ORIGINAL RESEARCH

Cardiovascular Effectiveness of Sodium-Glucose Cotransporter 2 Inhibitors and Glucagon-Like Peptide-1 Receptor Agonists in Older Patients in Routine Clinical Care With or Without History of Atherosclerotic Cardiovascular Diseases or Heart Failure

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BACKGROUND: Randomized trials demonstrate the cardioprotective effects of sodium-glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA). We evaluated their relative cardiovascular effectiveness in routine care populations with a broad spectrum of atherosclerotic cardiovascular diseases (CVDs) or heart failure (HF).

METHODS AND RESULTS: We identified Medicare beneficiaries from 2013 to 2017, aged >65 years, initiating SGLT2i (n=24 747) or GLP-1RA (n=22 596) after a 1-year baseline. On the basis of diagnoses during baseline, we classified patients into: (1) no HF or CVD, (2) HF but no CVD, (3) no HF but CVD, and (4) both HF and CVD. We identified hospitalized HF and atherosclerotic CVD outcomes from drug initiation until treatment changes, death, or disenrollment. We estimated propensity score–weighted 2-year risk ratios (RRs) and risk differences, accounting for measured confounding, informative censoring, and competing risk. In patients with no CVD or HF, SGLT2i reduced the hospitalized HF risk compared with GLP-1RA (propensity score–weighted RR, 0.65; 95% CI, 0.43–0.96). The association was strongest in those who had HF but no CVD (RR, 0.48; 95% CI, 0.25–0.85). The combined myocardial infarction, stroke, and mortality outcome risk was slightly higher for SGLT2i compared with GLP-1RA in those without CVD or HF (RR, 1.31; 95% CI, 1.09–1.56). The association was favorable toward SGLT2i in subgroups with a history of HF.

CONCLUSIONS: SGLT2i reduced the cardiovascular risk versus GLP-1RA in patients with a history of HF but no CVD. Atherosclerotic CVD events were less frequent with GLP-1RA in those without prior CVD or HF.

Key Words: glucagon-like peptide-1 receptor ■ heart failure ■ myocardial infarction ■ sodium-glucose transporter 2 inhibitors ■ type 2 diabetes

Nearly 30% of Americans aged >65 years have diabetes, and the prevalence has been increasing steadily over the past decades.[1] Diabetes is a major risk factor for cardiovascular diseases (CVDs), with patients with type 2 diabetes having a higher risk of coronary artery disease, myocardial infarction (MI), stroke, heart failure (HF), and other cardiovascular events than patients without diabetes.[2–4] Patients with diabetes and CVD are also more likely to have recurrent attacks (eg, reinfarction) and mortality compared with counterparts without

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CLINICAL PERSPECTIVE

What Is New?

- This study provides real-world evidence from a large population-based cohort study using federal insurance claims data (Medicare) on the head-to-head comparison of the cardioprotective glucose-lowering agents, sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists, with respect to heart failure, myocardial infarction, stroke, and mortality outcomes.
- We specifically examined such comparison within specific populations of interest presenting with varying history of atherosclerotic cardiovascular disease and/or heart failure at baseline.

What Are the Clinical Implications?

- Because our study was based on unselected older populations in routine clinical care who have a lower burden of established cardiovascular diseases, higher overall mean age, and higher burden of multimorbidity and frailty than clinical trial populations, our findings complement trial evidence, informing clinicians of the relevant subpopulations of interest who have varying risk for atherosclerotic cardiovascular disease and heart failure, and could benefit from particular cardioprotective glucose-lowering agents.

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Nonstandard Abbreviations and Acronyms

AT	as treated
GLP-1RA	glucagon-like peptide-1 receptor agonists
HHF	hospitalization for heart failure
IPCW	inverse probability of censoring weights
IPTW	inverse probability of treatment weighting
ITT	intent to treat
MACE	major adverse cardiovascular event
PS	propensity score
SGLT2i	sodium-glucose cotransporter-2 inhibitors

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diabetes.[3,4] Therefore, optimizing cardiovascular morbidity and mortality has become a critical focus of the management of patients with diabetes.[5]

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) were initially developed as glucose-lowering medications that improve glycemia by inhibiting the reabsorption of glucose in the renal proximal tubules.[6] However, these medications have been shown to reduce the risk of cardiovascular events, in particular hospitalization for HF (HHF), in large-scale, placebo-controlled, randomized trials.[7–10] Another class of antihyperglycemic agents, glucagon-like peptide-1 receptor agonists (GLP-1RA), has also demonstrated cardiovascular benefits in large-scale randomized trials.[11–14] Relative to placebo, they lower the risk of the composite outcome of MI, stroke, and cardiovascular mortality, although their effects on HHF have not been fully defined.[11–14]

Thus, recent guidelines endorsed the incorporation of newer agents with cardiovascular benefits (SGLT2i and GLP-1RA) into routine clinical practice, and screening of patients who are at high risk of CVD.[5,15] There are, however, several barriers to implementing these guidelines in clinical practice. There are no large head-to-head trials comparing cardiovascular benefits of SGLT2i relative to GLP-1RA, and most trial populations have a higher burden of established CVD or multiple cardiovascular risk factors, and a lower burden of multimorbidity and frailty compared with the patients in routine care.[7–9,16] It is therefore unknown whether real-world populations will benefit from SGLT2i relative to GLP-1RA and which subgroup of the population will benefit more from which agent, because populations in routine care typically have a broad spectrum of baseline CVD risk.

In addition, analyses of placebo-controlled trials suggest that cardiovascular benefits of SGLT2i may be in part restricted to HF events, particularly in those with a history of HF.[17] This further stressed the importance of evaluating the comparative effectiveness of SGLT2i versus GLP-1RA across the entire spectrum of major atherosclerotic CVD (MI, ischemic heart diseases, peripheral vascular diseases, and cerebrovascular diseases) and HF. Such real-world evidence could help guide clinicians and policy makers in choosing the optimal antihyperglycemic agents in vulnerable older patients based on their observable clinical history of established atherosclerotic CVD and HF. We therefore aimed to estimate the relative effects of SGLT2i versus GLP-1RA on the risk of (1) HHF, (2) the composite of MI, stroke, or mortality (major adverse cardiovascular events [MACEs]), and (3) the composite of MACE and HHF among older US Medicare beneficiaries, stratified by the clinical history of atherosclerotic CVD and HF.

METHODS

As our study was based on routinely collected electronic health care data, informed consent was waived and the study protocol was approved by the Institutional

Review Board at the University of North Carolina at Chapel Hill. Because of data user agreements with the Centers for Medicare and Medicaid Services, databases used in this study are not available to share, but are available to request from the Research Data Assistance Center.

Study Cohorts

We used an active comparator, new user study design identifying cohorts of new users of SGLT2i and GLP-1RA among Medicare fee-for-service beneficiaries from 2012 to 2017 after requiring 1-year washout period during which any SGLT2i or GLP-1RA users were excluded (Figure 1 and Figure S1).[18] During this baseline period, we required patients to have continuous coverage in fee-for-service Medicare plans A (inpatient services), B (physician and outpatient services), and D (prescription drugs) and no evidence of end-stage renal disease or chronic kidney disease (stage 4 or 5). We restricted our Medicare cohorts to those aged >65 years at the time of drug initiation. Medicare fee-for-service claims provide longitudinal health care data on prescription drug dispensing, and health care diagnoses and procedures in inpatient, outpatient, emergency, and institutional care settings for the services reimbursed by the Medicare plans.

We then identified 4 nonoverlapping subgroups based on codes for HF and major atherosclerotic CVD during the 12 months before drug initiation (MI, ischemic heart disease, stroke, cerebrovascular diseases, cardiovascular revascularization procedures, peripheral arterial diseases, and revascularization) (Table S1): (1) no history of HF or CVD, (2) history of HF but no CVD, (3) history of CVD but no HF, and (4) history of both HF and CVD. We identified these baseline conditions using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis and procedure codes, Current Procedural Terminology (CPT) codes, and Healthcare Common Procedure Coding System following claims data-based algorithms from prior validation studies.[19–24]

Exposure Assessment

We identified new drug users using National Drug Codes from the prescription pharmacy claims from Medicare part D claims data. Exposure and comparator drug classes of interest include the following: SGLT2i (canagliflozin, dapagliflozin, and empagliflozin) and GLP-1RA (exenatide, liraglutide, dulaglutide, and albiglutide) (Table S2). To reduce misclassification of pharmacy claims data attributable to patients not adhering to medications, we required beneficiaries to refill medications from the same drug class at least once during 90 days after drug initiation. The second prescription date is the index date from which follow-up of the cohort began.[25]
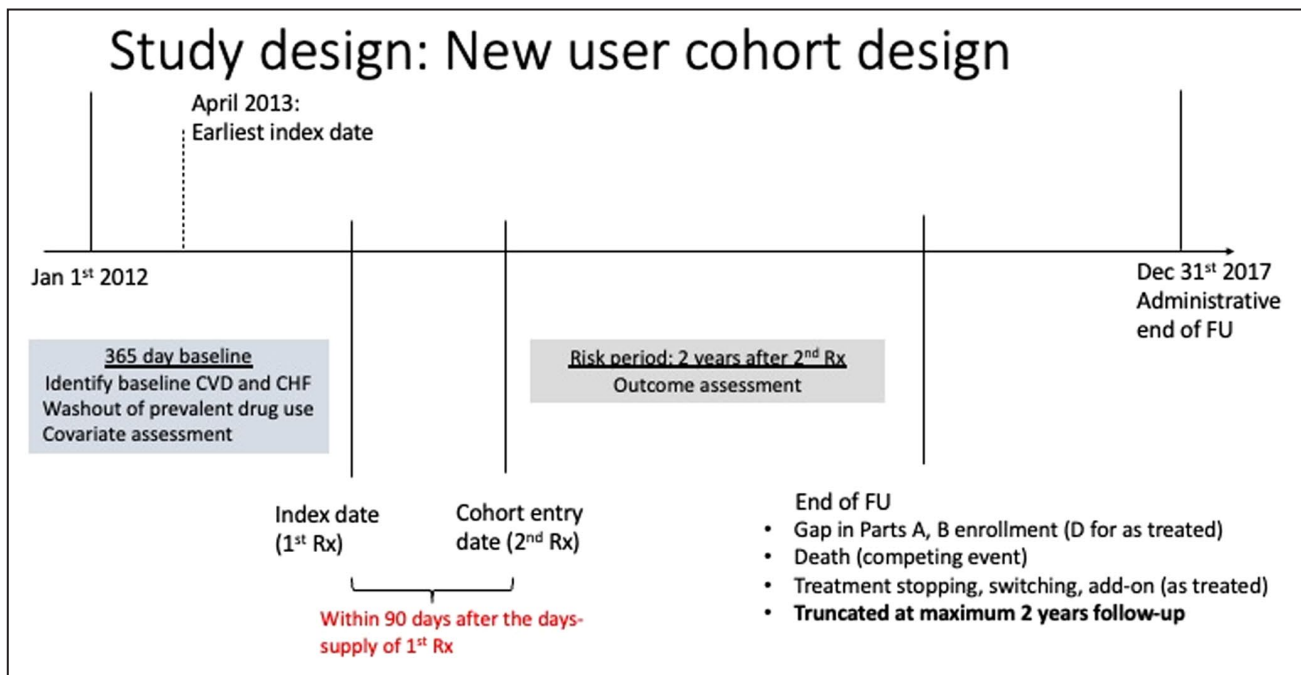
Figure 1. Study design diagram.
CHF indicates congestive heart failure; CVD, cardiovascular disease; FU, follow-up; and Rx, prescription.

Outcomes

We identified outcomes using prior published algorithms that have been shown to have high reported specificity (93%–98%) or positive predictive value (>95%).[19,22–24,26,27] The primary outcomes are as follows: (1) HHF, (2) composite end point of inpatient MI, inpatient stroke, or all-cause mortality (MACE outcome), and (3) the composite of MACE plus HHF. Because cardiovascular deaths account for ≈70% of diabetes-related deaths in adults aged ≥65 years, we used all-cause mortality as a proxy for cardiovascular mortality.[28] Secondary outcomes include individual components of the MACE outcome and MACE plus invasive cardiac procedures (stents, revascularization, and bypass surgery). We assumed death as a competing event for these cardiovascular outcomes (details below).

All outcomes were identified in an inpatient setting with *ICD-9-CM* or *ICD-10-CM* diagnosis codes in primary or secondary positions (Tables S3 through S5 for codes). We identified invasive cardiac procedures using standardized coding systems: Healthcare Common Procedure Coding System and CPT (Table S6). To prevent bias attributable to changes in coding practices (*ICD-9-CM* to *ICD-10-CM* transition after October 2015), we assessed trends in outcome codes over calendar time using various outcome definition algorithms following approaches outlined in literature.[29] Date of mortality was ascertained from the Medicare Master Beneficiary Summary File: National Death Index segment. Over 99% of dates of death reported in the Medicare Master Beneficiary Summary File have been validated using death certificate data according to the Research Data Assistance Center.[30]

Negative Control Outcome

We used all-cause cancer incidence and cataract surgery as negative control outcomes because these outcomes are not affected by SGLT2i or GLP-1RA, and thus should have null association with the exposures if our confounding adjustment and analytical strategies are sufficient to reduce confounding (under the assumption of a similar confounding structure to primary outcomes).[31] In the analyses for cancer, we excluded patients with evidence of cancer or cancer-related therapeutic procedures at baseline using a sensitive algorithm.[32] We repeated the analyses for primary cardiovascular outcomes in this population to ensure that we are comparing primary and control estimates in the same population. In identifying cancer outcomes, we used the claims-based algorithm (at least 2 *ICD-9-CM* or *ICD-10-CM* diagnosis codes during 2 months after the first diagnosis) that has been shown to have near-perfect specificity (>99%) across multiple cancer sites.[33] Similarly for cataract surgery outcome,

we excluded patients with prevalent cataract surgery claims during the baseline period, and primary cardiovascular analyses were repeated in this population.

Risk Periods

Patients were at risk of the outcome starting from the index date (second prescription date) until the end of Medicare enrollment, death, administrative censoring (December 31, 2017), or treatment discontinuation or initiation of (including switching to or adding on) the comparison drug class (as-treated [AT] or on-treatment analyses). We also performed intent-to-treat (ITT) like analyses, in which we did not censor for treatment changes. Patients were followed up for a maximum of 2 years after the start of follow-up to avoid follow-up of patients long after they potentially discontinued their medications (median treatment duration in our cohort was ≈1 year). In sensitivity analyses, we extended the follow-up to all-available years (maximum, 5 years).

Covariate Assessment and Confounding Control

We identified potential confounders using *ICD-9-CM/ICD-10-CM* diagnosis and procedure codes, Healthcare Common Procedure Coding System, and CPT codes during the 1-year baseline period, identifying conditions at high risk of cardiovascular morbidity and mortality: demographics, diabetes complications and proxies of diabetes severity (oral antihyperglycemic medications, short- and long-term insulin, number of hyperglycemia diagnoses, number of noninsulin antihyperglycemic prescriptions, foot ulcers, hypoglycemia, retinopathy, neuropathy, and nephropathy), cardiovascular disorders and proxies of CVD severity, chronic comorbid disorders, Charlson/Elixhauser combined comorbidity scores, proxies of frailty (durable medical equipment claims, disability, or chronic debilitating conditions), socioeconomic status indicators (low-income subsidy), proxies of smoking, smoking cessation, and alcohol, chronic disease medications use, and measures of health care use (including influenza vaccination, lipid tests, and hospital, emergency, or outpatient visits).

