the full cohort with and without CVD. GLP1RA users were considered the reference group. The persistence required analysis is most restrictive and requires persistence on medication to evaluate an association

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on outcomes, because patients must remain on the medication to be analyzed. A sensitivity analysis assumed patients remained in their initial exposure groups with a relaxed adherence requirement; but did not allow cross over to another new medication class. Thus, patients were censored only if they crossed over to another new agent. This analysis is akin to an intention to treat analysis in clinical trials without crossover and increases follow-up time and events but allows misclassification of person time as “time on drug”.

Subgroup analyses report weighted event rates with confidence intervals for the primary prevention cohort as the sample sizes were smaller within subgroups and diagnostic plots suggest that the proportional hazards assumption was violated. Subgroups include: age (≥65, < 65 years), timing of addition (add on as second vs third treatment), baseline estimated glomerular filtration rate (< 60, ≥60 ml/min/1.73m^2), and body mass index (<35 kg/m^2, ≥35 kg/m^2).

We tested the robustness of our findings to unmeasured confounding using an E-value, which quantifies the strength of an unmeasured confounder to render the study results inconclusive (42). That is, if the hypothetical unmeasured confounder could have been adjusted for, it would have shifted the boundary of the effect size's confidence interval to null. All analyses were conducted using R (version 4.1.2) (43).

Role of the Funding source

The VA Clinical Science Research and Development had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The contents do not represent the views of the U.S. Department of Veterans Affairs or the United States Government.

RESULTS

Study cohort and patient characteristics

We identified 557,586 new episodes of the three classes under investigation (Figure 2) among 361,226 patients. We excluded 76,917 episodes for concurrent use of another class under evaluation. Additional exclusions were for data errors (n=60); no VHA health system use in the prior 2 years (n=65,842); co- therapy was not metformin, insulin or sulfonylurea (n=109,502); prescription was outside the study time frame (n=462); missing key data (n=89), hospice care (n=1,894), organ transplant (n=1,961); or dialysis use in past 2 years (n=3,027). Episodes identified as having CVD included: 67,124 DPP4i; 25,093 GLP1RA and 20,687 SGLT2i. The unweighted sample included: 124,161 DPP4i episodes (104,575 patients); 37,660 GLP1RA (32,925 patients); and 23,107 SGLT2i (21,690 patients). Patients had on average 1.1 episodes of medication use (11.4% DPP4i; 9.2% GLP1RA; and 5.2% SGLT2i with 2 or more episodes). After propensity score calculation and weighting, the cohort included 28,759 GLP1RA vs 28,628 DPP4i episodes and 21,200 SGLT2i vs 21,170 DPP4i episodes.

The characteristics of the unweighted episodes for those without CVD are described in Supplemental Table 3. After weighting, patient characteristics were similar between each

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pairwise comparison group (GLP1RA vs DPP4i and SGLT2i vs DPP4i), demonstrating standardized mean differences of less than 0.1 (Table 1, Supplemental Figures 4-5). More than 60% of GLP1RA, SGLT2i or DPP4i episodes were added as a third agent to metformin, insulin and sulfonylurea combination regimens. Within the GLP1RA vs DPP4 weighted cohort, 50% had an HbA1c measured; 61% BMI; and 63% BP measurement within 30 days of the index date; 87% and 89% of had the HbA1c or BP measured within 180 days prior to index date. For the SGLT2 vs DPP4 weighted cohort 56% had HbA1c; 63% BMI; and 67% BP measurement within 30 days of the index date, 88% and 90% of the weighted cohort had the HbA1c and BP measured within 180 days of index date. The characteristics for the weighted cohort with and without cardiovascular disease are reported in Supplemental Table 4.

The median observed follow-up per episode (truncated at 3.5 years) was: 0.58 years (Interquartile range [IQR] 0.23, 1.36) for GLP1RA vs 0.58 years (IQR 0.25, 1.36) DPP4i. Censoring occurred for the following reasons among GLP1RA and DPP4i episodes: end of study 31.0% vs 27.8%; non persistence 53.2% vs 49.7% and 7.3% vs 11.9% for crossover to another study diabetes drug. Median follow-up was 0.42 years (IQR 0.18, 0.91) for SGLT2i vs 0.47 years (IQR 0.22, 0.98) DPP4i. Censoring occurred for 44.8% vs 45.4% study end; 38.5% vs 37.8% non-persistence of drug and 12.2% vs 10.9% for crossover to another study diabetes drug.

Outcomes: Major Adverse Cardiovascular Events (MACE) or Heart Failure Hospitalization

Exposure GLP1RA vs DPP4i—There were 359 composite events among GLP1RA and 482 events in DPP4i users, yielding 13.3 versus 17.8 events per 1,000 person-years of use, respectively; adjusted risk difference (aRD) of 3.2 events (1.1, 5.0) per 1,000 person-years. The matched weighted unadjusted hazard ratio for MACE or HF hospitalization was 0.75 (95% confidence intervals [CI] 0.67, 0.85) and with covariate adjustment the adjusted hazard ratio [aHR] was 0.82 (0.72, 0.94) for use of GLP1RA compared to DPP4i. The cumulative probability of MACE or HF hospitalization at 3.5 years was 1.2% for GLP1RA vs 1.7% for DPP4i (Figure 3A). Results were consistent for each component of the primary outcome but confidence intervals were wide (cardiovascular hospitalizations [aHR of 0.86 (0.70, 1.07)]; cardiovascular deaths [aHR of 0.71 (0.53, 0.94)]; and HF hospitalization [aHR of 0.80 (0.65, 0.99)] (Table 2, Supplemental Figure 6).

Exposure SGLT2i vs DPP4i—There were 186 composite events among SGLT2i and 233 events in DPP4i users without CVD, yielding 12.9 vs 14.9 events per 1,000 person-years with an aRD of 1.28 events (−1.12, 3.32) per 1,000 person-years. The matched weighted unadjusted HR for MACE or HF hospitalization was 0.87 (0.74, 1.03) and after covariate adjustment 0.91 (0.78, 1.08) for SGLT2i compared to DPP4i. The cumulative probability of MACE or HF hospitalization at 3.5 years was 0.9% for SGLT2i vs 1.1% DPP4i (Figure 3B). Results for each component of the outcome were: cardiovascular hospitalizations aHR of 0.99 (0.79, 1.26); cardiovascular deaths aHR of 0.98 (0.71, 1.34); and HF hospitalization aHR of 0.77 (0.57, 1.02) (Table 2, Supplemental Figure 7).

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Additional analyses

In confirmatory analyses for the complete cohort both with and without cardiovascular disease, we demonstrate that results for both GLP1RA and SGLT2i were associated with reduction in both MACE and HF events (Supplemental Table 5 and Supplemental Figure 8). A secondary analysis compared SGLT2i to GLP1RA among the cohort with and without CVD and restricted to the primary prevention cohort demonstrated no statistical differences in the association of MACE or HF hospitalization between groups (Supplemental Table 6A). Sensitivity analysis allowed for reduced medication adherence but no cross over from one class under investigation to another. These results were consistent with main results, but differences were attenuated (Supplemental Table 6B). Subgroup event rates were low but consistent with the main results (Supplemental Table 7 and 8). The E-value for the GLP1RA vs DPP4i analysis was 1.32, meaning a hypothetical confounder would need to have a relative risk of 1.32 between each exposure and the composite MACE and HF outcome to negate findings (**See Bias discussion in** Supplemental Methods)

DISCUSSION

Among a national cohort of older VHA patients with diabetes but without established CVD, we found that addition of GLP1RA to baseline diabetes therapy was associated with reduced MACE and HF hospitalization events compared with adding DPP4i. These findings were consistent with each outcome component. Adding SGLT2i was not associated with reduced MACE and HF hospitalizations compared with adding DPP4i. However, although not statistically significant, SGLT2i use(over a median follow up 0.42 years, was associated with numerically fewer HF hospitalizations. Among the complete cohort that included patients both with and without CVD, both GLP1RA and SGLT2i were associated with reduced MACE and HF hospitalizations compared with DPP4i users.

These findings have important implications for patient care and advance what we know about use of these medications in primary CVD prevention. Early cardiovascular outcomes trials excluded or had few participants without CVD. Our results expand on the work of a network meta-analysis by Zheng et al. which included over 50 clinical trials. Zheng reported that compared to DPP4i, both SGLT2i and GLP1RA were associated with reductions in mortality and cardiovascular hospitalizations among those with underlying CVD (44). Zelnicker et. al. conducted two meta-analyses of similar clinical trial data and restricted to those without CVD (primary prevention) and both GLP1RA and SGLT2i failed to meet statistical significance vs. placebo for primary CVD prevention (20,45,46).

There are GLP1RA trials that report statistically important reductions in MACE events among primary prevention participants. In both the recent Glycemia Reduction in Type 2 Diabetes trial and the REWIND clinical trial, GLP1RA demonstrated reduced incidence of any CVD (47) and MACE incidence for primary prevention (15). Data from SGLT2i trials have been more heterogeneous. The CREDENCE trial demonstrated reduction in MACE and HF hospitalization (48) while DECLARE TIMI 58 trial found no difference in MACE but a reduction in CV death and HF events among the primary prevention group (14,49).

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Our analyses demonstrate consistency with the results of the GLP1RA clinical trials, with larger sample sizes and more real world clinical use among populations who were older, with multiple comorbidities, but without significant CVD. We also report reductions in HF hospitalization outcomes. These findings in aggregate suggest that GLP1RA may have a role in CVD prevention which pertain to all users irrespective of CVD history.