Statistical Analysis

Within each cardiovascular subgroup of interest, we estimated propensity scores (PSs), the probability of SGLT2i versus GLP-1RA initiation, conditional on baseline covariates using logistic regression. We controlled measured confounding by inverse probability of treatment weighting (IPTW) by assigning weights of 1/PS and 1/(1-PS) multiplied by the marginal proportion of SGLT2i and GLP-1RA initiators to SGLT2i and GLP-1RA cohorts, respectively.[34,35] This creates
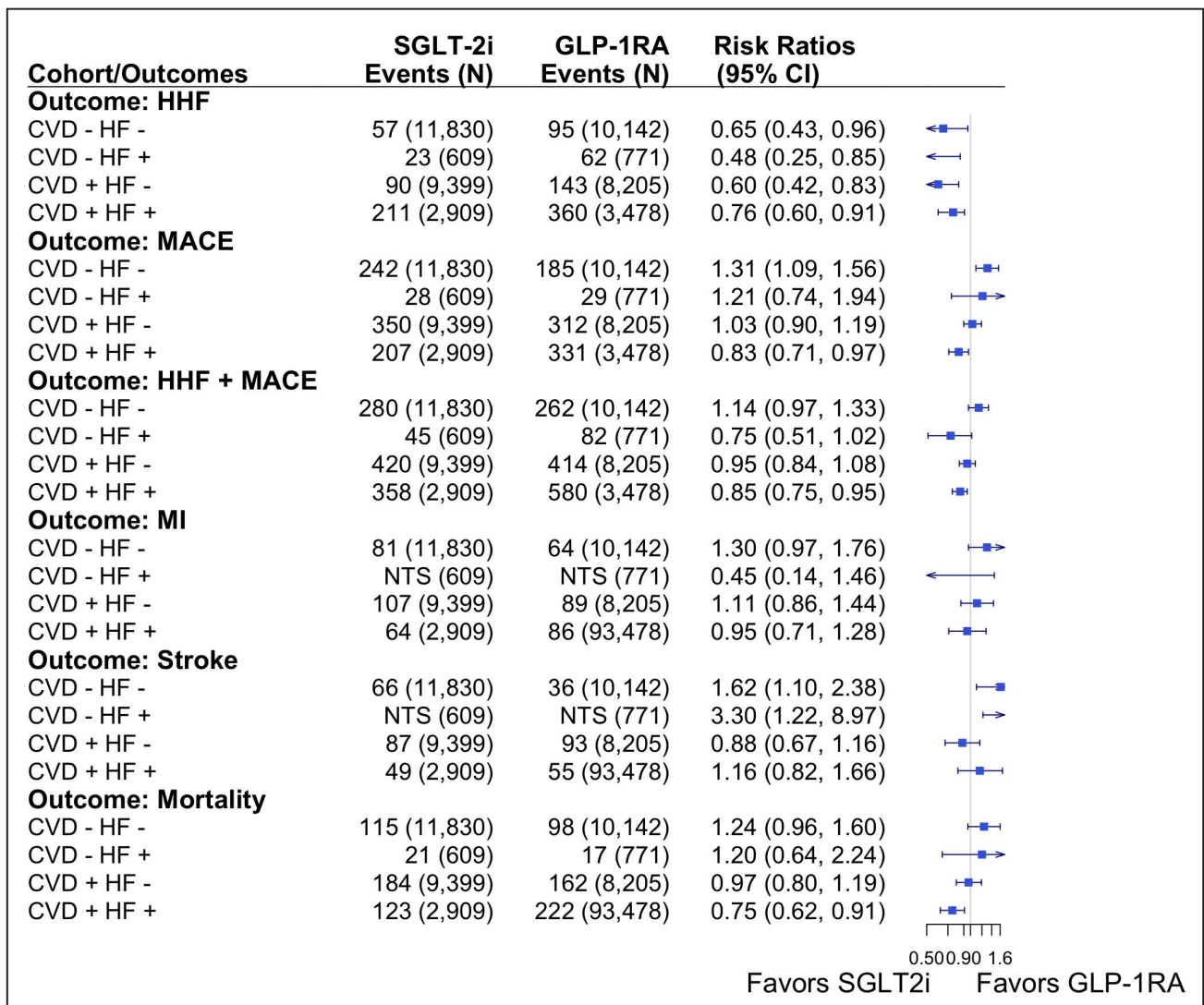
pseudopopulations within each subgroup in which each exposure arm has the same distribution of covariates in each respective subgroup and therefore all measured covariates were balanced across treatment arms. We assessed balance in covariate distributions by absolute standardized mean differences (Tables S7 through S11).[36]

We accounted for potential informative censoring attributable to loss to follow-up (treatment discontinuation in AT analyses and insurance disenrollment in ITT analyses), using inverse probability of censoring weights (IPCW).[37] First, we predicted the probability of not dropping out (ie, probability of not getting censored) at each quintile of the follow-up time, conditional on baseline covariates (similar to those used in IPTW), and we pooled these probabilities over the follow-up

duration using pooled linear logistic regression. We then assigned weights of 1/probability of remaining uncensored through time t for observed times t, multiplied by the proportion of patients not lost to follow-up to reduce variance.[37] The final weight is IPTW multiplied by IPCW to account for baseline confounding as well as potential informative censoring attributable to lost follow-up.

We estimated 2-year risks of outcomes of interest, risk differences, and risk ratios (RRs) for SGLT2i versus GLP-1RA after weighting by IPTW and IPCW (Figures 2 and 3). The CIs were derived from 2.5th and 97.5th percentiles of estimates from 500 bootstrap resamples of the study population (random resampling with replacement). When estimating risks of cardiovascular outcomes in older Medicare patients, censoring

Cohort/Outcomes	SGLT-2i Events (N)	GLP-1RA Events (N)	Risk Ratios (95% CI)
Outcome: HHF			
CVD - HF -	57 (11,830)	95 (10,142)	0.65 (0.43, 0.96)
CVD - HF +	23 (609)	62 (771)	0.48 (0.25, 0.85)
CVD + HF -	90 (9,399)	143 (8,205)	0.60 (0.42, 0.83)
CVD + HF +	211 (2,909)	360 (3,478)	0.76 (0.60, 0.91)
Outcome: MACE			
CVD - HF -	242 (11,830)	185 (10,142)	1.31 (1.09, 1.56)
CVD - HF +	28 (609)	29 (771)	1.21 (0.74, 1.94)
CVD + HF -	350 (9,399)	312 (8,205)	1.03 (0.90, 1.19)
CVD + HF +	207 (2,909)	331 (3,478)	0.83 (0.71, 0.97)
Outcome: HHF + MACE			
CVD - HF -	280 (11,830)	262 (10,142)	1.14 (0.97, 1.33)
CVD - HF +	45 (609)	82 (771)	0.75 (0.51, 1.02)
CVD + HF -	420 (9,399)	414 (8,205)	0.95 (0.84, 1.08)
CVD + HF +	358 (2,909)	580 (3,478)	0.85 (0.75, 0.95)
Outcome: MI			
CVD - HF -	81 (11,830)	64 (10,142)	1.30 (0.97, 1.76)
CVD - HF +	NTS (609)	NTS (771)	0.45 (0.14, 1.46)
CVD + HF -	107 (9,399)	89 (8,205)	1.11 (0.86, 1.44)
CVD + HF +	64 (2,909)	86 (93,478)	0.95 (0.71, 1.28)
Outcome: Stroke			
CVD - HF -	66 (11,830)	36 (10,142)	1.62 (1.10, 2.38)
CVD - HF +	NTS (609)	NTS (771)	3.30 (1.22, 8.97)
CVD + HF -	87 (9,399)	93 (8,205)	0.88 (0.67, 1.16)
CVD + HF +	49 (2,909)	55 (93,478)	1.16 (0.82, 1.66)
Outcome: Mortality			
CVD - HF -	115 (11,830)	98 (10,142)	1.24 (0.96, 1.60)
CVD - HF +	21 (609)	17 (771)	1.20 (0.64, 2.24)
CVD + HF -	184 (9,399)	162 (8,205)	0.97 (0.80, 1.19)
CVD + HF +	123 (2,909)	222 (93,478)	0.75 (0.62, 0.91)

0.50 0.90 1.6

Favors SGLT2i   Favors GLP-1RA

Figure 2. Competing risk estimators (inverse probability of treatment and censoring weighted risk ratios) for the effect of sodium-glucose cotransporter-2 inhibitors (SGLT2i) vs glucagon-like peptide-1 receptor agonists (GLP-1RA) on primary cardiovascular and mortality outcomes (as-treated analyses).
CVD indicates cardiovascular disease; HF, heart failure; HHF, hospitalization for HF; MACE, major adverse cardiovascular outcome; and MI, myocardial infarction.

Cohort/Outcome	SGLT-2i Events (N)	GLP-1RA Events (N)	Risk Differences (95% CI)
Outcome: HHF			
CVD - HF -	57 (11,830)	95 (10,142)	-0.62 (-1.23, -0.06)
CVD - HF +	23 (609)	62 (771)	-7.38 (-12.08, -1.71)
CVD + HF -	90 (9,399)	143 (8,205)	-1.64 (-2.69, -0.54)
CVD + HF +	211 (2,909)	360 (3,478)	-4.77 (-8.31, -1.65)
Outcome: MACE			
CVD - HF -	242 (11,830)	185 (10,142)	0.55 (0.19, 0.91)
CVD - HF +	28 (609)	29 (771)	0.75 (-1.18, 2.68)
CVD + HF -	350 (9,399)	312 (8,205)	0.12 (-0.42, 0.67)
CVD + HF +	207 (2,909)	331 (3,478)	-1.60 (-2.89, -0.31)
Outcome: HHF + MACE			
CVD - HF -	280 (11,830)	262 (10,142)	0.34 (-0.06, 0.75)
CVD - HF +	45 (609)	82 (771)	-2.50 (-5.14, 0.13)
CVD + HF -	420 (9,399)	414 (8,205)	-0.23 (-0.84, 0.38)
CVD + HF +	358 (2,909)	580 (3,478)	-2.36 (-4.00, -0.72)
Outcome: MI			
CVD - HF -	81 (11,830)	64 (10,142)	0.20 (-0.02, 0.42)
CVD - HF +	NTS (609)	NTS (771)	-0.62 (-1.48, 0.24)
CVD + HF -	107 (9,399)	89 (8,205)	0.13 (-0.18, 0.44)
CVD + HF +	64 (2,909)	86 (93,478)	-0.12 (-0.83, 0.59)
Outcome: Stroke			
CVD - HF -	66 (11,830)	36 (10,142)	0.22 (0.05, 0.39)
CVD - HF +	NTS (609)	NTS (771)	1.35 (0.24, 2.47)
CVD + HF -	87 (9,399)	93 (8,205)	-0.14 (-0.42, 0.15)
CVD + HF +	49 (2,909)	55 (93,478)	0.25 (-0.34, 0.85)
Outcome: Mortality			
CVD - HF -	115 (11,830)	98 (10,142)	0.22 (-0.03, 0.47)
CVD - HF +	21 (609)	17 (771)	0.43 (-1.04, 1.90)
CVD + HF -	184 (9,399)	162 (8,205)	-0.05 (-0.45, 0.34)
CVD + HF +	123 (2,909)	222 (93,478)	-1.55 (-2.59, -0.51)

-3 -1 0 1 2

Favors SGLT2i   Favors GLP-1RA

Figure 3. Competing risk estimators (inverse probability of treatment and censoring weighted risk differences) for the effect of sodium-glucose cotransporter-2 inhibitors (SGLT2i) vs glucagon-like peptide-1 receptor agonists (GLP-1RA) on primary cardiovascular and mortality outcomes (as-treated analyses).
CVD indicates cardiovascular disease; HF, heart failure; HHF, hospitalization for HF; MACE, major adverse cardiovascular outcome; and MI, myocardial infarction.

those who died before having the outcome of interest, as commonly done in survival analyses, could bias the risks.[37,38] To avoid this, we used Aalen Johansen estimators to estimate risks.[35] We first estimated the overall survival function for 2 years and the hazard function for each event type (outcome of interest as well as death) in a population weighted by IPTW and IPCW. We then multiplied the hazard function of the outcome of interest at each event time by the overall survival at the previous time point to obtain the Aalen Johansen estimators. This estimator treated death as a competing risk, by setting the risk of patients to 0 after death.[39] Causal diagram (directed acyclic graph) summarizing the relationships between these censoring (treatment changes) and competing events (death) is presented in Figure S2.[39]

For comparison, we also estimated risk differences and RRs by linear and log binomial regression models, respectively, instead of Aalen Johansen estimators, after applying IPTW and IPCW; and CIs were derived by robust variance estimators. We did not treat death as a censoring event in such analyses. We also reported cumulative risk curves as a function of the follow-up time (adjusted for baseline confounding and informative censoring) for each analytic comparison of interest (Figures 4 through 6 and Figures S3 through S5).

Sensitivity Analysis

We conducted several sensitivity analyses to assess the robustness of our claims-based algorithms of outcomes and baseline subgroup definitions: (1) we excluded each of the following conditions from baseline
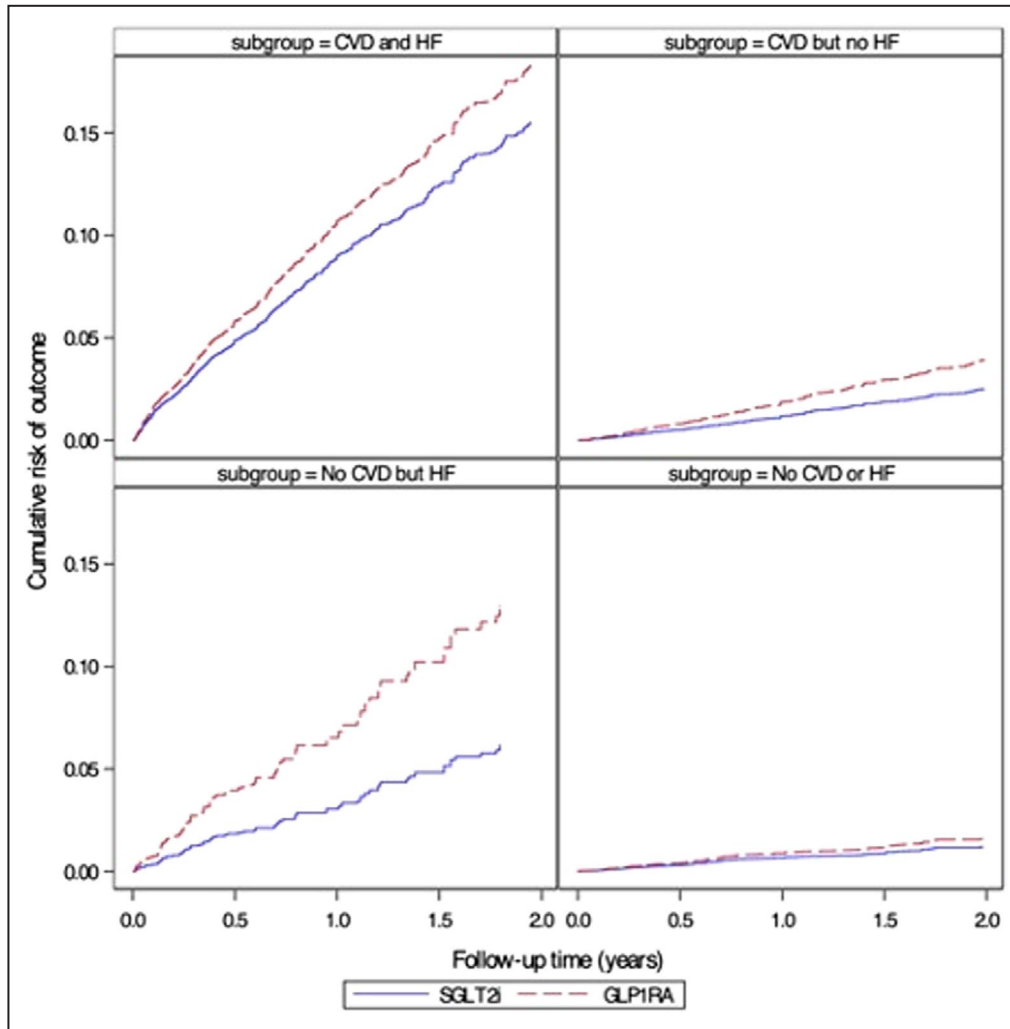
Figure 4. Cumulative risk of hospitalization for heart failure, stratified by baseline atherosclerotic cardiovascular diseases (CVDs) and heart failure (HF) (as-treated analyses adjusted for baseline confounding and informative censoring).
GLP-1RA indicates glucagon-like peptide-1 receptor agonists; and SGLT2i, sodium-glucose cotransporter-2 inhibitors.

CVD definition: peripheral arterial disease, nonspecific angina/ischemic heart disease, and cardiomyopathy; (2) we limited all codes for baseline CVD/HF conditions to inpatient settings only to increase the specificity of codes; (3) we varied our outcome definitions for HF by including rheumatic and hypertensive HF codes in addition to the primary congestive HF codes; (4) we varied our stroke definition by limiting to codes for ischemic stroke only; and (5) we included cardiovascular revascularization procedures (stents, bypass, and primary coronary intervention) to MACE outcome definitions. To check the distributions of HF events with preserved versus reduced ejection fractions, we predicted éjection fraction based on a selected set of covariates using the algorithm published by Desai et al.[40] To check the informative censoring, we allowed time-varying covariates in censoring weight models by including codes for

hyperglycemia (ketoacidosis, uncontrolled diabetes, or hyperosmolar nonketosis) and any hospitalization in 3-monthly periods before the interval when treatment discontinuation or switching occurred. We extended the follow-up to all-available years (maximum, 5 years) and estimated the hazard ratios (HRs) using competing risk–adjusted Fine and Gray Cox models, truncating the weights at 1% and 99% to deal with large weights associated with long-term follow-up, as suggested by Cole and Hernan.[56] We also excluded patients with diagnosis dates for congestive HF and major CVD conditions during 2 months before drug initiation to reduce bias related to recurrent outcome events (similar to an exclusion criterion in EMPA-REG OUTCOME [Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus PatientseRemoving Excess Glucose] trial).[8] We excluded earlier GLP-1RA agents
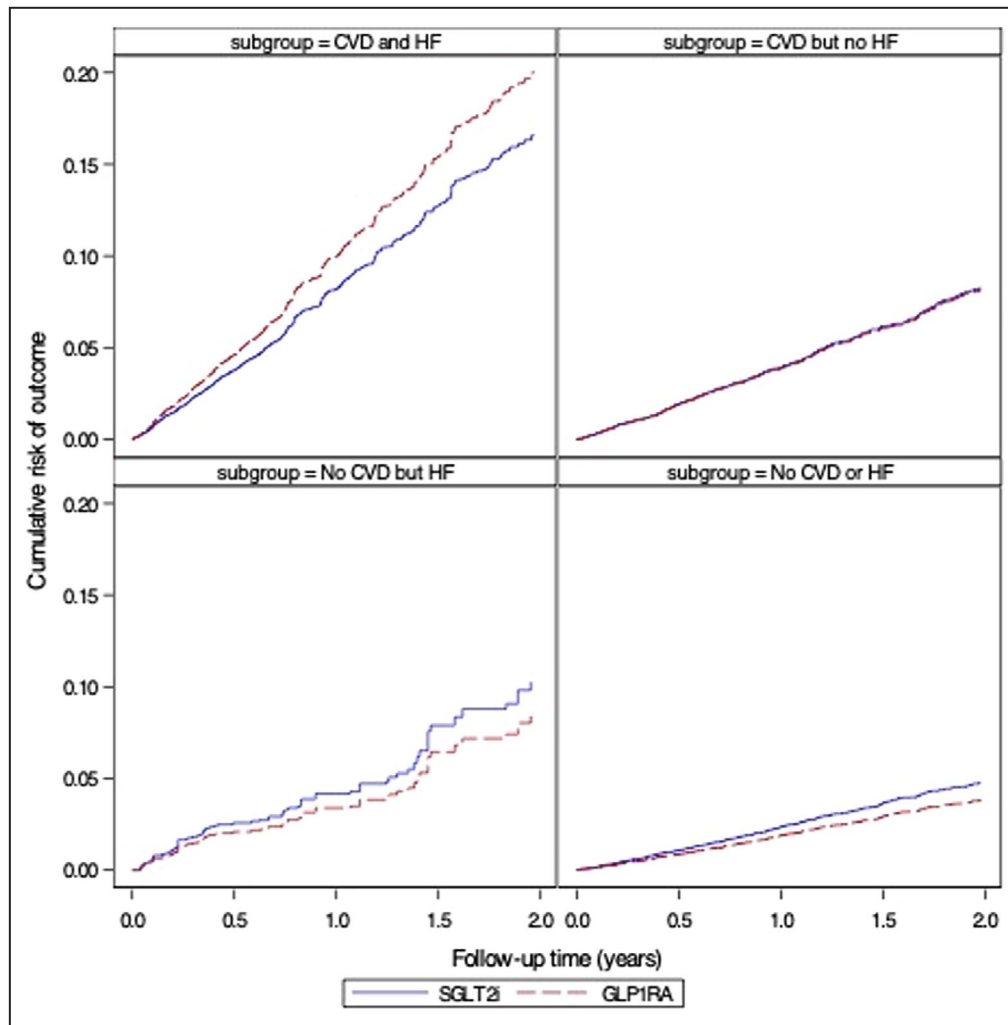
Figure 5. **Cumulative risk of major adverse cardiovascular outcomes (myocardial infarction, stroke, and mortality), stratified by baseline atherosclerotic cardiovascular diseases (CVDs) and heart failure (HF) (as-treated analyses adjusted for baseline confounding and informative censoring).**
GLP-1RA indicates glucagon-like peptide-1 receptor agonists; and SGLT2i, sodium-glucose cotransporter-2 inhibitors.

(exenatide) from analyses and compared the most commonly used agent in each class: SGLT2i (canagliflozin) versus GLP-1RA (liraglutide). To assess the potential for differential detection bias, we evaluated the proportions of health-seeking behaviors (flu shots and lipid tests) during the first 6 months following drug initiation among SGLT2i versus GLP-1RA initiators.

RESULTS

Our overall cohort included 24 747 SGLT2i and 22 596 GLP-1RA initiators. Compared with GLP-1RA initiators, SGLT2i initiators were slightly older (mean age, 73.4 versus 72.7 years), more likely to be men (50.9% versus 44.0%), and less likely to be White race (79.8% versus 82.5%). The prevalence of baseline HF was lower among SGLT2i versus GLP-1RA initiators (12.6% versus 17.2%), whereas the prevalence of MI or cerebrovascular diseases was similar between the groups. The Charlson/Elixhauser combined comorbidity score was slightly lower among SGLT2i, with the mean (SD) of 1.9 (2.3) versus GLP-1RA initiators: mean (SD) of 2.5 (2.6). In the Table, we present unweighted distributions of baseline characteristics in the overall study population. Distributions after weighting along with standardized mean difference statistics are presented in Tables S7 through S11.

There were 11 830 SGLT-2i and 10 142 GLP-1RA initiators who had no baseline HF or CVD. In AT analyses, we identified 57 and 95 HHF events, respectively, in this subgroup with the PS-weighted RR of 0.65 (95% CI, 0.43–0.96) after accounting for informative
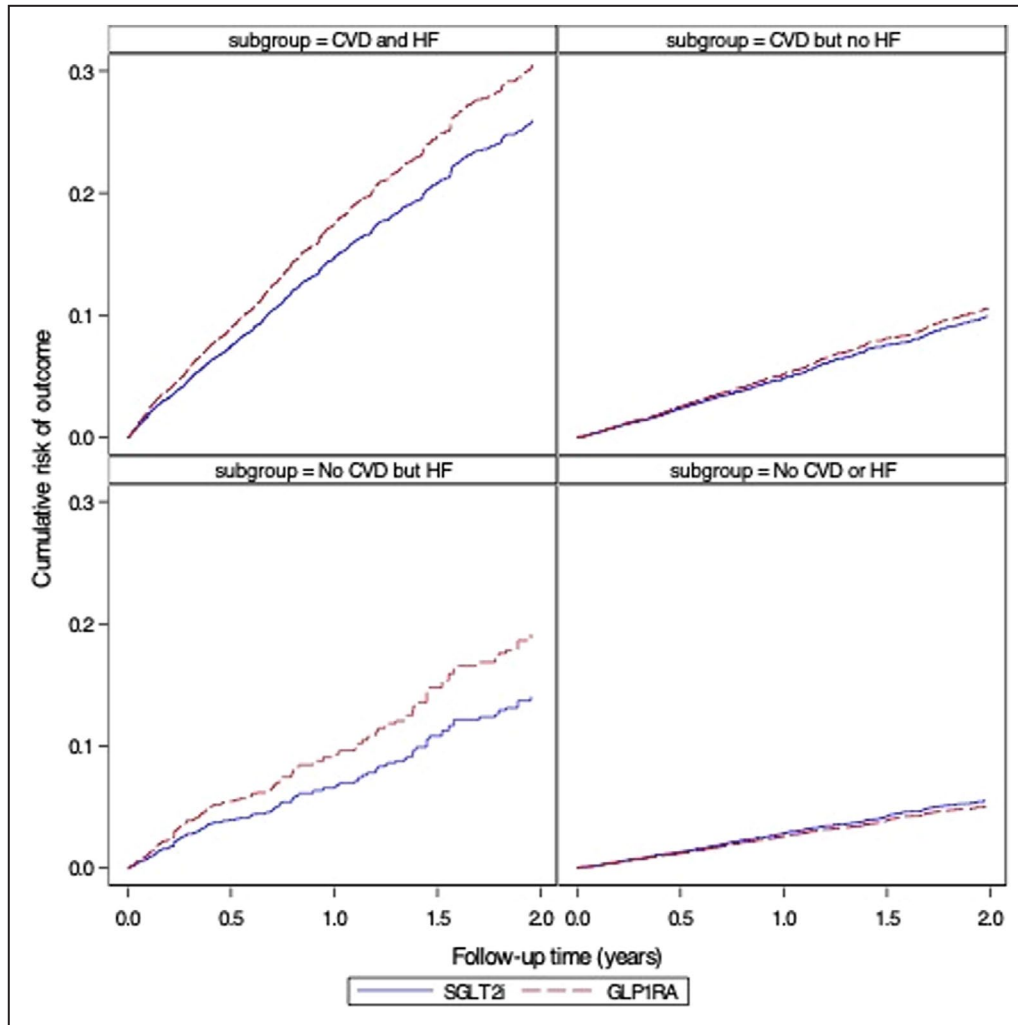
Figure 6. Cumulative risk of a composite of hospitalization for heart failure (HF) or major adverse cardiovascular outcomes (myocardial infarction, stroke, and mortality), stratified by baseline atherosclerotic cardiovascular diseases (CVDs) and HF (as-treated analyses adjusted for baseline confounding and informative censoring).

GLP-1RA indicates glucagon-like peptide-1 receptor agonists; and SGLT2i, sodium-glucose cotransporter-2 inhibitors.

censoring and competing risk attributable to mortality (Figure 2). In patients with baseline HF only but no CVD, this RR became much lower, 0.48 (95% CI, 0.25–0.85), based on 23 and 62 HF hospitalized events among 609 SGLT2i and 771 GLP-1RA initiators, indicating greater benefit with SGLT2i. The RR in patients without HF but with CVD was approximately similar to the RR in patients without HF and without CVD: 0.60 (95% CI, 0.42–0.83), whereas the RR in patients with both HF and CVD was more attenuated toward the null: 0.76 (95% CI, 0.60–0.91). As expected, 2-year mortality was highest in patients with HF and CVD: 5.5% among SGLT-2i and 6.4% among GLP-1RA initiators (Table S12). Approximately 45% to 50% of patients were censored because of treatment discontinuation, switching, or augmentation with the comparator

drug before the maximum follow-up period of 2 years (Table S13). ITT analyses produced similar patterns of estimates across subgroups, although in general slightly attenuated toward the null compared with AT (Table S14).

For analyses of MACE outcomes, we observed PS-weighted RR of 1.31 (95% CI, 1.09–1.56) among patients with no history of HF or evidence of atherosclerotic CVD based on 242 and 185 events in SGLT2i and GLP-1RA initiators, respectively. Estimates were similar among patients with HF but no CVD, with weighted RR: 1.21 (95% CI, 0.75–1.94). In the subgroup of patients with history of both HF and CVD, the PS-weighted RR was 0.83 (95% CI, 0.71–0.97) based on the 207 and 331 events in SGLT2i and GLP-1RA initiators. Risk differences produced similar patterns of estimates. The

Table. Distributions of Baseline Characteristics in the Total Cohort Before PS Weighting

Characteristic	SGLT2i (N=24 747)	GLP-1RA (N=22 596)	Total (N=47 343)	Absolute standardized mean differences
Demographic characteristics				
Age, mean (SD), y	73.4 (5.70)	72.7 (5.43)	73.1 (5.58)	0.127
Race or ethnicity				
White	19 753 (79.8)	18 643 (82.5)	38 396 (81.1)	0.069
Black	1865 (7.5)	2104 (9.3)	3969 (8.4)	0.064
Other *	3129 (12.6)	1849 (8.2)	4978 (10.5)	0.146
Male sex	12 601 (50.9)	9937 (44.0)	22 538 (47.6)	0.139
Low-income subsidy, mean (SD)	187.7 (414.74)	216.3 (456.29)	201.4 (435.30)	0.066
Measures of diabetes severity/complications				
Diabetes retinopathy	3623 (14.6)	3621 (16.0)	7244 (15.3)	0.038
Diabetes nephropathy	2835 (11.5)	4204 (18.6)	7039 (14.9)	0.201
Diabetes neuropathy	6985 (28.2)	7598 (33.6)	14 583 (30.8)	0.117
Other diabetes complications	11 158 (45.1)	10 812 (47.8)	21 970 (46.4)	0.055
No. of antihyperglycemic drugs				
0	2139 (8.6)	4036 (17.9)	6175 (13.0)	0.274
1	6799 (27.5)	7109 (31.5)	13 908 (29.4)	0.088
2	9167 (37.0)	7142 (31.6)	16 309 (34.4)	0.115
3	5698 (23.0)	3708 (16.4)	9406 (19.9)	0.167
≥4	944 (3.8)	601 (2.7)	1545 (3.3)	0.065
No. of hyperglycemia diagnoses				
0	10 991 (44.4)	8858 (39.2)	19 849 (41.9)	0.106
1	3195 (12.9)	2854 (12.6)	6049 (12.8)	0.008
2	1957 (7.9)	1894 (8.4)	3851 (8.1)	0.017
3	2887 (11.7)	2721 (12.0)	5608 (11.8)	0.012
≥4	5717 (23.1)	6269 (27.7)	11 986 (25.3)	0.107
Hypoglycemia	565 (2.3)	710 (3.1)	1275 (2.7)	0.053
Foot ulcers	733 (3.0)	894 (4.0)	1627 (3.4)	0.054
Cardiovascular disorders				
Angina	1309 (5.3)	1222 (5.4)	2531 (5.3)	0.005
MI	1574 (6.4)	1629 (7.2)	3203 (6.8)	0.034
Cardiac revascularization or bypass	472 (1.9)	476 (2.1)	948 (2.0)	0.014
Atherosclerosis	3148 (12.7)	2946 (13.0)	6094 (12.9)	0.009
Ischemic heart diseases	8246 (33.3)	7899 (35.0)	16 145 (34.1)	0.035
Cerebrovascular diseases	3763 (15.2)	3523 (15.6)	7286 (15.4)	0.011
Cardiomyopathy	982 (4.0)	1024 (4.5)	2006 (4.2)	0.028
Congestive heart failure	3123 (12.6)	3884 (17.2)	7007 (14.8)	0.129
Peripheral vascular diseases	4341 (17.5)	4422 (19.6)	8763 (18.5)	0.052
Atrial fibrillation	2947 (11.9)	2940 (13.0)	5887 (12.4)	0.033
Arrhythmia disorders	3468 (14.0)	3616 (16.0)	7084 (15.0)	0.056
Cardiac arrest	37 (0.1)	38 (0.2)	75 (0.2)	0.005
Defibrillator	364 (1.5)	435 (1.9)	799 (1.7)	0.035
Comorbid conditions				
Combined comorbidity score, mean (SD)	1.9 (2.32)	2.5 (2.58)	2.2 (2.46)	0.224
Anemia	6364 (25.7)	6245 (27.6)	12 609 (26.6)	0.043
Alcohol disorders	205 (0.8)	174 (0.8)	379 (0.8)	0.007
Asthma	2389 (9.7)	2806 (12.4)	5195 (11.0)	0.088
Brain injury	631 (2.5)	720 (3.2)	1351 (2.9)	0.038

(Continued)

Table. (Continued)