The exact mechanisms of cardio-protection for these two novel medication classes remain relatively unknown. GLP1RAs are postulated to exert their cardioprotective effects via many clinical pathways, including reductions in weight, blood pressure, cholesterol or HBA1c lowering; despite short interval follow up (median 0.58 years; [IQR 0.23, 1.36]) in our cohort, the GLP1RA group still met statistical significance in regards to the primary composite outcome, suggesting there may be alternative explanations for the cardioprotection. Other mechanisms suggest that GLP1RAs may improve endothelial function, vascular responses to ischemia, and platelet function, which could plausibly result in clinically meaningful outcomes in a shorter time course (50-53).

SGLT2i medications are posited to exert cardioprotective effects through indirect systemic effects (diuresis, improved renal function, erythropoiesis), and direct myocardial effects (improved cardiac energy metabolism and inflammation reduction)(54). It is possible our study did not observe statistically significant effects on MACE and HF outcomes, possibly due to the short-observed follow-up (median follow-up was 0.42 years (IQR 0.18, 0.91)). For example, post-hoc analyses of the SGLT2i trials show that sustained and robust efficacy can be observed as early as 28 days after initiation, but primarily among those with pre-existing HF, and it is presumed that these early effects are driven by the diuretic as opposed to myocardial metabolic changes which requires time to manifest (55). In contrast, another cohort comparing SGLT2i to metformin as first line treatment demonstrated SGLT2i use was associated with lower risk of HF but cumulative incidence curves began to separate after about 6 months of use (56).

This study also adds a secondary analysis that compares GLP1RA vs SGLT2i among the complete cohort and the primary prevention population. We are unaware of randomized data directly comparing these two novel classes. In a study by Patorno et. al, no statistical differences in MACE outcomes were found, but results favored SGLT2i when evaluating HF hospitalization (57). Our results are also similar to a Danish study (58) in which cardiovascular outcomes were evaluated after addition of GLP1RA or SGLT2i and found no difference between groups.

There are several study limitations. First, patients were excluded if the initial diabetes therapy did not include metformin, sulfonylurea, or insulin. The American Diabetes Association guidelines continue to recommend that most patients' treatment includes metformin and lifestyle modifications with risk assessment (CVD, HF, or chronic kidney disease) (59). This differs from the European cardiology and diabetes guidelines which recommend using SGLT2i as first line for those with CVD. This study did not evaluate patients who initiated use of DPP4i, GLP1RA, or SGLT2i, as first line therapy; and it should be noted that most patients added the GLP1RA or SGLT2i onto existing combination regimens (as a third agent). Second, there was a short median follow-up in each weighted

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cohort; which may have impacted the ability to detect statistical differences between SGLT2i and DPP4i on MACE and HF hospitalization. Third, veterans may not receive all their care at VHA facilities, therefore, misclassification of those without CVD may have occurred and outcomes may have been missed despite the linkage to Medicare and Medicaid data. This also resulted in many patients without echocardiograms. Because of the high proportion of missing echocardiograms, the number and rates for HF type should be interpreted with caution. Fourth, although propensity score weighting and direct covariate adjustment were used to address confounding, there may be residual confounding. An E value of 1.32 indicates that a moderate confounder is needed to negate the study findings. The plausibility of moderate confounders depends on the thoroughness of the covariates. The VHA data merged with Medicare and Medicaid data allowed this study to extensively control for possible confounders. Finally, the study population was mostly white men who based on our data did not have a recorded history of CVD, thus, results may not be generalizable to populations with lower representation in VHA.

In conclusion, this study demonstrates that among a national cohort of VHA patients, adding GLP1RA was associated with primary prevention for MACE and HF vs DPP4i. In contrast, SGLT2i was not associated with primary prevention for MACE and HF although may have been limited by short follow-up time. These findings are hypothesis generating and further evaluation of these medications as part of primary CVD prevention strategy is needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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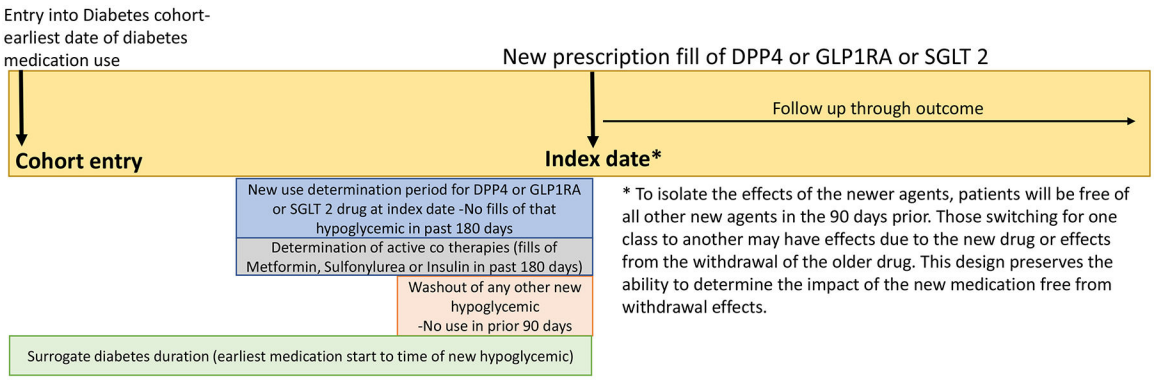

Figure 1:
Schematic of study entry and index date

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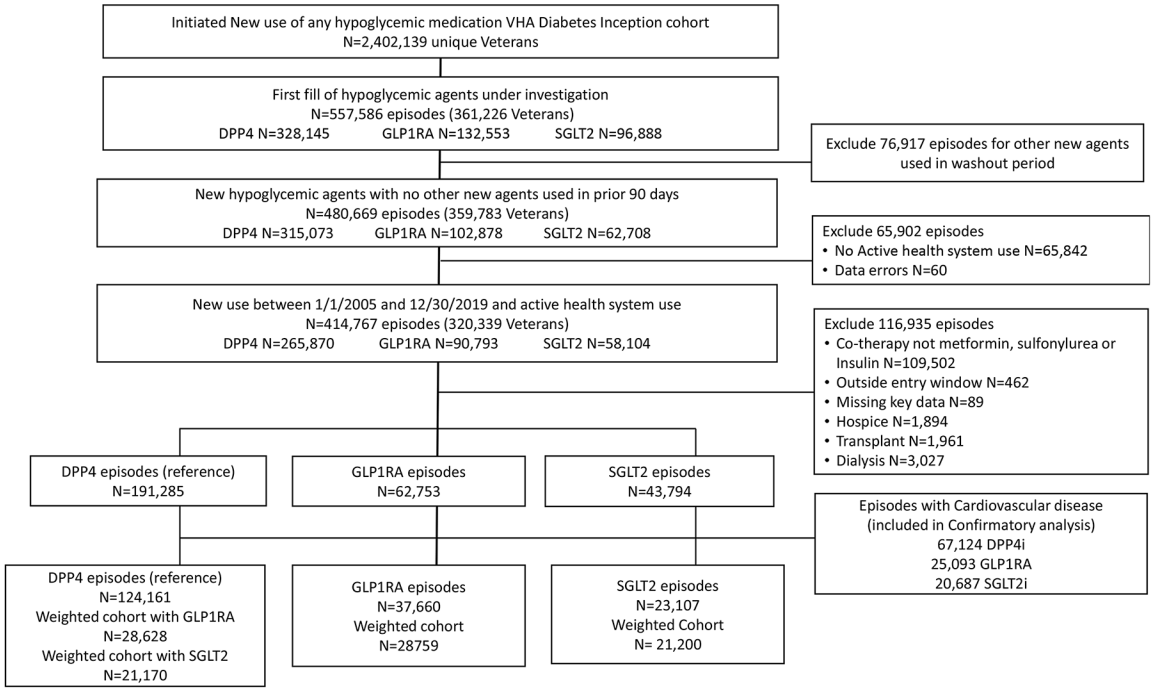

Figure 2:
Flow chart of eligible episodes of care and final study sample

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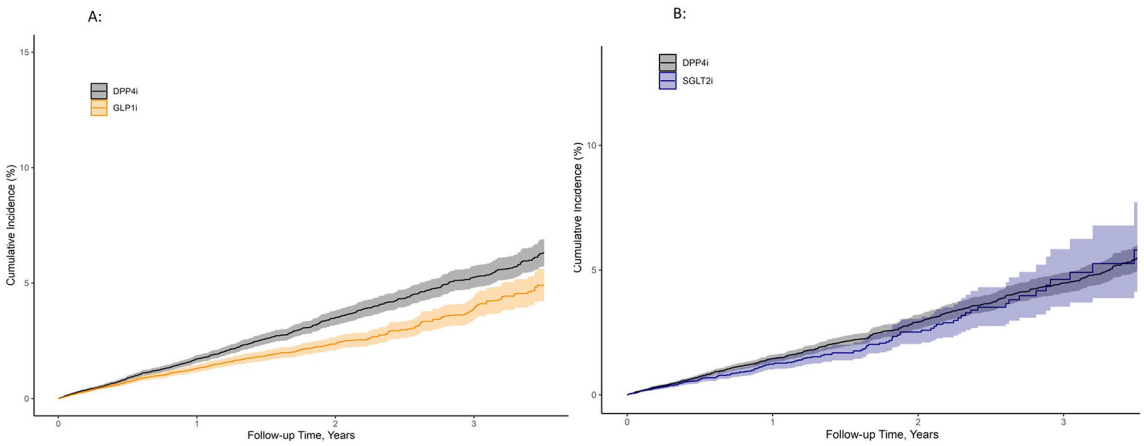

Figure 3:

Part A: Cumulative incidence of Major Adverse Cardiovascular and heart failure events among GLP1RA vs DPP4i users without cardiovascular disease.

timePoints	0	0.5	1	1.5	2	2.5	3	3.5
atRiskDPP4	28628	15476	9617	6398	4227	2816	1891	873
atRiskGLP1	28759	15534	9797	6408	4156	2756	1767	732

Part B: Cumulative incidence of Major Adverse Cardiovascular and heart failure events among SGLT2i vs DPP4i users without cardiovascular disease.

timePoints	0	0.5	1	1.5	2	2.5	3	3.5
atRiskDPP4	21170	9910	5188	3019	1762	1053	620	257
atRiskSGLT2	21200	9463	4670	2680	1394	748	357	125

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Ann Intern Med. Author manuscript; available in PMC 2023 December 01.