Characteristic	SGLT2i (N=24 747)	GLP-1RA (N=22 596)	Total (N=47 343)	Absolute standardized mean differences
Cancer (except for nonmelanoma skin)	3129 (12.6)	2721 (12.0)	5850 (12.4)	0.018
Chronic lung disorders	5835 (23.6)	6385 (28.3)	12 220 (25.8)	0.107
CKD (stage 1–3)	3590 (14.5)	5853 (25.9)	9443 (19.9)	0.287
Coagulopathy	816 (3.3)	874 (3.9)	1690 (3.6)	0.031
Connective tissue disorders	878 (3.5)	1018 (4.5)	1896 (4.0)	0.049
Dementia	588 (2.4)	598 (2.6)	1186 (2.5)	0.017
Deficiency anemia	5927 (24.0)	5715 (25.3)	11 642 (24.6)	0.031
Depression	3788 (15.3)	4778 (21.1)	8566 (18.1)	0.152
Difficulty walking	3473 (14.0)	3840 (17.0)	7313 (15.4)	0.082
Dyslipidemia	21 932 (88.6)	19 651 (87.0)	41 583 (87.8)	0.051
Endocrine disorders	9833 (39.7)	9788 (43.3)	19 621 (41.4)	0.073
Edema	2749 (11.1)	3414 (15.1)	6163 (13.0)	0.119
Electrolyte disorders	2969 (12.0)	3504 (15.5)	6473 (13.7)	0.102
HIV	47 (0.2)	47 (0.2)	94 (0.2)	0.004
Hematological disorders	7362 (29.7)	7283 (32.2)	14 645 (30.9)	0.054
Hypertension	14 167 (57.2)	12 435 (55.0)	26 602 (56.2)	0.045
Hypotension	801 (3.2)	900 (4.0)	1701 (3.6)	0.040
Immune disorders	365 (1.5)	417 (1.8)	782 (1.7)	0.029
Metabolic disorders	22 084 (89.2)	20 005 (88.5)	42 089 (88.9)	0.022
Metastatic cancers	265 (1.1)	210 (0.9)	475 (1.0)	0.014
Mild liver disorders	1208 (4.9)	1149 (5.1)	2357 (5.0)	0.009
Moderate liver disorders	142 (0.6)	128 (0.6)	270 (0.6)	0.001
Nutritional disorders	7584 (30.6)	7203 (31.9)	14 787 (31.2)	0.027
Nervous system disorders	11 445 (46.2)	12 354 (54.7)	23 799 (50.3)	0.169
Paraplegia	226 (0.9)	268 (1.2)	494 (1.0)	0.027
Parkinsonism	250 (1.0)	276 (1.2)	526 (1.1)	0.020
Pneumonia	1162 (4.7)	1389 (6.1)	2551 (5.4)	0.064
Psychosis	1129 (4.6)	1287 (5.7)	2416 (5.1)	0.051
Pulmonary circulation disorders	623 (2.5)	845 (3.7)	1468 (3.1)	0.070
Rehabilitation	1184 (4.8)	1326 (5.9)	2510 (5.3)	0.048
Renal disorders	3650 (14.7)	5927 (26.2)	9577 (20.2)	0.287
Rheumatic disorders	845 (3.4)	823 (3.6)	1668 (3.5)	0.012
Smoking and smoking cessation	1309 (5.3)	1204 (5.3)	2513 (5.3)	0.002
Thromboembolism	167 (0.7)	151 (0.7)	318 (0.7)	0.001
Vulvular disorders	3061 (12.4)	2931 (13.0)	5992 (12.7)	0.018
Weight loss	185 (0.7)	190 (0.8)	375 (0.8)	0.011
Durable medical equipment claims				
Ambulance	2519 (10.2)	2853 (12.6)	5372 (11.3)	0.077
Hospital beds	132 (0.5)	174 (0.8)	306 (0.6)	0.029
Home oxygen	955 (3.9)	1419 (6.3)	2374 (5.0)	0.111
Wheelchairs	275 (1.1)	348 (1.5)	623 (1.3)	0.038
History of medication use				
Metformin	19 134 (77.3)	14 824 (65.6)	33 958 (71.7)	0.262
Short-acting insulin	2835 (11.5)	4923 (21.8)	7758 (16.4)	0.280
Long-acting insulin	6450 (26.1)	9867 (43.7)	16 317 (34.5)	0.376
Thiazolidinedione	2810 (11.4)	2219 (9.8)	5029 (10.6)	0.050
Meglitinide	728 (2.9)	656 (2.9)	1384 (2.9)	0.002

(Continued)

Table. (Continued)

Characteristic	SGLT2i (N=24 747)	GLP-1RA (N=22 596)	Total (N=47 343)	Absolute standardized mean differences
Sulphonylurea	12 133 (49.0)	9721 (43.0)	21 854 (46.2)	0.121
DPP-4i	10 971 (44.3)	7337 (32.5)	18 308 (38.7)	0.246
Immunosuppressive drugs	174 (0.7)	217 (1.0)	391 (0.8)	0.028
Steroids	4084 (16.5)	4060 (18.0)	8144 (17.2)	0.039
ACEI	10 964 (44.3)	10 089 (44.6)	21 053 (44.5)	0.007
ARB	9094 (36.7)	8338 (36.9)	17 432 (36.8)	0.003
CCB	8274 (33.4)	7862 (34.8)	16 136 (34.1)	0.029
BB	13 125 (53.0)	12 511 (55.4)	25 636 (54.1)	0.047
NSAIDS	7169 (29.0)	6436 (28.5)	13 605 (28.7)	0.011
Aspirin	1134 (4.6)	1366 (6.0)	2500 (5.3)	0.065
Oral contraceptives	475 (1.9)	589 (2.6)	1064 (2.2)	0.046
Estrogen	1338 (5.4)	1411 (6.2)	2749 (5.8)	0.036
Loop diuretics	4582 (18.5)	6153 (27.2)	10 735 (22.7)	0.209
Other diuretics	9313 (37.6)	9238 (40.9)	18 551 (39.2)	0.067
Statin	19 098 (77.2)	17 360 (76.8)	36 458 (77.0)	0.008
Measures of health care use				
HbA1C tests				
0	1313 (5.3)	1689 (7.5)	3002 (6.3)	0.089
1	3028 (12.2)	2730 (12.1)	5758 (12.2)	0.005
2	5723 (23.1)	4703 (20.8)	10 426 (22.0)	0.056
3	6956 (28.1)	5921 (26.2)	12 877 (27.2)	0.043
4	4955 (20.0)	4573 (20.2)	9528 (20.1)	0.005
≥5	2772 (11.2)	2980 (13.2)	5752 (12.1)	0.061
Flu shots				
0	9441 (38.2)	8670 (38.4)	18 111 (38.3)	0.005
1	12 361 (49.9)	11 163 (49.4)	23 524 (49.7)	0.011
2	2056 (8.3)	1900 (8.4)	3956 (8.4)	0.004
≥3	889 (3.6)	863 (3.8)	1752 (3.7)	0.012
Lipid tests				
0	2964 (12.0)	3504 (15.5)	6468 (13.7)	0.103
1	7262 (29.3)	6838 (30.3)	14 100 (29.8)	0.020
2	6928 (28.0)	5886 (26.0)	12 814 (27.1)	0.044
3	4325 (17.5)	3546 (15.7)	7871 (16.6)	0.048
≥4	3268 (13.2)	2822 (12.5)	6090 (12.9)	0.021
No. of hospital admissions				
0	21 249 (85.9)	18 529 (82.0)	39 778 (84.0)	0.105
1	2486 (10.0)	2774 (12.3)	5260 (11.1)	0.071
≥2	1012 (4.1)	1293 (5.7)	2305 (4.9)	0.076
No. of days of hospitalization				
0	21 249 (85.9)	18 529 (82.0)	39 778 (84.0)	0.105
1	1583 (6.4)	1760 (7.8)	3343 (7.1)	0.054
≥2	1915 (7.7)	2307 (10.2)	4222 (8.9)	0.087
No. of emergency visits				
0	17 646 (71.3)	15 032 (66.5)	32 678 (69.0)	0.103
1	3903 (15.8)	3831 (17.0)	7734 (16.3)	0.032
2	1619 (6.5)	1794 (7.9)	3413 (7.2)	0.054
≥3	1579 (6.4)	1939 (8.6)	3518 (7.4)	0.084

(Continued)

Table. **(Continued)**

Characteristic	SGLT2i (N=24 747)	GLP-1RA (N=22 596)	Total (N=47 343)	Absolute standardized mean differences
No. of emergency visits attributable to diabetes				
0	24 395 (98.6)	22 194 (98.2)	46 589 (98.4)	0.028
1	296 (1.2)	335 (1.5)	631 (1.3)	0.025
≥2	56 (0.2)	67 (0.3)	123 (0.3)	0.014
No. of outpatient visits				
0	1047 (4.2)	1276 (5.6)	2323 (4.9)	0.065
1	4446 (18.0)	3564 (15.8)	8010 (16.9)	0.059
2	6491 (26.2)	5147 (22.8)	11 638 (24.6)	0.080
3	5063 (20.5)	4400 (19.5)	9463 (20.0)	0.025
4	3223 (13.0)	3155 (14.0)	6378 (13.5)	0.027
≥5	4477 (18.1)	5054 (22.4)	9531 (20.1)	0.107
No. of outpatient visits attributable to diabetes	11 172 (45.1)	10 110 (44.7)	21 282 (45.0)	0.008
No. of days between first and second scripts, mean (SD)	47.5 (29.47)	47.4 (27.76)	47.4 (28.66)	0.002
Markers of diabetes and cardiovascular disease severity				
HbA1C <7%	945 (3.8)	868 (3.8)	1813 (3.8)	0.001
HbA1C 7%–9%	1982 (8.0)	1762 (7.8)	3744 (7.9)	0.008
HbA1C >9%	1075 (4.3)	1176 (5.2)	2251 (4.8)	0.040
LDL <100 mg/dL	861 (3.5)	879 (3.9)	1740 (3.7)	0.022
LDL 100–129 mg/dL	202 (0.8)	202 (0.9)	404 (0.9)	0.008
LDL >130 mg/dL	93 (0.4)	115 (0.5)	208 (0.4)	0.020
SBP <130 mm Hg	167 (0.7)	209 (0.9)	376 (0.8)	0.028
SBP 130–139 mm Hg	115 (0.5)	125 (0.6)	240 (0.5)	0.012
SBP ≥140 mm Hg	118 (0.5)	139 (0.6)	257 (0.5)	0.019
DBP <80 mm Hg	214 (0.9)	275 (1.2)	489 (1.0)	0.035
DBP 80–89 mm Hg	118 (0.5)	116 (0.5)	234 (0.5)	0.005
DBP ≥90 mm Hg	25 (0.1)	31 (0.1)	56 (0.1)	0.010

Data are given as number (percentage), unless otherwise indicated. All covariates (except for the number of days between first and second prescriptions) are measured 12 months before the first prescription date. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β blocker; CCB, calcium channel blocker; CKD, chronic kidney disease; DBP, diastolic blood pressure; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonists; HbA1C, hemoglobin A1C; LDL, low-density lipoprotein; MI, myocardial infarction; PS, propensity score; SBP, systolic blood pressure; and SGLT2i, sodium-glucose cotransporter 2 inhibitors.

*American Indian or Alaskan Native, Asian, Hispanic or Latino, Native Hawaiian or other Pacific Islander, or unknown

risk of MACE plus HHF outcome was lower among SGLT2i versus GLP-1RA in patients with history of HF, with RRs ranging from 0.73 to 0.85, whereas the risk was similar between treatment groups in those with no history of HF: RRs ranged from 0.95 to 1.14 (Figure 2).

Using the Desai et al algorithm, 24.3% of HF outcome events were classified as HF with reduced ejection fraction, the rest being classified as HF with preserved ejection fraction. Negative control outcomes produced near-null estimates, except in a group with a small number of events (Table S15). We reestimated RRs and risk differences for primary outcomes among patients with no prevalent cancers (ie, negative control outcome) at baseline, and estimates are similar (Tables S16 and S17). Varying the outcome definitions

to define HHF, MACE, and stroke definitions produced similar estimates across all subgroups (Figures S6 through S8). Varying baseline CVD and HF definitions produced similar subgroup-specific estimates to the primary analyses (Tables S18 through S20). Limiting baseline CVD codes to inpatient setting produced similar findings and so did allowing time-varying covariates in censoring weight models and extending the follow-up to all-available years (Tables S21 through S23). Inclusion of cardiac revascularization procedures in the MACE definitions produced consistent estimates (Tables S24 and S25). Other sensitivity analyses, such as exclusion of prevalent HHF and MACE outcome dates within 2 months of drug initiation date and examining health care use patterns after drug initiation,

produced findings that support the primary analysis (Tables S26 through S29). Analyses after excluding exenatide and comparison of cardiovascular outcomes between canagliflozin and liraglutide produced similar findings to the primary (Tables S30 and S31). The trends in outcome risk were stable over time, showing that *ICD-10-CM* transition in 2015 did not materially change the outcome incidence, consistent with prior published findings.[27] Inverse probability–weighted subdistribution HRs from Fine and Gray Cox model are also similar to 2-year RRs (Table S29).

DISCUSSION

In our large population-based cohort study, we found evidence that SGLT2i initiators compared with GLP-1RA had a lower risk of HHF in all subgroups (with or without HF and/or CVD) and, to a lesser extent, HHF+MACE particularly in those patients with HF with or without atherosclerotic CVD. The estimated effects on MACE are comparable but generally more favorable toward GLP-1RA, except in a group with both CVD and HF. Our findings extend evidence from the large body of cardiovascular outcome trials documenting the CVD and HF benefits of SGLT2i and GLP-1RA compared with placebo by examining the comparative effectiveness of the 2 classes. We believe these findings can help inform clinicians about the optimal choice of cardioprotective antihyperglycemic medications in patients with varying background CVDs.

Dapagliflozin is the first SGLT2i to be approved by the US Food and Drug Administration for treatment in patients with HF with reduced ejection fraction.[41] Analyses of placebo-controlled, randomized trials suggest that protective effects of SGLT2i on HHF and MACE may be restricted to those with established HF with reduced ejection fraction, whereas benefits on stroke are uncertain.[42] In general, SGLT2i effects on HHF are more compelling than their effects on MACE outcomes, whereas GLP-1RA effects seem to be stronger for MACE outcomes, with their effects on HHF inconsistent across trials.[7–9,11–13] Subgroup analyses from trials demonstrate MACE effects of GLP-1RA more consistently among those with established CVD.[11,12,14] Prior meta-analysis of clinical trial data suggested that the beneficial effects of SGLT2i (and, to a lesser extent, GLP-1RA) on MACE relative to placebo are more uncertain in regional subgroup analysis in North America.[43] A nonexperimental study, based on US Medicare data, also reported findings similar to ours, although our subgroup definitions and analytical approaches are different.[44]

Recently, the evidence from the empagliflozin trials suggested that it reduced the relative risk of HHF to a similar extent in patients with HF with reduced ejection fraction and in patients with HF with preserved ejection fraction.[45,46] Following these estimates, we would expect the same benefits of SGLT2i on HHF in patients with HF with reduced ejection fraction and HF with preserved ejection fraction.[45,46]

Our findings are consistent with those from randomized trials and prior claims-based studies, although prior studies have not as explicitly examined the head-to-head efficacy of SGLT2i and GLP-1RA for cardiovascular events among subgroups defined by varying burden of prevalent CVD diagnoses. We estimated beneficial effects of SGLT2i over GLP-1RA for HHF outcomes in all subgroups and for MACE and mortality among those with a history of both CVD and HF. On the other hand, GLP-1RA were more favorable than SGLT2i for MACE outcomes and stroke, and to a lower extent for MI and mortality, in those without documented CVD or HF. For the composite of HHF+MACE, the risk difference is relatively large (>2%) to the benefit of SGLT2i for patients with HF with or without CVD; on the other hand, the risk difference is relatively small (<0.5%) and statistically not significant to the benefit of GLP-1RA for patients without HF with or without CVD. In this study, we examined the 3-way interaction of SGLT2i with history of HF and/or atherosclerotic CVD, with an aim to estimate the valid treatment effects and help guide treatment decision making among subpopulations of interest. While most trials have a median follow-up of 3 years, our study is limited by real-world drug use patterns because the median treatment duration in our Medicare population is 1 year. We allowed maximum follow-up of up to 5 years in sensitivity analyses and both AT and ITT analyses supported our primary findings.

We used validated claims-based algorithms to identify baseline subgroups. These validation algorithms vary in setting, sensitivity, and specificity but in general show high specificity (70%–95%) of codes for ischemic heart diseases, stroke, peripheral vascular diseases, and HF (see Tables S1, S3 through S6 for codes and their validity).[19–24,26,27] We varied the claims-based conditions used to define subgroups in sensitivity analyses to study their impact on subgroup estimates; and findings were consistent with the primary estimates in our study (Tables S18 through S20). We also limited codes for these baseline conditions to inpatient settings only to better reflect prior validation studies and to increase the accuracy of codes; and these analyses (Tables S21) showed similar findings to primary analyses.

Our restriction of the study population to new users reduced the available sample size, yet it avoids immortal time and other time-related biases by allowing us to anchor our follow-up on the timing of drug initiation.[18,25,47] It allows us to emulate randomized clinical trials, because the initiation of drugs and the beginning of follow-up were synchronized, while reducing

biases associated with long-term (prevalent) drug use, such as the healthy user/adherer bias and depletion of susceptibles.[48]

Head-to-head comparison with alternative second-line medications (SGLT2i and GLP-1RA in this case) also reduced the potential for confounding by indication by limiting the study comparison to patients with similar indications and similar disease progression (underlying disease severity).[18] Remaining confounding should be minimized by using propensity score–based approaches that allow us to control for a wide range of covariates in various health care settings.

Nonetheless, our observational cohort study could still experience unmeasured or residual confounding attributable to diabetes or CVD severity, given the lack of clinically relevant biomarkers in claims data. We used the results from a prior claims-based validation study to control for diabetes severity, by adjusting for the number of classes of antihyperglycemic medication use, microvascular or macrovascular complications (nephropathy, neuropathy, retinopathy, peripheral vascular complications, and amputation), hypoglycemia, and the number of hyperglycemia-related diagnoses. The algorithm has been shown to balance risk factors related to diabetes severity in claims data.[49] We also controlled for conditions that have been shown in a prior study to predict HF severity.[40] Although we did not include hemoglobin A1C and lipid levels in our analyses, a subset (≈10%) of patients have Healthcare Common Procedure Coding System/CPT codes for categories of hemoglobin A1C, low-density lipoproteins, and systolic and diastolic blood pressures. We measured their distributions across our treatment cohorts, and they were balanced before and after PS weighting (Table and Table S7). We also included markers of frailty following a prior algorithm to minimize concerns that older, frail patients might not be prescribed beneficial medications and have worse clinical outcomes.[50]

We tailored confounding control in each subgroup by estimating PS separately and applied treatment and censoring weights in each subgroup. This approach allows us to control confounding and informative censoring attributable to treatment nonadherence separately within each subgroup, instead of assuming that PS estimated in the whole cohort could balance covariates within each subgroup. We conducted both ITT and AT analyses using both time-fixed and time-varying predictors of treatment nonadherence, allowing variable follow-up times; and all sensitivity analyses supported our primary findings (Tables S14, S22, and S23). We also observed the similar distribution of baseline characteristics among patients who dropped out because of treatment changes versus those who did not, supporting our assumption that censoring of patients because of treatment nonadherence might not lead to selection bias (data not presented).

Because failure to deal with death as a competing event could result in overestimation of risks, especially in older, vulnerable populations, we used PS weighting approach using the Aalen Johansen estimator that allows us to estimate accurate risks without making the implausible assumption that death could be eliminated.[37,39] Yet, our analyses could be biased if the risk of death is higher in one treatment group versus another, especially in groups with evidence of both atherosclerotic CVDs and HF, where the risk of mortality is high. However, the proportion of patients who died without having the outcomes of interest is relatively similar across treatment groups, minimizing such concerns (Table S12).

We relied on outcome definitions using *ICD-9-CM*, *ICD-10-CM*, Healthcare Common Procedure Coding System, or CPT codes, with high specificity and positive predictive values that have been validated in Medicare or similar claims data, against electronic health records or population-based cohort studies (eg, ARIC [Atherosclerosis Risk in Communities] study).[19,22,24] Highly specific definitions have been shown to minimize bias in RR attributable to outcome misclassification.[39] We only focused on the first hospitalization event following drug initiation, and our models did not account for recurrent events.

We also used negative control (falsifying) outcomes that are known to be not affected by either SGLT-2i or GLP-1RA, with the assumption that if the confounding structure is similar and our confounding control is sufficient, we should be able to observe null effects. Indeed, estimates for all-cancer incidence were near null across subgroups (Table S15), supporting the strength of our study design and analytical approaches.[31] Cancer and cardiovascular outcomes share many risk factors; therefore, any deviations from the null estimate should reflect the insufficient confounding control in analyses of primary outcomes, apart from random variability.[31] Estimates for cataract surgery outcomes were also near null across subgroups, allowing us to estimate effects with higher precision than cancer outcomes (Table S15).

Our study provides evidence that complements cardiovascular outcome trials and recent observational studies.[44,51–53] Compared with trial populations, our Medicare fee-for-service populations have overall higher average age, higher burden of multimorbidity and frailty, and lower burden of established CVDs, and thus our estimates are more generalizable to older and vulnerable populations in routine care in the United States. The RCT-DUPLICATE (Randomized Controlled Trials Duplicated Using Prospective Longitudinal Insurance Claims: Applying Techniques of Epidemiology) initiative, funded by the US Food and Drug Administration, is the systematic effort to replicate trial findings in real-world data; and recent findings reported that agreement in

findings between trials and real-world evidence varies across studies. However, cardiovascular outcome studies on patients with diabetes using active comparators with similar indications and use patterns (as used in our study) were shown to produce estimates close to trial findings.[54] Another real-world study using Medicare and commercial claims data aimed to predict Carolina trial findings reported the effect estimates of linagliptin versus glimepiride on MACE and 2 control (a positive and a negative) outcomes before the trial finished, and they were ultimately shown to be consistent with trial findings.[55]

In conclusion, we observed variations in treatment effect estimates across patient subgroups defined by history of atherosclerotic CVD and HF. Well-designed nonexperimental studies with validated claims-based algorithms in routine clinical care settings could be useful to help guide clinicians and policy makers on the optimal choice of medications. Further studies on the topic could shed lights on the potential cardioprotective mechanism of these antihyperglycemic agents as well as support the optimal prescribing practices in older, vulnerable patients with varying underlying cardiovascular comorbidities.

ARTICLE INFORMATION

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Disclosures

Supplemental Material

Tables S1–S31
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SUPPLEMENTAL MATERIAL

Table S1. Cardiovascular conditions and codes used to define baseline subgroups of interest

Condition	ICD-9-CM Codes	ICD-10-CM codes	HCPCS/ CPT codes	Subgroup	Accuracy of codes (Validation study)
MI	410.xx	I20.xx, I21.xx		CVD	Specificity >93%; Sensitivity >86% [McCormick, 2014] PPV >94% [Kiyota 2004]
Cerebrovascular diseases	430.xx, 431.xx, 433.xx, 434.xx, 436.xx, 437.xx, 438.xx	I60.xx, I61.xx, I63.xx- I67.xx, I69.xxx		CVD	PPV 76%, sensitivity 68% [Jones, 2014] Specificity >95%, Sensitivity >82% [McCormick, 2015]
Ischemic heart diseases	411.xx, 414.xx	I24.xxx, I25.xxx		CVD	Specificity 96%, PPV 96%, Sensitivity 57% [Birman-Deych, 2005]
Angina	413.0, 413.9	I20.0, I20.8, I20.9		CVD	
Atherosclerosis	440.xx, 441.xx	I70.xx, I71.xx		CVD	
Peripheral vascular diseases	443.9, 249.70, 249.71, 250.70, 250.71, 250.72, 250.73	I739, E115.x, E105.x, E085.x, E095.x, E135.x	27295, 27590, 27591, 27592, 27594, 27596, 27598,27599,27880, 27881, 27882, 27888, 27889, 28800, 28805,	CVD	Community-based sample: Specificity: 92.0 (86.1 to 95.9), Sensitivity: 38.7 (27.6 to 50.6) Vascular laboratory sample:

			28810, 28820, 28825, 35221, 35226, 35256, 35286, 35302, 35303, 35304, 35305, 35306, 35331, 35351, 35355, 35361, 35363, 35371, 35372, 35381, 35452, 35454, 35456, 35459, 35470, 35472, 35473, 35474, 35480, 35481, 35482, 35483, 35485, 35490, 35491, 35492, 35493, 35495, 35500, 35521, 35533, 35537, 35538, 35539, 35540, 35541, 35546, 35548, 35549, 35551, 35556, 35558, 35563, 35565, 35566, 35583, 35585, 35587, 35621, 35623, 35646, 35647, 35651, 35654, 35656, 35661, 35663, 35665, 35666, 35671, 35681, 35682, 35700, 35875, 35876, 35879, 35881, 35883, 35884, 35903		Specificity: 89.3 (88.6 to 90.0), Sensitivity: 76.9 (76.2 to 77.6) [Fan et al., 2013]
Heart failure	428.xx, 398.91, 402.x1, 402.x3, 404.x1, 404.x3	I09.9, I11.0, I50.x		CHF	Specificity: 99%, [Birman-Deych, 2005], PPV 93% [Ezekowitz, 2008], sensitivity = 80.0% (67.0 - 90.0); specificity = 97.8% (93.8 - 99.6);

				PPV: 93.6% [Go, 2006]
Cardiomyopathy	425.xx	I42.xx, I43.xx	CHF	

Table S2. Distribution of drug classes by exposure drugs of interest

Drug classes	Frequency	Percent
SGLT2i		
CANAGLIFLOZIN	20273	30.58
EMPAGLIFLOZIN	6543	9.87
DAPAGLIFLOZIN	4588	6.92
LINAGLIPTIN AND EMPAGLIFLOZIN	390	0.59
METFORMIN AND CANAGLIFLOZIN	1225	1.85
METFORMIN AND DAPAGLIFLOZIN	307	0.46
METFORMIN AND EMPAGLIFLOZIN	182	0.27
GLP-1RA		
LIRAGLUTIDE	18265	27.55
DULAGLUTIDE	7293	11.00
EXENATIDE	6373	9.61
ALBIGLUTIDE	680	1.03
INSULIN DEGLUDEC AND LIRAGLUTIDE	31	0.05
INSULIN GLARGINE AND LIXISENATIDE	126	0.19
Multiple	16	0.02

Table S3. Cardiovascular conditions and codes used to define outcomes of interest

Condition	ICD-9-CM Codes	ICD-10-CM codes	Positions	Setting	Accuracy of codes (Validation study)
Myocardial infarction	410.xx	I20.xx, I21.xx	Primary or secondary	Inpatient	Specificity >93%; Sensitivity >86% [McCormick, 2014] PPV >94% [Kiyota 2004]
Cerebrovascular diseases or stroke	430.xx, 431.xx, 433.xx, 434.xx, 436.xx	I60.xx, I61.xx, I63.xx-I67.xx, I69.xxx	Primary or secondary	Inpatient	PPV 76%, sensitivity 68% [Jones, 2014] Specificity >95%, Sensitivity >82% [McCormick, 2015]
Heart failure (primary definition)	428.xx	I09.9, I11.0, I50.x	Primary or secondary	Inpatient	Specificity: 99%, [Birman-Deych, 2005], PPV 93% [Ezekowitz, 2008], sensitivity = 80.0% (67.0 - 90.0); specificity = 97.8% (93.8 - 99.6); PPV: 93.6% [So, 2006]
Heart failure (secondary definition)	428.xx, 398.91, 402.x1, 402.x3, 404.x1, 404.x3	I09.9, I11.0, I50.x	Primary or secondary	Inpatient	Specificity: 99%, [Birman-Deych, 2005], PPV 93% [Ezekowitz, 2008], sensitivity = 80.0% (67.0 - 90.0); specificity = 97.8% (93.8 - 99.6); PPV: 93.6% [So, 2006]

Table S4. Codes used to define primary outcome of heart failure hospitalization

Code type	Codes	Description
ICD-9-CM diagnosis	428	Heart Failure
ICD-9-CM diagnosis	4280	Congestive heart Failure not otherwise specified (NOS)
ICD-9-CM diagnosis	4281	Left Heart Failure
ICD-9-CM diagnosis	42820	Systolic Heart Failure NOS
ICD-9-CM diagnosis	42821	Acute Systolic Heart Failure
ICD-9-CM diagnosis	42822	Chronic Systolic Heart Failure
ICD-9-CM diagnosis	42823	Acute on Chronic Systolic Heart Failure
ICD-9-CM diagnosis	42830	Diastolic Heart Failure NOS
ICD-9-CM diagnosis	42831	Acute Diastolic Heart Failure
ICD-9-CM diagnosis	42832	Chronic Diastolic Heart Failure
ICD-9-CM diagnosis	42833	Acute on Chronic Diastolic Heart Failure
ICD-9-CM diagnosis	42840	Systolic/Diastolic Heart Failure NOS
ICD-9-CM diagnosis	42841	Acute Systolic/Diastolic Heart Failure
ICD-9-CM diagnosis	42842	Chronic Systolic/Diastolic Heart Failure
ICD-9-CM diagnosis	42843	Acute/Chronic Systolic/Diastolic Heart Failure
ICD-9-CM diagnosis	4289	Heart Failure NOS
ICD-10-CM diagnosis	I50	Heart Failure
ICD-10-CM diagnosis	I501	Left ventricular Failure
ICD-10-CM diagnosis	I502	Systolic (congestive) heart Failure
ICD-10-CM diagnosis	I5020	Unspecified Systolic (congestive) heart Failure
ICD-10-CM diagnosis	I5021	Acute Systolic (congestive) heart Failure
ICD-10-CM diagnosis	I5022	Chronic Systolic (congestive) heart Failure
ICD-10-CM diagnosis	I5023	Acute on chronic Systolic (congestive) heart failure
ICD-10-CM diagnosis	I503	Diastolic (congestive) heart Failure
ICD-10-CM diagnosis	I5030	Unspecified diastolic (congestive) heart Failure
ICD-10-CM diagnosis	I5031	Acute diastolic (congestive) heart Failure

ICD-10-CM diagnosis	I5032	Chronic diastolic (congestive) heart Failure
ICD-10-CM diagnosis	I5033	Acute on chronic diastolic (congestive) heart failure
ICD-10-CM diagnosis	I504	Combined systolic and diastolic (congestive) heart failure
ICD-10-CM diagnosis	I5040	Unspecific combined systolic and diastolic (congestive)
ICD-10-CM diagnosis	I5041	Acute combined systolic and diastolic (congestive)
ICD-10-CM diagnosis	I5042	Chronic combined systolic and diastolic heart fail
ICD-10-CM diagnosis	I5043	Acute on chronic combined systolic and diastolic heart failure
ICD-10-CM diagnosis	I509	Heart failure, unspecified

Table S5. Codes used to define myocardial infarction outcomes

Code	Code type	Description
41000	ICD-9-CM diagnosis	Acute myocardial infarction (AMI) anterolateral, unspecified
41001	ICD-9-CM diagnosis	Acute myocardial infarction (AMI) anterolateral, initial
41002	ICD-9-CM diagnosis	Acute myocardial infarction (AMI) anterolateral, subsequent
41010	ICD-9-CM diagnosis	AMI anterior wall, unspecified
41011	ICD-9-CM diagnosis	AMI anterior wall, initial
41012	ICD-9-CM diagnosis	AMI anterior wall, subsequent
41020	ICD-9-CM diagnosis	AMI inferolateral, unspecified
41021	ICD-9-CM diagnosis	Acute myocardial infarction (AMI) inferolateral, initial
41022	ICD-9-CM diagnosis	AMI inferolateral, subsequent
41030	ICD-9-CM diagnosis	AMI inferoposterial, unspecified
41031	ICD-9-CM diagnosis	AMI inferoposterial, initial
41032	ICD-9-CM diagnosis	AMI inferoposterial, subsequent
41040	ICD-9-CM diagnosis	AMI inferior wall, unspecified
41041	ICD-9-CM diagnosis	AMI inferior wall, initial
41042	ICD-9-CM diagnosis	AMI INFERIOR WALL, subsequent
41050	ICD-9-CM diagnosis	AMI lateral, unspecified
41051	ICD-9-CM diagnosis	AMI lateral, initial
41052	ICD-9-CM diagnosis	AMI LATERAL NEC, subsequent
41060	ICD-9-CM diagnosis	True posterior wall infarction episode of care unspecified
41061	ICD-9-CM diagnosis	True posterior wall infarction; initial episode of care
41062	ICD-9-CM diagnosis	True posterior wall infarction; subsequent episode of care
41070	ICD-9-CM diagnosis	Subendocardial infarction, episode of care unspecified
41071	ICD-9-CM diagnosis	Subendocardial infarction, initial episode of care
41072	ICD-9-CM diagnosis	Subendocardial infarction, subsequent episode of care
41080	ICD-9-CM diagnosis	Of other specified sites, episode of care unspecified
41081	ICD-9-CM diagnosis	Of other specified sites, initial episode of care
41082	ICD-9-CM diagnosis	Of other specified sites, subsequent episode of care

41090	ICD-9-CM diagnosis	Unspecified site, episode of care unspecified
41091	ICD-9-CM diagnosis	Unspecified site, initial episode of care
41092	ICD-9-CM diagnosis	Unspecified site, subsequent episode of care
I21	ICD-10-CM diagnosis	STEMI & NSTEMI
I210	ICD-10-CM diagnosis	ST elevation (STEMI) myocardial infarction of anterior wall
I2101	ICD-10-CM diagnosis	STEMI involving left main coronary artery
I2102	ICD-10-CM diagnosis	STEMI involving left anterior descending coronary artery
I2109	ICD-10-CM diagnosis	STEMI involving other coronary artery of anterior wall
I211	ICD-10-CM diagnosis	ST elevation (STEMI) myocardial infarction of inferior wall
I2111	ICD-10-CM diagnosis	STEMI involving right coronary artery
I2119	ICD-10-CM diagnosis	STEMI involving other coronary artery of inferior wall
I212	ICD-10-CM diagnosis	ST elevation (STEMI) myocardial infarction of other sites
I2121	ICD-10-CM diagnosis	STEMI involving left circumflex coronary artery
I2129	ICD-10-CM diagnosis	STEMI involving other sites
I213	ICD-10-CM diagnosis	ST elevation (STEMI) myocardial infarction of Unspecified site
I214	ICD-10-CM diagnosis	ST elevation (NSTEMI) myocardial infarction
I22	ICD-10-CM diagnosis	Subsequent STEMI & NSTEMI
I220	ICD-10-CM diagnosis	Subsequent STEMI of anterior wall
I221	ICD-10-CM diagnosis	Subsequent STEMI of inferior wall
I222	ICD-10-CM diagnosis	ST elevation (NSTEMI) myocardial infarction
I228	ICD-10-CM diagnosis	Subsequent STEMI of sites
I229	ICD-10-CM diagnosis	Subsequent STEMI of Unspecified site

Table S6. Codes used to define invasive cardiac revascularization and bypass procedures