Table 1:

Patient Characteristics on Index date for those without Cardiovascular Disease

	DPP4i N=28,628	GLP1RA N=28,628	SMD	DPP4i N=28,628	SGLT2i N=28,628	SMD
Age, years *	66.0 [57.9, 71.0]	66.2 [57.9, 71.1]	0.001	66.9 [59.1,71.5]	67.0 [59.1,71.5]	0.016
Male, (No., %)	26337 (92.0)	26488 (92.1)	0.004	19929 (94.1)	19974 (94.2)	0.003
Race, (No., %)			0.005			0.004
Other	1117 (4.1)	1146 (4.2)		773 (3.9)	774 (3.9)	
Black	5905 (21.9)	5908 (21.8)		4406 (21.9)	4446 (22.1)	
White	19979 (74.0)	20058 (74.0)		14900 (74.2)	14888 (74.0)	
Missing Race (No., %)	1627 (5.7)	1647 (5.7)	0.002	1091 (5.2)	1092 (5.2)	<0.001
Medication start to index date, years *	8.5 (4.8, 12.9)	8.5 (4.8, 12.9)	0.004	8.8 [5.4, 13.2]	8.8 [5.3, 13.2]	0.001
Co-Therapy, (No., %)			0.005			0.005
Metformin	2915 (10.2)	2931 (10.2)		3574 (16.9)	3552(16.8)	
Sulfonylurea	1069 (3.7)	1064 (3.7)		1174 (5.5)	1166 (5.5)	
Insulin	6191 (21.6)	6249 (21.7)		2802 (13.2)	2814 (13.3)	
Metformin + Sulfonylurea	5283 (18.5)	5271 (18.3)		6676 (31.5)	6674 (31.5)	
Metformin + Insulin	11172 (39.0)	11253 (39.1)		6191 (29.2)	6231 (29.4)	
Sulfonylurea + Insulin	1997 (7.0)	1991 (6.9)		754 (3.6)	764 (3.6)	
Year of cohort entry, (No., %)			0.098			0.054
2005-2007	167 (0.6)	309 (1.1)		0 (0)	0 (0)	
2008-2010	1067 (3.7)	883 (3.1)		0 (0)	0 (0)	
2011-2013	2340 (8.2)	2476 (8.6)		110 (0.5)	59 (0.3)	
2014-2016	7223 (25.2)	7314 (25.4)		2958 (14.0)	2966 (13.9)	
2017-2019	17831 (62.3)	17777 (61.8)		18103 (85.5)	18175 (85.7)	
Clinical Variables						
Body Mass Index, kg/m2 *	34.3 [30.4, 38.9]	34.6 [30.7, 39.2]	0.039	32.8 [29.1,37.2]	33.0 [29.3, 37.4]	0.023
Missing BMI Measure (No., %)	6276 (21.9)	6264 (21.8)	0.003	4838 (22.9)	4779 (22.5)	0.007
Systolic Blood Pressure, mm/Hg *	133 [123, 143]	133 [123, 143]	0.004	133 [124, 143]	133 [123, 143]	0.003
Diastolic Blood Pressure mm/Hg *	76 [70, 82]	76 [70, 83]	0.001	77 [70, 83]	77 [70, 83]	0.005
Missing Diastolic Blood Pressure (No., %)	688 (2.4)	675 (2.3)	0.004	410 (1.9)	379 (1.8)	0.011