Codes	Description	Code type
92920	Angioplasty, single vessel	CPT
92921	Angioplasty, additional branch	CPT
92924	Atherectomy, single vessel	CPT
92925	Atherectomy, additional branch	CPT
92928	Stent, single vessel	CPT
92929	Stent, additional branch	CPT
92933	Atherectomy + stent, single vessel	CPT
92934	Atherectomy + stent, additional branch	CPT
92937	PCI of or through bypass, any method(s)	CPT
92938	PCI of or through bypass, additional branch	CPT
92941	PCI of acute MI, all interventions, single vessel	CPT
92943	PCI of chronic total occlusion, any method(s)	CPT
92944	PCI of chronic total occlusion, additional branch	CPT
92973	Percutaneous coronary thrombectomy, mechanical	CPT
92975	Thrombolysis, coronary, by intracoronary infusion	CPT
92977	Thrombolysis, coronary, by intravenous infusion	CPT
33508	Endoscopy, surgical, including video-assisted harvest of vein(s) for coronary artery bypass procedure (List separately in addition to code for primary procedure)	CPT
33510	Coronary artery bypass, vein only; single coronary venous graft	CPT
33511	Coronary artery bypass, vein only; 2 coronary venous grafts	CPT
33512	Coronary artery bypass, vein only; 3 coronary venous grafts	CPT
33513	Coronary artery bypass, vein only; 4 coronary venous grafts	CPT
33514	Coronary artery bypass, vein only; 5 coronary venous grafts	CPT

33516	Coronary artery bypass, vein only; 6 or more coronary venous grafts	CPT
33517	Coronary artery bypass, using venous graft(s) and arterial graft(s); single vein graft (list separately in addition to code for primary procedure)	CPT
33518	Coronary artery bypass, using venous graft(s) and arterial graft(s); 2 venous grafts (list separately in addition to code for primary procedure)	CPT
33519	Coronary artery bypass, using venous graft(s) and arterial graft(s); 3 venous grafts (list separately in addition to code for primary procedure)	CPT
33520	Coronary Artery Bypass, Nonautogenous Graft (eg, Synthetic Or Cadaver); Single Graft	CPT
33521	Coronary artery bypass, using venous graft(s) and arterial graft(s); 4 venous grafts (list separately in addition to code for primary procedure)	CPT
33522	Coronary artery bypass, using venous graft(s) and arterial graft(s); 5 venous grafts (list separately in addition to code for primary procedure)	CPT
33523	Coronary artery bypass, using venous graft(s) and arterial graft(s); 6 or more venous grafts (list separately in addition to code for primary procedure)	CPT
33525	Coronary Artery Bypass, Nonautogenous Graft (eg, Synthetic Or Cadaver); Two Coronary Grafts	CPT
33528	Coronary Artery Bypass, Nonautogenous Graft (eg, Synthetic Or Cadaver); Three Or More Coronary Grafts	CPT
33530	Reoperation, coronary artery bypass procedure or valve procedure, more than 1 month after original operation (List	CPT

	separately in addition to code for primary procedure)	
33533	Coronary artery bypass, using arterial graft(s); single arterial graft	CPT
33534	Coronary artery bypass, using arterial graft(s); 2 coronary arterial grafts	CPT
33535	Coronary artery bypass, using arterial graft(s); 3 coronary arterial grafts	CPT
33536	Coronary artery bypass, using arterial graft(s); 4 or more coronary arterial grafts	CPT
35600	Harvest of upper extremity artery, 1 segment, for coronary artery bypass procedure (list separately in addition to code for primary procedure)	CPT
33572	Coronary endarterectomy, open, any method, of left anterior descending, circumflex, or right coronary artery performed in conjunction with coronary artery bypass graft procedure, each vessel (List separately in addition to primary procedure)	CPT
00566	Anesthesia for direct coronary artery bypass grafting; without pump oxygenator	CPT
00567	Anesthesia for direct coronary artery bypass grafting; with pump oxygenator	CPT
35500	Harvest of upper extremity vein, 1 segment, for lower extremity or coronary artery bypass procedure (List separately in addition to code for primary procedure)	CPT
4110F	Internal mammary artery graft performed for primary, isolated coronary artery bypass graft procedure (CABG)	CPT
C9600	Drug eluting stent, single vessel	HCPCS
C9601	Drug eluting stent, additional branch	HCPCS
C9602	Atherectomy + drug eluting stent, single vessel	HCPCS
C9603	Atherectomy + drug eluting stent, additional branch	HCPCS

C9604	PCI of or through bypass, any method(s), with drug-eluting stent	HCPCS
C9605	PCI of or through bypass, any method(s), with drug-eluting stent, additional branch	HCPCS
C9606	PCI of acute MI, all interventions, with drug-eluting stent, single vessel	HCPCS
C9607	PCI of chronic total occlusion, any method(s), with drug-eluting stent	HCPCS
C9608	PCI of chronic total occlusion, any method(s), with drug-eluting stent, additional branch	HCPCS
G8497	All quality actions for the applicable measures in the coronary artery bypass graft (CABG) measures group have been performed for this patient	HCPCS
S2208	Minimally invasive direct coronary artery bypass surgery involving mini-thoracotomy or mini-sternotomy surgery, performed under direct vision; using single arterial and venous graft(s), single venous graft	HCPCS
S2207	Minimally invasive direct coronary artery bypass surgery involving mini-thoracotomy or mini-sternotomy surgery, performed under direct vision; using venous graft only, single coronary venous graft	HCPCS
S2209	Minimally invasive direct coronary artery bypass surgery involving mini-thoracotomy or mini-sternotomy surgery, performed under direct vision; using two arterial grafts and single venous graft	HCPCS
S2205	Minimally invasive direct coronary artery bypass surgery involving mini-thoracotomy or mini-sternotomy surgery, performed under direct vision; using arterial graft(s), single coronary arterial graft	HCPCS
S2206	Minimally invasive direct coronary artery bypass surgery involving mini-thoracotomy or mini-sternotomy surgery, performed under direct vision;	HCPCS

	using arterial graft(s), two coronary arterial grafts	
G8159	Patient documented to have received coronary artery bypass graft without use of internal mammary artery	HCPCS
G8158	Patient documented to have received coronary artery bypass graft with use of internal mammary artery	HCPCS
G8171	Patient with isolated coronary artery bypass graft not documented to have been discharged on aspirin or clopidogrel	HCPCS
G8170	Patient with isolated coronary artery bypass graft documented to have been discharged on aspirin or clopidogrel	HCPCS
G8164	Patient with isolated coronary artery bypass graft documented to have prolonged intubation	HCPCS
G8161	Patient with isolated coronary artery bypass graft documented to have received pre-operative beta-blockade	HCPCS
G8166	Patient with isolated coronary artery bypass graft documented to have required surgical re-exploration	HCPCS
G8162	Patient with isolated coronary artery bypass graft not documented to have received preoperative beta-blockade	HCPCS
G8165	Patient with isolated coronary artery bypass graft not documented to have prolonged intubation	HCPCS
G8167	Patient with isolated coronary artery bypass graft did not require surgical re-exploration	HCPCS
36.03	Open chest coronary artery angioplasty	ICD-9-CM procedure
36.04	Intracoronary artery thrombolytic infusion	ICD-9-CM procedure
36.06	Insertion of non-drug-eluting coronary artery stent(s)	ICD-9-CM procedure
36.07	Insertion of drug-eluting coronary artery stent(s)	ICD-9-CM procedure
36.09	other coronary angioplasty - Other removal of coronary artery obstruction	ICD-9-CM procedure

36.10	Aortocoronary bypass for heart revascularization, not otherwise specified	ICD-9-CM procedure
36.11	(Aorto)coronary bypass of one coronary artery	ICD-9-CM procedure
36.12	(Aorto)coronary bypass of two coronary arteries	ICD-9-CM procedure
36.13	(Aorto)coronary bypass of three coronary arteries	ICD-9-CM procedure
36.14	(Aorto)coronary bypass of four or more coronary arteries	ICD-9-CM procedure
36.15	Single internal mammary-coronary artery bypass	ICD-9-CM procedure
36.16	Double internal mammary-coronary artery bypass	ICD-9-CM procedure
36.17	Abdominal - coronary artery bypass	ICD-9-CM procedure
36.19	Other bypass anastomosis for heart revascularization	ICD-9-CM procedure
36.2	Heart revascularization by arterial implant	ICD-9-CM procedure
36.31	Open chest transmyocardial revascularization	ICD-9-CM procedure
36.32	Other transmyocardial revascularization	ICD-9-CM procedure
36.33	Endoscopic transmyocardial revascularization	ICD-9-CM procedure
36.34	Percutaneous transmyocardial revascularization	ICD-9-CM procedure
36.39	Other heart revascularization	ICD-9-CM procedure
00.66	Percutaneous transluminal coronary angioplasty [PTCA] or coronary atherectomy	ICD-9-CM procedure
0210xxx	Bypass Coronary Artery, One Artery	ICD-10-CM procedure
0211xxx	Bypass Coronary Artery, Two Arteries	ICD-10-CM procedure
0212xxx	Bypass Coronary Artery, Three Arteries	ICD-10-CM procedure
0213xxx	Bypass Coronary Artery, Four or More Arteries	ICD-10-CM procedure

Table S7. Distributions of baseline characteristics after propensity score weighting to balance covariates

between cohorts in the total study population

Characteristic	SGLT2i N=24,747 (%)	GLP-1RA N=22,596 (%)	Total N=47,343	Absolute Standardized Mean Differences
Demographic characteristics				
Age, mean (SD)	73.4(5.70)	72.7(5.43)	73.1(5.58)	0.127
Race				
Whites	19,753 (79.8%)	18,644 (82.5%)	38,397 (81.1%)	0.068
African Americans	1,865 (7.5%)	2,105 (9.3%)	3,970 (8.4%)	0.064
Others	3,129 (12.6%)	1,851 (8.2%)	4,980 (10.5%)	0.146
Sex, Males	12,601 (50.9%)	9,938 (44.0%)	22,539 (47.6%)	0.139
Low-income subsidy, mean (SD)	187.7(414.74)	216.4(456.26)	201.4(435.28)	0.066
Measures of DM severity/complications				
Diabetes retinopathy	3,623 (14.6%)	3,622 (16.0%)	7,245 (15.3%)	0.038
Diabetes nephropathy	2,835 (11.5%)	4,204 (18.6%)	7,039 (14.9%)	0.201
Diabetes neuropathy	6,985 (28.2%)	7,599 (33.6%)	14,584 (30.8%)	0.117
Other diabetes complications	11,158 (45.1%)	10,814 (47.8%)	21,972 (46.4%)	0.055
Number of antihyperglycemic drugs				
0	2,139 (8.6%)	4,036 (17.9%)	6,175 (13.0%)	0.274
1	6,799 (27.5%)	7,109 (31.5%)	13,908 (29.4%)	0.087
2	9,167 (37.0%)	7,145 (31.6%)	16,312 (34.5%)	0.115
3	5,698 (23.0%)	3,709 (16.4%)	9,407 (19.9%)	0.167
4+	944 (3.8%)	601 (2.7%)	1,545 (3.3%)	0.065
Number of hyperglycemia diagnoses				
0	10,991 (44.4%)	8,858 (39.2%)	19,849 (41.9%)	0.106

Characteristic	SGLT2i N=24,747 (%)	GLP-1RA N=22,596 (%)	Total N=47,343	Absolute Standardized Mean Differences
1	3,195 (12.9%)	2,857 (12.6%)	6,052 (12.8%)	0.008
2	1,957 (7.9%)	1,894 (8.4%)	3,851 (8.1%)	0.017
3	2,887 (11.7%)	2,721 (12.0%)	5,608 (11.8%)	0.012
4+	5,717 (23.1%)	6,270 (27.7%)	11,987 (25.3%)	0.107
Hypoglycemia	565 (2.3%)	710 (3.1%)	1,275 (2.7%)	0.053
Foot ulcers	733 (3.0%)	894 (4.0%)	1,627 (3.4%)	0.054
Cardiovascular disorders				
Angina	1,309 (5.3%)	1,222 (5.4%)	2,531 (5.3%)	0.005
MI	1,574 (6.4%)	1,629 (7.2%)	3,203 (6.8%)	0.034
Cardiac revascularization or bypass	472 (1.9%)	476 (2.1%)	948 (2.0%)	0.014
Atherosclerosis	3,148 (12.7%)	2,946 (13.0%)	6,094 (12.9%)	0.009
Ischemic heart diseases	8,246 (33.3%)	7,900 (35.0%)	16,146 (34.1%)	0.034
Cerebrovascular diseases	3,763 (15.2%)	3,523 (15.6%)	7,286 (15.4%)	0.011
Cardiomyopathy	982 (4.0%)	1,024 (4.5%)	2,006 (4.2%)	0.028
Congestive heart failure	3,123 (12.6%)	3,884 (17.2%)	7,007 (14.8%)	0.128
Peripheral vascular diseases	4,345 (17.6%)	4,427 (19.6%)	8,772 (18.5%)	0.052
Atrial fibrillation	2,947 (11.9%)	2,940 (13.0%)	5,887 (12.4%)	0.033
Arrhythmia disorders	3,468 (14.0%)	3,617 (16.0%)	7,085 (15.0%)	0.056
Cardiac arrest	37 (0.1%)	38 (0.2%)	75 (0.2%)	0.005
Defibrillator	364 (1.5%)	435 (1.9%)	799 (1.7%)	0.035
Comorbid conditions				
Combined comorbidity score, mean (SD)	1.9(2.32)	2.5(2.58)	2.2(2.46)	0.224
Anemia	6,364 (25.7%)	6,245 (27.6%)	12,609 (26.6%)	0.043
Alcohol disorders	205 (0.8%)	174 (0.8%)	379 (0.8%)	0.007
Asthma	2,389 (9.7%)	2,807 (12.4%)	5,196 (11.0%)	0.088
Brain injury	631 (2.5%)	720 (3.2%)	1,351 (2.9%)	0.038

Characteristic	SGLT2i N=24,747 (%)	GLP-1RA N=22,596 (%)	Total N=47,343	Absolute Standardized Mean Differences
Cancer (except for non-melanoma skin)	3,129 (12.6%)	2,721 (12.0%)	5,850 (12.4%)	0.018
Chronic lung disorders	5,835 (23.6%)	6,386 (28.3%)	12,221 (25.8%)	0.107
CKD (stage 1-3)	3,590 (14.5%)	5,853 (25.9%)	9,443 (19.9%)	0.287
Coagulopathy	816 (3.3%)	874 (3.9%)	1,690 (3.6%)	0.031
Connective tissue disorders	878 (3.5%)	1,018 (4.5%)	1,896 (4.0%)	0.049
Dementia	588 (2.4%)	598 (2.6%)	1,186 (2.5%)	0.017
Deficiency anemia	5,927 (24.0%)	5,717 (25.3%)	11,644 (24.6%)	0.031
Depression	3,788 (15.3%)	4,778 (21.1%)	8,566 (18.1%)	0.152
Difficulty walking	3,473 (14.0%)	3,841 (17.0%)	7,314 (15.4%)	0.082
Dyslipidemia	21,932 (88.6%)	19,654 (87.0%)	41,586 (87.8%)	0.051
Endocrine disorders	9,833 (39.7%)	9,789 (43.3%)	19,622 (41.4%)	0.073
Edema	2,749 (11.1%)	3,414 (15.1%)	6,163 (13.0%)	0.119
Electrolytes disorders	2,969 (12.0%)	3,504 (15.5%)	6,473 (13.7%)	0.102
HIV	47 (0.2%)	47 (0.2%)	94 (0.2%)	0.004
Hematological disorders	7,362 (29.7%)	7,285 (32.2%)	14,647 (30.9%)	0.054
Hypertension	14,167 (57.2%)	12,437 (55.0%)	26,604 (56.2%)	0.045
Hypotension	801 (3.2%)	900 (4.0%)	1,701 (3.6%)	0.040
Immune disorders	365 (1.5%)	417 (1.8%)	782 (1.7%)	0.029
Metabolic disorders	22,084 (89.2%)	20,008 (88.5%)	42,092 (88.9%)	0.023
Metastatic cancers	265 (1.1%)	210 (0.9%)	475 (1.0%)	0.014
Mild liver disorders	1,208 (4.9%)	1,149 (5.1%)	2,357 (5.0%)	0.009
Moderate liver disorders	142 (0.6%)	128 (0.6%)	270 (0.6%)	0.001
Nutritional disorders	7,584 (30.6%)	7,203 (31.9%)	14,787 (31.2%)	0.026
Nervous system disorders	11,445 (46.2%)	12,356 (54.7%)	23,801 (50.3%)	0.169
Paraplegia	226 (0.9%)	268 (1.2%)	494 (1.0%)	0.027
Parkinsonism	250 (1.0%)	276 (1.2%)	526 (1.1%)	0.020
Pneumonia	1,162 (4.7%)	1,390 (6.2%)	2,552 (5.4%)	0.064

Characteristic	SGLT2i N=24,747 (%)	GLP-1RA N=22,596 (%)	Total N=47,343	Absolute Standardized Mean Differences
Psychosis	1,129 (4.6%)	1,287 (5.7%)	2,416 (5.1%)	0.051
Pulmonary circulation disorders	623 (2.5%)	845 (3.7%)	1,468 (3.1%)	0.070
Rehabilitation	1,184 (4.8%)	1,326 (5.9%)	2,510 (5.3%)	0.048
Renal disorders	3,650 (14.7%)	5,927 (26.2%)	9,577 (20.2%)	0.287
Rheumatic disorders	845 (3.4%)	824 (3.6%)	1,669 (3.5%)	0.013
Smoking and smoking cessation	1,309 (5.3%)	1,204 (5.3%)	2,513 (5.3%)	0.002
Thromboembolism	167 (0.7%)	151 (0.7%)	318 (0.7%)	0.001
Vulvular disorders	3,061 (12.4%)	2,932 (13.0%)	5,993 (12.7%)	0.018
Weight loss	185 (0.7%)	190 (0.8%)	375 (0.8%)	0.010
Durable medical equipment claims				
Ambulance	2,519 (10.2%)	2,853 (12.6%)	5,372 (11.3%)	0.077
Hospital beds	132 (0.5%)	174 (0.8%)	306 (0.6%)	0.029
Home oxygen	955 (3.9%)	1,419 (6.3%)	2,374 (5.0%)	0.110
Wheelchairs	275 (1.1%)	348 (1.5%)	623 (1.3%)	0.037
History of medications use				
Metformin	19,134 (77.3%)	14,828 (65.6%)	33,962 (71.7%)	0.261
Short acting insulin	2,835 (11.5%)	4,924 (21.8%)	7,759 (16.4%)	0.280
Long acting insulin	6,450 (26.1%)	9,869 (43.7%)	16,319 (34.5%)	0.376
TZD	2,810 (11.4%)	2,219 (9.8%)	5,029 (10.6%)	0.050
Meglitinide	728 (2.9%)	656 (2.9%)	1,384 (2.9%)	0.002
SU	12,133 (49.0%)	9,725 (43.0%)	21,858 (46.2%)	0.121
DPP-4i	10,971 (44.3%)	7,338 (32.5%)	18,309 (38.7%)	0.246
Immunosuppressive drugs	174 (0.7%)	217 (1.0%)	391 (0.8%)	0.028
Steroids	4,084 (16.5%)	4,060 (18.0%)	8,144 (17.2%)	0.039
ACEI	10,964 (44.3%)	10,090 (44.6%)	21,054 (44.5%)	0.007
ARB	9,094 (36.7%)	8,341 (36.9%)	17,435 (36.8%)	0.003

Characteristic	SGLT2i N=24,747 (%)	GLP-1RA N=22,596 (%)	Total N=47,343	Absolute Standardized Mean Differences
CCB	8,274 (33.4%)	7,866 (34.8%)	16,140 (34.1%)	0.029
BB	13,125 (53.0%)	12,514 (55.4%)	25,639 (54.2%)	0.047
NSAIDS	7,169 (29.0%)	6,437 (28.5%)	13,606 (28.7%)	0.011
Aspirin	1,134 (4.6%)	1,366 (6.0%)	2,500 (5.3%)	0.065
Oral contraceptives	475 (1.9%)	589 (2.6%)	1,064 (2.2%)	0.046
Estrogen	1,338 (5.4%)	1,411 (6.2%)	2,749 (5.8%)	0.036
Loop diuretics	4,582 (18.5%)	6,153 (27.2%)	10,735 (22.7%)	0.209
Other diuretics	9,313 (37.6%)	9,241 (40.9%)	18,554 (39.2%)	0.067
Statin	19,098 (77.2%)	17,363 (76.8%)	36,461 (77.0%)	0.008
Measures of healthcare utilization				
HbA1C tests				
0	1,313 (5.3%)	1,690 (7.5%)	3,003 (6.3%)	0.089
1	3,028 (12.2%)	2,731 (12.1%)	5,759 (12.2%)	0.005
2	5,723 (23.1%)	4,703 (20.8%)	10,426 (22.0%)	0.056
3	6,956 (28.1%)	5,923 (26.2%)	12,879 (27.2%)	0.043
4	4,955 (20.0%)	4,573 (20.2%)	9,528 (20.1%)	0.005
5+	2,772 (11.2%)	2,980 (13.2%)	5,752 (12.1%)	0.061
Flu shots				
0	9,441 (38.2%)	8,673 (38.4%)	18,114 (38.3%)	0.005
1	12,361 (49.9%)	11,163 (49.4%)	23,524 (49.7%)	0.011
2	2,056 (8.3%)	1,901 (8.4%)	3,957 (8.4%)	0.004
3+	889 (3.6%)	863 (3.8%)	1,752 (3.7%)	0.012
Lipid tests				
0	2,964 (12.0%)	3,505 (15.5%)	6,469 (13.7%)	0.103
1	7,262 (29.3%)	6,839 (30.3%)	14,101 (29.8%)	0.020
2	6,928 (28.0%)	5,888 (26.1%)	12,816 (27.1%)	0.044
3	4,325 (17.5%)	3,546 (15.7%)	7,871 (16.6%)	0.048
4+	3,268 (13.2%)	2,822 (12.5%)	6,090 (12.9%)	0.021

Characteristic	SGLT2i N=24,747 (%)	GLP-1RA N=22,596 (%)	Total N=47,343	Absolute Standardized Mean Differences
Number of hospital admissions				
0	21,249 (85.9%)	18,533 (82.0%)	39,782 (84.0%)	0.105
1	2,486 (10.0%)	2,774 (12.3%)	5,260 (11.1%)	0.071
2+	1,012 (4.1%)	1,293 (5.7%)	2,305 (4.9%)	0.076
Number of days of hospitalization				
0	21,249 (85.9%)	18,533 (82.0%)	39,782 (84.0%)	0.105
1	1,583 (6.4%)	1,760 (7.8%)	3,343 (7.1%)	0.054
2+	1,915 (7.7%)	2,307 (10.2%)	4,222 (8.9%)	0.086
Number of emergency visits				
0	17,646 (71.3%)	15,036 (66.5%)	32,682 (69.0%)	0.103
1	3,903 (15.8%)	3,831 (17.0%)	7,734 (16.3%)	0.032
2	1,619 (6.5%)	1,794 (7.9%)	3,413 (7.2%)	0.054
3+	1,579 (6.4%)	1,939 (8.6%)	3,518 (7.4%)	0.084
Number of emergency visits due to DM				
0	24,395 (98.6%)	22,198 (98.2%)	46,593 (98.4%)	0.028
1	296 (1.2%)	335 (1.5%)	631 (1.3%)	0.025
2+	56 (0.2%)	67 (0.3%)	123 (0.3%)	0.014
Number of outpatient visits				
0	1,047 (4.2%)	1,277 (5.7%)	2,324 (4.9%)	0.066
1	4,446 (18.0%)	3,565 (15.8%)	8,011 (16.9%)	0.059
2	6,491 (26.2%)	5,147 (22.8%)	11,638 (24.6%)	0.080
3	5,063 (20.5%)	4,401 (19.5%)	9,464 (20.0%)	0.025
4	3,223 (13.0%)	3,156 (14.0%)	6,379 (13.5%)	0.028
5+	4,477 (18.1%)	5,054 (22.4%)	9,531 (20.1%)	0.106
Number of outpatient visits due to DM	11,172 (45.1%)	10,111 (44.7%)	21,283 (45.0%)	0.008

Characteristic	SGLT2i N=24,747 (%)	GLP-1RA N=22,596 (%)	Total N=47,343	Absolute Standardized Mean Differences
Number of days between first and second scripts, mean (SD)	47.5(29.47)	47.4(27.76)	47.4(28.66)	0.002
Markers of diabetes and cardiovascular disease severity				
HbA1C <7%	945 (3.8%)	868 (3.8%)	1,813 (3.8%)	0.001
HbA1C 7-9%	1,982 (8.0%)	1,762 (7.8%)	3,744 (7.9%)	0.008
HbA1C >9%	1,075 (4.3%)	1,176 (5.2%)	2,251 (4.8%)	0.040
LDL <100 mg/dl	861 (3.5%)	879 (3.9%)	1,740 (3.7%)	0.022
LDL 100-129 mg/dl	202 (0.8%)	202 (0.9%)	404 (0.9%)	0.008
LDL >130 mg/dl	93 (0.4%)	115 (0.5%)	208 (0.4%)	0.020
SBP <130	167 (0.7%)	209 (0.9%)	376 (0.8%)	0.028
SBP 130-139	115 (0.5%)	125 (0.6%)	240 (0.5%)	0.012
SBP >=140	118 (0.5%)	139 (0.6%)	257 (0.5%)	0.019
DBP <80	214 (0.9%)	275 (1.2%)	489 (1.0%)	0.035
DBP 80-89	118 (0.5%)	116 (0.5%)	234 (0.5%)	0.005
DBP >=90	25 (0.1%)	31 (0.1%)	56 (0.1%)	0.010

Table S8. Distribution of baseline characteristics after inverse probability of treatment and censoring weighting among patients with no evidence of atherosclerotic CVDs or heart failure

Characteristic	SGLT-2i N=13,017	GLP-1RA N=10,777	Total N=23,794	Standardized Absolute Mean Differences
Demographic characteristics				
Age, mean (SD)	72.0(4.92)	71.9(4.90)	71.9(4.91)	0.009
Race				
Whites	10,604 (81.5%)	8,802 (81.7%)	19,405 (81.6%)	0.006
African Americans	1,216 (9.3%)	999 (9.3%)	2,216 (9.3%)	0.003
Others	1,197 (9.2%)	976 (9.1%)	2,172 (9.1%)	0.005
Sex, Males	5,258 (40.4%)	4,399 (40.8%)	9,657 (40.6%)	0.009
Low-income subsidy, mean (SD)	134.5(358.10)	132.6(340.48)	133.6(350.22)	0.006
Measures of DM severity				
Diabetes retinopathy	1,587 (12.2%)	1,280 (11.9%)	2,867 (12.0%)	0.010
Diabetes nephropathy	1,300 (10.0%)	1,081 (10.0%)	2,381 (10.0%)	0.001
Diabetes neuropathy	2,730 (21.0%)	2,240 (20.8%)	4,971 (20.9%)	0.005
Other diabetes complications	3,723 (28.6%)	3,095 (28.7%)	6,818 (28.7%)	0.002
Number of antihyperglycemic drugs				
0	1,719 (13.2%)	1,352 (12.5%)	3,071 (12.9%)	0.020
1	3,766 (28.9%)	3,111 (28.9%)	6,877 (28.9%)	0.001
2	4,528 (34.8%)	3,806 (35.3%)	8,333 (35.0%)	0.011
3	2,608 (20.0%)	2,166 (20.1%)	4,774 (20.1%)	0.002
4+	396 (3.0%)	342 (3.2%)	738 (3.1%)	0.007
Number of hyperglycemia diagnoses				
0	5,989 (46.0%)	4,980 (46.2%)	10,969 (46.1%)	0.004
1	1,616 (12.4%)	1,387 (12.9%)	3,003 (12.6%)	0.014
2	1,020 (7.8%)	858 (8.0%)	1,879 (7.9%)	0.005
3	1,487 (11.4%)	1,248 (11.6%)	2,735 (11.5%)	0.005
4+	2,904 (22.3%)	2,303 (21.4%)	5,207 (21.9%)	0.023
Hypoglycemia	207 (1.6%)	160 (1.5%)	366 (1.5%)	0.009
Foot ulcers	227 (1.7%)	165 (1.5%)	392 (1.6%)	0.017

Characteristic	SGLT-2i N=13,017	GLP-1RA N=10,777	Total N=23,794	Standardized Absolute Mean Differences
Cardiovascular disorders				
Atrial fibrillation	626 (4.8%)	511 (4.7%)	1,137 (4.8%)	0.003
Arrhythmia disorders	858 (6.6%)	696 (6.5%)	1,554 (6.5%)	0.005
Cardiac arrest	NTSR	NTSR	NTSR	0.004
Comorbid conditions				
Combined comorbidity score, mean (SD)	1.2(1.58)	1.2(1.58)	1.2(1.58)	0.009
Alcohol disorders	58 (0.4%)	56 (0.5%)	114 (0.5%)	0.010
Asthma	1,079 (8.3%)	894 (8.3%)	1,972 (8.3%)	0.000
Brain injury	113 (0.9%)	91 (0.8%)	204 (0.9%)	0.003
Cancer (except for non-melanoma skin)	1,409 (10.8%)	1,167 (10.8%)	2,576 (10.8%)	0.000
Chronic lung disorders	2,232 (17.1%)	1,847 (17.1%)	4,079 (17.1%)	0.000
CKD (stage 1-3)	1,651 (12.7%)	1,386 (12.9%)	3,037 (12.8%)	0.005
Coagulopathy	279 (2.1%)	224 (2.1%)	503 (2.1%)	0.005
Connective tissue disorders	417 (3.2%)	321 (3.0%)	737 (3.1%)	0.013
Dementia	129 (1.0%)	96 (0.9%)	225 (0.9%)	0.011
Deficiency anemia	2,178 (16.7%)	1,783 (16.5%)	3,960 (16.6%)	0.005
Depression	1,860 (14.3%)	1,499 (13.9%)	3,359 (14.1%)	0.011
Difficulty walking	1,045 (8.0%)	831 (7.7%)	1,876 (7.9%)	0.012
Dyslipidemia	10,804 (83.0%)	8,936 (82.9%)	19,740 (83.0%)	0.002
Endocrine disorders	4,740 (36.4%)	3,835 (35.6%)	8,575 (36.0%)	0.017
Edema	1,108 (8.5%)	879 (8.2%)	1,987 (8.4%)	0.013
Electrolytes disorders	987 (7.6%)	779 (7.2%)	1,766 (7.4%)	0.013
HIV	20 (0.2%)	17 (0.2%)	37 (0.2%)	0.001
Hematological disorders	2,797 (21.5%)	2,292 (21.3%)	5,088 (21.4%)	0.005
Hypertension	5,083 (39.0%)	4,236 (39.3%)	9,319 (39.2%)	0.005
Immune disorders	162 (1.2%)	129 (1.2%)	291 (1.2%)	0.004
Metabolic disorders	10,903 (83.8%)	9,011 (83.6%)	19,914 (83.7%)	0.004
Metastatic cancers	138 (1.1%)	108 (1.0%)	245 (1.0%)	0.006
Mild liver disorders	591 (4.5%)	495 (4.6%)	1,087 (4.6%)	0.003
Moderate liver disorders	58 (0.4%)	45 (0.4%)	103 (0.4%)	0.005
Nutritional disorders	3,524 (27.1%)	2,893 (26.8%)	6,417 (27.0%)	0.005

Characteristic	SGLT-2i N=13,017	GLP-1RA N=10,777	Total N=23,794	Standardized Absolute Mean Differences
Nervous system disorders	4,913 (37.7%)	4,025 (37.3%)	8,938 (37.6%)	0.008
Paraplegia	34 (0.3%)	22 (0.2%)	56 (0.2%)	0.013
Parkinsonism	89 (0.7%)	69 (0.6%)	158 (0.7%)	0.006
Pneumonia	338 (2.6%)	269 (2.5%)	607 (2.5%)	0.007
Psychosis	524 (4.0%)	421 (3.9%)	945 (4.0%)	0.006
Pulmonary circulation disorders	96 (0.7%)	89 (0.8%)	185 (0.8%)	0.010
Rehabilitation	519 (4.0%)	426 (4.0%)	946 (4.0%)	0.002
Renal disorders	1,670 (12.8%)	1,401 (13.0%)	3,071 (12.9%)	0.005
Rheumatic disorders	113 (0.9%)	92 (0.9%)	205 (0.9%)	0.002
Smoking and smoking cessation	517 (4.0%)	422 (3.9%)	939 (3.9%)	0.003
Thromboembolism	NTSR	NTSR	14 (0.1%)	0.002
Vulvular disorders	543 (4.2%)	422 (3.9%)	964 (4.1%)	0.013
Weight loss	37 (0.3%)	26 (0.2%)	63 (0.3%)	0.009
Durable medical equipment claims				
Ambulance	553 (4.2%)	452 (4.2%)	1,005 (4.2%)	0.003
Hospital beds	25 (0.2%)	21 (0.2%)	46 (0.2%)	0.000
Home oxygen	339 (2.6%)	278 (2.6%)	617 (2.6%)	0.002
Wheelchairs	64 (0.5%)	52 (0.5%)	116 (0.5%)	0.001
History of medications use				
Metformin	9,538 (73.3%)	7,990 (74.1%)	17,528 (73.7%)	0.020
Short acting insulin	1,536 (11.8%)	1,166 (10.8%)	2,702 (11.4%)	0.031
Long acting insulin	3,991 (30.7%)	3,116 (28.9%)	7,107 (29.9%)	0.038
TZD	1,476 (11.3%)	1,219 (11.3%)	2,695 (11.3%)	0.001
Meglitinide	313 (2.4%)	246 (2.3%)	560 (2.4%)	0.008
SU	6,111 (47.0%)	5,127 (47.6%)	11,238 (47.2%)	0.013
DPP-4i	4,700 (36.1%)	3,936 (36.5%)	8,636 (36.3%)	0.009
Immunosuppressive drugs	99 (0.8%)	78 (0.7%)	177 (0.7%)	0.005
Steroids	1,806 (13.9%)	1,487 (13.8%)	3,293 (13.8%)	0.002
ACEI	5,868 (45.1%)	4,895 (45.4%)	10,763 (45.2%)	0.007
ARB	4,456 (34.2%)	3,659 (34.0%)	8,115 (34.1%)	0.006
CCB	3,942 (30.3%)	3,340 (31.0%)	7,282 (30.6%)	0.015