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	DPP4i N=28,628	GLP1RA N=28,628	SMD	DPP4i N=28,628	SGLT2i N=28,628	SMD
Echocardiogram Ejection Fraction Category (No., %)			0.019			0.018
Normal < 50%	5044 (17.6)	5129 (17.8)		3724 (17.6)	3756 (17.7)	
Indeterminate 40-49%	676 (2.4)	664 (2.3)		507 (2.4)	515 (2.4)	
Reduced/Severe < 40%	630 (2.2)	652 (2.3)		519 (2.5)	551 (2.6)	
Missing/Unavailable	22277 (77.8)	22314 (77.6)	0.005	16421(77.6)	16378 (77.3)	0.007
Laboratory Variables						
HbA1c, % *	8.4 [7.6, 9.6]	8.6 [7.6, 9.7]	0.004	8.4 [7.7, 9.4]	8.5 [7.7, 9.5]	0.013
Missing HbA1c (No., %)	2152 (7.5)	2095 (7.3)	0.009	1560 (7.4)	1510 (7.1)	0.01
Hemoglobin, g/dL *	14.1 [13.1, 15.1]	14.1 [13.1, 15.1]	0.005	14.3 [13.3, 15.2]	14.3 [13.3, 15.2]	0.003
Missing Hemoglobin (No.,%)	2905 (10.1)	2902 (10.1)	0.002	1841 (8.7)	1803 (8.5)	0.007
Estimated Glomerular Filtration rate, ml/min/1.73 m2 *	79.5 [60.5, 95.8]	79.5 [60.1, 95.7]	0.002	83 [68, 95]	82 [67, 96]	0.004
Serum Creatinine mg/dL *	1.03 [0.89, 1.30]	1.03 [0.89, 1.30]	0.001	1.00 [0.87, 1.19]	1.00 [0.87, 1.20]	0.016
Missing Creatinine (No.,%)	1905 (6.7)	1893 (6.6)	0.003	1241 (5.9)	1172 (5.5)	0.014
Low Density Lipoprotein mg/dL *	81 [63, 105]	81 [63, 105]	0.003	81 [62, 105]	81 [62, 106]	<0.001
Missing Low Density Lipoprotein (No., %)	1984 (6.9)	1945 (6.8)	0.007	1239 (5.9)	1175 (5.5)	0.013
Urine protein on urinalysis (No., %)			0.002			0.009
Negative	11585 (40.5)	11615 (40.4)		8851 (41.8)	8879 (41.9)	
trace or 1+	3302 (11.5)	3321 (11.5)		2020 (9.5)	2048 (9.7)	
2+	1879 (6.6)	1901 (6.6)		1117 (5.3)	1142 (5.4)	
3+/4+/trace to 4+	527 (1.8)	529 (1.8)		220 (1.0)	227 (1.1)	
Missing Urine protein measure (No., %)	11335 (39.6)	11392 (39.6)		8962 (42.3)	8904 (42.0)	
Microalbumin to Creatinine ratio (MACR) stage N (No., %)			0.006			0.008
A1 (<30 mg/g- normal to mild increase albuminuria)	11676 (40.8)	11769 (40.9)		9161 (43.3)	9182 (43.3)	
A2 (30-300 mg/g- moderate increase albuminuria)	5284 (18.5)	5348 (18.6)		3993 (18.9)	4037 (19.0)	
A3 and positive (>300 mg/g severely increased albuminuria)	2068 (7.2)	2078 (7.2)		1310 (6.2)	1334 (6.3)	
Missing MACR measure	9599 (33.5)	9564 (33.3)		6706 (31.7)	6647 (31.4)	
Baseline Comorbidities (No., %) ≠						
Cardiovascular conditions						
Congestive Heart Failure	1366 (4.8)	1383 (4.8)	0.002	978 (4.6)	991.4 (4.7)	0.003
Arrhythmias	1557 (5.4)	1558 (5.4)	0.001	950 (4.5)	944.3 (4.5)	0.002

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	DPP4i N=28,628	GLP1RA N=28,628	SMD	DPP4i N=28,628	SGLT2i N=28,628	SMD
Cardiac valve disease	392 (1.4)	395 (1.4)	<0.001	322 (1.5)	322.4 (1.5)	<0.001
Pulmonary Conditions						
Smoking	2978 (10.4)	2987 (10.4)	<0.001	1816 (8.6)	1831 (8.6)	0.002
Chronic Obstructive Pulmonary Disease	3868 (13.5)	3888 (13.5)	<0.001	2691 (12.7)	2694 (12.7)	<0.001
History of Respiratory failure	713 (2.5)	712 (2.5)	0.001	468 (2.2)	476 (2.2)	0.002
Neuro- Psychiatric Conditions						
Serious Mental Illness	9440 (33.0)	9532 (33.1)	0.004	6277 (29.6)	6318 (29.8)	0.003
Parkinson's	209 (0.7)	215 (0.7)	0.002	149 (0.7)	146 (0.7)	0.002
Retinopathy	3642 (12.7)	3666 (12.7)	0.001	2183 (10.3)	2233 (10.5)	0.007
Infectious Conditions						
History of Sepsis	494 (1.7)	488 (1.7)	0.002	267 (1.3)	263 (1.2)	0.002
History of Pneumonia	502 (1.8)	499 (1.7)	0.001	316 (1.5)	313 (1.5)	0.001
HIV	130 (0.5)	134 (0.5)	0.002	95 (0.4)	97 (0.5)	0.001
Urinary tract infection	1266 (4.4)	1274 (4.4)	<0.001	626 (3.0)	625 (2.9)	<0.001
Osteomyelitis	229 (0.8)	222 (0.8)	0.003	100 (0.5)	101 (0.5)	0.001
Other serious illness and disabilities						
Malignancy	2729 (9.5)	2761 (9.6)	0.002	2119 (10.0)	2119 (10.0)	0.001
Liver disease	1306 (4.6)	1323 (4.6)	0.002	1108 (5.2)	1133 (5.3)	0.005
History of Kidney disease	7 (0.0)	7 (0.0)	<0.001	1 (0.0)	1 (0.0)	0.003
Osteoporosis	197 (0.7)	195 (0.7)	0.001	130 (0.6)	128 (0.6)	0.001
Falls	248 (0.9)	246 (0.9)	0.001	197 (0.9)	194 (0.9)	0.002
Fractures	510 (1.8)	506 (1.8)	0.002	323 (1.5)	319 (1.5)	0.002
Amputation	113 (0.4)	115 (0.4)	<0.001	56 (0.3)	58 (0.3)	0.001
Use of Medications (No., %)						
ACE Inhibitors	14682 (51.3)	14739 (51.2)	0.001	11031 (52.1)	11061 (52.2)	0.001
Angiotensin Receptor Blockers	6916 (24.2)	6960 (24.2)	0.001	4908 (23.2)	4921 (23.2)	0.001
Beta Blockers	10508 (36.7)	10564 (36.7)	0.001	7697 (36.4)	7713 (36.4)	<0.001
Calcium Channel Blockers	8852 (30.9)	8920 (31.0)	0.002	6385 (30.2)	6404 (30.2)	0.001
Thiazide/potassium sparing diuretics	9886 (34.5)	9945 (34.6)	0.001	6914 (32.7)	6947 (32.8)	0.002
Loop diuretics	4215 (14.7)	4218 (14.7)	0.002	2252 (10.6)	2259 (10.7)	0.001
Other antihypertensives	7996 (27.9)	8020 (27.9)	0.001	5499 (26.0)	5459 (25.8)	0.005

Ann Intern Med. Author manuscript; available in PMC 2023 December 01.

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	DPP4i N=28,628	GLP1RA N=28,628	SMD	DPP4i N=28,628	SGLT2i N=28,628	SMD
Lipid-lowering statins	22020 (76.9)	22159 (77.1)	0.003	16680 (78.8)	16724 (78.9)	0.002
Non-statin lipid-lowering agents	4407 (15.4)	4427 (15.4)	<0.001	3019 (14.3)	3003 (14.2)	0.003
Anti-arrhythmic digoxin and inotropes	1387 (4.8)	1397 (4.9)	<0.001	1190 (5.6)	1177 (5.6)	0.003
Anticoagulants	2114 (7.4)	2129 (7.4)	0.001	1686 (8.0)	1677 (7.9)	0.002
Nitrates	841 (2.9)	834 (2.9)	0.002	617(2.9)	616 (2.9)	<0.001
Aspirin	5641 (19.7)	5723 (19.9)	0.005	4228 (20.0)	4296 (20.3)	0.007
Platelet inhibitors	949 (3.3)	941 (3.3)	0.002	857 (4.1)	848 (4.0)	0.003
Antipsychotics	1853 (6.5)	1879 (6.5)	0.002	1284 (6.1)	1287 (6.1)	<0.001
Oral Glucocorticoids	2749 (9.6)	2734 (9.5)	0.003	1970 (9.3)	1921 (9.1)	0.008
Indicators of Utilization (No.,%)						
Hospitalization within year (Veterans Health)	2014 (7.0)	2030 (7.1)	0.001	1247 (5.9)	1284 (6.1)	0.007
Hospitalizations within 30 days (Veterans Health)	301 (1.1)	303 (1.1)	<0.001	208 (1.0)	216 (1.0)	0.004
Hospitalizations within year (Medicaid/ Medicare)	1121 (3.9)	1113 (3.9)	0.002	649 (3.1)	630 (3.0)	0.006
Hospitalizations within 30 days (Medicaid/ Medicare)	118 (0.4)	114 (0.4)	0.002	72 (0.3)	73 (0.3)	<0.001
Medicaid insurance use in last year	638 (2.2)	615 (2.1)	0.006	262 (1.2)	252 (1.2)	0.004
Medicare insurance use in last year	11733 (41.0)	11499 (40.0)	0.02	8286 (39.1)	7886 (37.2)	0.04
Nursing home encounters	78 (0.3)	80 (0.3)	0.001	45 (0.2)	48 (0.2)	0.002
Outpatient visits in last year *	6.0 [3.0, 10.0]	6.0 [3.0, 11.0]	0.012	5 [2, 9]	5 [2, 10]	0.016
Outpatient Medications§	5.0 [3.0, 6.0]	5.0 [4.0, 6.0]	0.004	4 [3, 6]	4 [3, 6]	0.001
Medicare Advantage Use	l 7336 (25.6)	7271 (25.3)	0.008	5047 (23.8)	4880 (23.0)	0.019

*Median and IQR = Interquartile range

†See Supplemental Figures 4 and 5 for the plot of the mean Standardized differences of the pre- matched and matched cohort.

‡Definitions of co-morbidities in Supplemental Table 2

§xcludes Diabetes medications, topical and ophthalmic medications and medical supplies)

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Table 2:

MACE and Heart failure event rates and Adjusted Risk difference and Hazard ratios for those without Cardiovascular disease for GLP1RA and SGLT2i vs DPP4i

	DPP4i	GLP1RA	DPP4i	SGLT2i
N at risk in weighted cohort	28,628	28,759	21,170	21,200
N events primary outcome:	482	359	233	186
Composite Major Adverse Cardiovascular				
Events and Heart Failure Hospitalization				
Person-Years	27082	26921	15590	14330
Event Rate/1000 person-years (95% CI)	17.8 (16.3, 19.4)	13.3 (12.0, 14.8)	14.9 (13.1, 17.0)	12.9 (11.2, 14.9)
Adjusted Risk Difference (95% CI) †	3.20 (1.12, 5.01)		1.28 (−1.12, 3.32)	
Weighted Unadjusted Hazard Ratio (95% CI)	Ref	0.75 (0.67, 0.85)	Ref	0.87 (0.74, 1.03)
Adjusted Hazard Ratio (95% CI) *	Ref	0.82 (0.72, 0.94)	Ref	0.91 (0.78, 1.08)
Secondary Outcomes				
N events cardiovascular hospitalization (Acute Myocardial Infarction, Stroke)	189	140	99	89
Person-Years	27217	27025	15638	14358
Event Rate/1000 person-years (95% CI)	6.9 (6.0, 8.0)	5.2 (4.4, 6.1)	6.4 (5.2, 7.7)	6.2 (5.0, 7.6)
Adjusted Risk Difference (95% CI) †	0.93 (−0.47, 2.06)		.04 (−1.64, 1.36)	
Weighted Unadjusted Hazard Ratio (95% CI)	Ref	0.75 (0.62, 0.91)	Ref	0.98 (0.77, 1.25)
Adjusted Hazard Ratio (95% CI) *	Ref	0.87 (0.70, 1.07)	Ref	0.99 (0.79, 1.26)
N events cardiovascular death	121	79	61	48
Person-Years	27348	27113	15700	14400
Event Rate/1000 person-years (95% CI)	4.4 (3.7, 5.3)	2.9 (2.3, 3.6)	3.9 (3.0, 4.9)	3.4 (2.5, 4.5)
Adjusted Risk Difference (95% CI) †	1.29 (0.26, 2.07)		0.10 (−1.31, 1.12)	
Weighted Unadjusted Hazard Ratio (95% CI)	Ref	0.66 (0.51, 0.85)	Ref	0.88 (0.64, 1.22)
Adjusted Hazard Ratio (95% CI) *	Ref	0.71 (0.53, 0.94)	Ref	0.98 (0.71, 1.34)
N events heart failure hospitalization	204	153	85	56
Person-Years	27207	27007	15650	14372
Event Rate/1000 person-years (95% CI)	7.5 (6.5, 8.6)	5.7 (4.8, 6.6)	5.4 (4.4, 6.7)	3.9 (3.0, 5.0)
Adjusted Risk Difference (95% CI) †	1.47 (0.11, 2.59)		1.27 (−0.13, 2.32)	
Weighted Unadjusted Hazard Ratio (95% CI)	Ref	0.76 (0.63, 0.91)	Ref	0.73 (0.54, 0.97)
Adjusted Hazard Ratio (95% CI) *	Ref	0.80 (0.66, 0.99)	Ref	0.77 (0.57, 1.02)
Preserved EF ≥50%	25 events	13 events	10 events	4 events
Event Rate/1000 person-years (95% CI)	0.9 (0.6, 1.3)	0.5 (0.3, 0.8)	0.6 (0.3, 1.2)	0.3 (0.1, 0.7)
Midrange EF 40-50%	11 events	7 events	4 events	1 event
Event Rate/1000 person-years (95% CI)	0.4 (0.2, 0.7)	0.3 (0.1, 0.5)	0.3 (0.1, 0.7)	0.1 (0.01, 0.4)
Reduced EF <40%	13 events	11 events	6 events	6 events
Event Rate/1000 person-years (95% CI)	0.5 (0.3, 0.8)	0.4 (0.2, 0.7)	0.4 (0.2, 0.8)	0.4 (0.2, 0.9)
Unknown EF	155 events	122 events	65 events	45 events
Event Rate/1000 person-years (95% CI)	5.7 (4.9, 6.7)	4.5 (3.8, 5.4)	4.2 (3.3, 5.3)	3.1 (2.3, 4.2)

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[*] Fully adjusted model uses weighted cohort and adjust for all covariates listed in Table 1 All continuous variables were modeled as restricted cubic splines.

[†] The adjusted rate difference is estimated by multiplying the unadjusted incident rate for DPP4i by the adjusted hazard ratio minus 1. Confidence bounds are calculated using the respective bounds from the hazard ratio