Characteristic	SGLT-2i N=13,017	GLP-1RA N=10,777	Total N=23,794	Standardized Absolute Mean Differences
BB	4,982 (38.3%)	4,052 (37.6%)	9,034 (38.0%)	0.014
NSAIDS	3,579 (27.5%)	2,933 (27.2%)	6,512 (27.4%)	0.006
Aspirin	535 (4.1%)	430 (4.0%)	965 (4.1%)	0.006
Oral contraceptives	360 (2.8%)	289 (2.7%)	649 (2.7%)	0.005
Estrogen	799 (6.1%)	656 (6.1%)	1,455 (6.1%)	0.002
Loop diuretics	1,529 (11.7%)	1,251 (11.6%)	2,780 (11.7%)	0.004
Other diuretics	5,219 (40.1%)	4,317 (40.1%)	9,536 (40.1%)	0.001
Statin	9,078 (69.7%)	7,475 (69.4%)	16,553 (69.6%)	0.008
Measures of healthcare utilization				
HbA1C tests				
0	1,123 (8.6%)	940 (8.7%)	2,063 (8.7%)	0.003
1	1,708 (13.1%)	1,467 (13.6%)	3,175 (13.3%)	0.014
2	3,022 (23.2%)	2,491 (23.1%)	5,513 (23.2%)	0.003
3	3,482 (26.7%)	2,897 (26.9%)	6,378 (26.8%)	0.003
4	2,474 (19.0%)	2,005 (18.6%)	4,478 (18.8%)	0.010
5+	1,208 (9.3%)	978 (9.1%)	2,186 (9.2%)	0.007
Flu shots				
0	5,215 (40.1%)	4,348 (40.3%)	9,563 (40.2%)	0.006
1	6,420 (49.3%)	5,315 (49.3%)	11,735 (49.3%)	0.000
2	984 (7.6%)	796 (7.4%)	1,780 (7.5%)	0.007
3+	398 (3.1%)	317 (2.9%)	715 (3.0%)	0.007
Lipid tests				
0	2,062 (15.8%)	1,698 (15.8%)	3,760 (15.8%)	0.002
1	4,243 (32.6%)	3,550 (32.9%)	7,793 (32.8%)	0.007
2	3,481 (26.7%)	2,863 (26.6%)	6,344 (26.7%)	0.004
3	1,944 (14.9%)	1,614 (15.0%)	3,558 (15.0%)	0.001
4+	1,286 (9.9%)	1,052 (9.8%)	2,339 (9.8%)	0.004
Number of hospital admissions				
0	12,207 (93.8%)	10,103 (93.7%)	22,310 (93.8%)	0.001
1	695 (5.3%)	587 (5.4%)	1,283 (5.4%)	0.005
2+	115 (0.9%)	87 (0.8%)	201 (0.8%)	0.008

Characteristic	SGLT-2i N=13,017	GLP-1RA N=10,777	Total N=23,794	Standardized Absolute Mean Differences
Number of days of hospitalization				
0	12,207 (93.8%)	10,103 (93.7%)	22,310 (93.8%)	0.001
1	471 (3.6%)	414 (3.8%)	885 (3.7%)	0.012
2+	339 (2.6%)	260 (2.4%)	599 (2.5%)	0.012
Number of emergency visits				
0	10,427 (80.1%)	8,607 (79.9%)	19,034 (80.0%)	0.006
1	1,686 (13.0%)	1,425 (13.2%)	3,111 (13.1%)	0.008
2	548 (4.2%)	460 (4.3%)	1,008 (4.2%)	0.003
3+	355 (2.7%)	285 (2.6%)	640 (2.7%)	0.005
Number of emergency visits due to DM				
0	12,876 (98.9%)	10,656 (98.9%)	23,532 (98.9%)	0.004
1	127 (1.0%)	108 (1.0%)	236 (1.0%)	0.003
2+	13 (0.1%)	13 (0.1%)	26 (0.1%)	0.005
Number of outpatient visits				
0	918 (7.1%)	765 (7.1%)	1,683 (7.1%)	0.002
1	2,967 (22.8%)	2,497 (23.2%)	5,463 (23.0%)	0.009
2	3,779 (29.0%)	3,141 (29.2%)	6,921 (29.1%)	0.003
3	2,595 (19.9%)	2,160 (20.0%)	4,755 (20.0%)	0.003
4	1,369 (10.5%)	1,102 (10.2%)	2,471 (10.4%)	0.010
5+	1,388 (10.7%)	1,111 (10.3%)	2,500 (10.5%)	0.012
Number of outpatient visits due to DM	6,544 (50.3%)	5,436 (50.4%)	11,980 (50.4%)	0.003

SGLT2i – sodium glucose cotransporter 2 inhibitors; GLP-1RA – glucagon like peptide-1 receptor agonist;

SD – standard deviations; DM – diabetes mellitus; ACEI – angiotensin converting enzyme inhibitors; ARB

– angiotensin receptor blockers; BB – beta blockers; CCB – calcium channel blockers; NSAIDs - nonsteroidal

anti-inflammatory drugs; DPP-4i – dipeptidyl peptidase-4 inhibitors; SU – sulphonylureas; TZD -

thiazolidinediones

Table S9. Distribution of baseline characteristics after inverse probability of treatment and censoring weighting among patients with no evidence of atherosclerotic CVDs but heart failure

Characteristic	SGLT-2i N=744	GLP-1RA N=865	Total N=1,609	Standardized Absolute Mean Differences
Demographic characteristics				
Age, mean (SD)	73.1(6.02)	73.3(5.92)	73.2(5.97)	0.044
Race				
Whites	612 (82.3%)	707 (81.8%)	1,320 (82.0%)	0.013
African Americans	75 (10.1%)	95 (11.0%)	170 (10.6%)	0.027
Others	56 (7.6%)	63 (7.3%)	119 (7.4%)	0.012
Sex, Males	275 (37.0%)	334 (38.5%)	609 (37.8%)	0.032
Low-income subsidy, mean (SD)	223.6(395.14)	234.6(428.80)	229.5(413.49)	0.027
Measures of DM severity				
Diabetes retinopathy	80 (10.7%)	96 (11.0%)	175 (10.9%)	0.011
Diabetes nephropathy	91 (12.3%)	131 (15.1%)	222 (13.8%)	0.083
Diabetes neuropathy	211 (28.4%)	265 (30.6%)	476 (29.6%)	0.049
Other diabetes complications	259 (34.8%)	326 (37.7%)	585 (36.4%)	0.061
Number of antihyperglycemic drugs				
0	178 (23.9%)	169 (19.6%)	347 (21.6%)	0.104
1	221 (29.8%)	275 (31.8%)	497 (30.9%)	0.044
2	212 (28.5%)	252 (29.1%)	464 (28.8%)	0.015
3	115 (15.4%)	142 (16.4%)	257 (16.0%)	0.027
4+	18 (2.5%)	27 (3.1%)	45 (2.8%)	0.038
Number of hyperglycemia diagnoses				
0	260 (34.9%)	298 (34.4%)	557 (34.6%)	0.010
1	95 (12.8%)	126 (14.6%)	221 (13.8%)	0.053
2	77 (10.3%)	80 (9.3%)	157 (9.8%)	0.036
3	94 (12.6%)	112 (12.9%)	205 (12.8%)	0.009
4+	219 (29.4%)	249 (28.8%)	468 (29.1%)	0.012
Hypoglycemia	25 (3.4%)	27 (3.2%)	53 (3.3%)	0.013
Foot ulcers	16 (2.1%)	26 (3.0%)	42 (2.6%)	0.057

Characteristic	SGLT-2i N=744	GLP-1RA N=865	Total N=1,609	Standardized Absolute Mean Differences
Cardiovascular disorders				
Cardiomyopathy	189 (25.4%)	220 (25.4%)	409 (25.4%)	0.001
Congestive heart failure	637 (85.5%)	748 (86.4%)	1,384 (86.0%)	0.026
Peripheral vascular diseases	744 (100%)	865 (100%)	1,609 (100%)	
Atrial fibrillation	204 (27.4%)	239 (27.7%)	444 (27.6%)	0.005
Arrhythmia disorders	181 (24.3%)	187 (21.6%)	367 (22.8%)	0.064
Cardiac arrest	744 (100%)	865 (100%)	1,609 (100%)	
Comorbid conditions				
Combined comorbidity score, mean (SD)	4.2(2.30)	4.2(2.36)	4.2(2.33)	0.010
Alcohol disorders	NTSR	12 (1.4%)	19 (1.2%)	0.057
Asthma	141 (19.0%)	145 (16.8%)	286 (17.8%)	0.058
Brain injury	31 (4.1%)	40 (4.6%)	71 (4.4%)	0.025
Cancer (except for non-melanoma skin)	74 (10.0%)	91 (10.6%)	166 (10.3%)	0.019
Chronic lung disorders	308 (41.4%)	357 (41.2%)	665 (41.3%)	0.003
CKD (stage 1-3)	211 (28.3%)	243 (28.1%)	454 (28.2%)	0.005
Coagulopathy	39 (5.2%)	58 (6.7%)	97 (6.0%)	0.063
Connective tissue disorders	41 (5.5%)	44 (5.1%)	85 (5.3%)	0.017
Dementia	27 (3.6%)	24 (2.8%)	51 (3.2%)	0.049
Deficiency anemia	245 (32.9%)	276 (31.9%)	521 (32.4%)	0.020
Depression	221 (29.7%)	223 (25.7%)	444 (27.6%)	0.089
Difficulty walking	154 (20.7%)	186 (21.4%)	340 (21.1%)	0.017
Dyslipidemia	632 (85.0%)	727 (84.1%)	1,359 (84.5%)	0.025
Endocrine disorders	315 (42.3%)	409 (47.3%)	724 (45.0%)	0.100
Edema	189 (25.4%)	227 (26.2%)	416 (25.8%)	0.020
Electrolytes disorders	175 (23.5%)	183 (21.2%)	358 (22.2%)	0.055
HIV	NTSR	NTSR	NTSR	0.012
Hematological disorders	317 (42.6%)	349 (40.3%)	666 (41.4%)	0.046
Hypertension	329 (44.2%)	429 (49.6%)	758 (47.1%)	0.108
Immune disorders	15 (1.9%)	27 (3.1%)	41 (2.6%)	0.072
Metabolic disorders	662 (89.0%)	767 (88.6%)	1,429 (88.8%)	0.013
Metastatic cancers	NTSR	NTSR	12 (0.8%)	0.053

Characteristic	SGLT-2i N=744	GLP-1RA N=865	Total N=1,609	Standardized Absolute Mean Differences
Mild liver disorders	35 (4.6%)	66 (7.6%)	100 (6.2%)	0.124
Moderate liver disorders	NTSR	NTSR	18 (1.1%)	0.019
Nutritional disorders	223 (30.0%)	258 (29.8%)	481 (29.9%)	0.003
Nervous system disorders	416 (55.8%)	556 (64.3%)	972 (60.4%)	0.173
Paraplegia	NTSR	NTSR	18 (1.1%)	0.002
Parkinsonism	NTSR	13 (1.5%)	24 (1.5%)	0.007
Pneumonia	121 (16.3%)	97 (11.2%)	218 (13.5%)	0.148
Psychosis	114 (15.3%)	89 (10.2%)	202 (12.6%)	0.151
Pulmonary circulation disorders	54 (7.2%)	81 (9.3%)	135 (8.4%)	0.077
Rehabilitation	85 (11.5%)	90 (10.4%)	175 (10.9%)	0.035
Renal disorders	212 (28.5%)	248 (28.7%)	460 (28.6%)	0.004
Rheumatic disorders	45 (6.0%)	54 (6.2%)	99 (6.2%)	0.008
Smoking and smoking cessation	65 (8.7%)	33 (3.8%)	98 (6.1%)	0.206
Thromboembolism	NTSR	NTSR	NTSR	0.042
Vulvular disorders	149 (20.1%)	177 (20.5%)	327 (20.3%)	0.011
Weight loss	NTSR	NTSR	NTSR	0.018
Durable medical equipment claims				
Ambulance	138 (18.5%)	170 (19.7%)	308 (19.1%)	0.029
Hospital beds	NTSR	NTSR	16 (1.0%)	0.004
Home oxygen	91 (12.2%)	124 (14.4%)	215 (13.4%)	0.065
Wheelchairs	NTSR	21 (2.4%)	30 (1.9%)	0.090
History of medications use				
Metformin	425 (57.2%)	538 (62.2%)	963 (59.9%)	0.102
Short acting insulin	182 (24.5%)	210 (24.3%)	392 (24.4%)	0.006
Long acting insulin	321 (43.2%)	354 (40.9%)	675 (42.0%)	0.046
TZD	70 (9.4%)	89 (10.3%)	158 (9.8%)	0.031
Meglitinide	NTSR	16 (1.8%)	23 (1.4%)	0.079
SU	315 (42.4%)	370 (42.8%)	685 (42.6%)	0.009
DPP-4i	233 (31.3%)	300 (34.6%)	533 (33.1%)	0.071
Immunosuppressive drugs	NTSR	NTSR	17 (1.1%)	0.035
Steroids	188 (25.2%)	196 (22.7%)	384 (23.8%)	0.060

Characteristic	SGLT-2i N=744	GLP-1RA N=865	Total N=1,609	Standardized Absolute Mean Differences
ACEI	338 (45.4%)	392 (45.4%)	730 (45.4%)	0.001
ARB	292 (39.2%)	349 (40.3%)	641 (39.8%)	0.023
CCB	288 (38.7%)	348 (40.2%)	636 (39.5%)	0.031
BB	478 (64.2%)	595 (68.8%)	1,073 (66.7%)	0.097
NSAIDS	219 (29.4%)	251 (29.0%)	470 (29.2%)	0.010
Aspirin	68 (9.2%)	53 (6.1%)	121 (7.5%)	0.118
Oral contraceptives	22 (2.9%)	25 (2.9%)	47 (2.9%)	0.000
Estrogen	36 (4.8%)	44 (5.1%)	79 (4.9%)	0.013
Loop diuretics	404 (54.4%)	484 (56.0%)	889 (55.2%)	0.033
Other diuretics	302 (40.5%)	362 (41.8%)	663 (41.2%)	0.026
Statin	490 (65.8%)	605 (70.0%)	1,095 (68.1%)	0.089
Measures of healthcare utilization				
HbA1C tests				
0	60 (8.1%)	48 (5.5%)	108 (6.7%)	0.101
1	91 (12.2%)	114 (13.2%)	205 (12.7%)	0.027
2	138 (18.6%)	155 (17.9%)	293 (18.2%)	0.016
3	194 (26.1%)	241 (27.8%)	435 (27.0%)	0.039
4	166 (22.3%)	193 (22.3%)	359 (22.3%)	0.000
5+	95 (12.7%)	115 (13.2%)	209 (13.0%)	0.016
Flu shots				
0	338 (45.4%)	319 (36.8%)	656 (40.8%)	0.174
1	309 (41.5%)	423 (48.9%)	732 (45.5%)	0.148
2	58 (7.8%)	77 (8.9%)	134 (8.4%)	0.040
3+	40 (5.4%)	47 (5.5%)	87 (5.4%)	0.004
Lipid tests				
0	166 (22.3%)	146 (16.8%)	312 (19.4%)	0.138
1	211 (28.4%)	241 (27.9%)	453 (28.1%)	0.011
2	142 (19.0%)	225 (26.0%)	367 (22.8%)	0.166
3	139 (18.7%)	157 (18.2%)	296 (18.4%)	0.013
4+	86 (11.6%)	96 (11.1%)	183 (11.3%)	0.015
Number of hospital admissions				

Characteristic	SGLT-2i N=744	GLP-1RA N=865	Total N=1,609	Standardized Absolute Mean Differences
0	544 (73.2%)	659 (76.1%)	1,203 (74.8%)	0.068
1	157 (21.2%)	146 (16.9%)	303 (18.8%)	0.110
2+	42 (5.7%)	61 (7.0%)	103 (6.4%)	0.054
Number of days of hospitalization				
0	544 (73.2%)	659 (76.1%)	1,203 (74.8%)	0.068
1	71 (9.6%)	82 (9.4%)	153 (9.5%)	0.005
2+	128 (17.2%)	125 (14.4%)	253 (15.7%)	0.077
Number of emergency visits				
0	399 (53.6%)	482 (55.7%)	880 (54.7%)	0.042
1	162 (21.8%)	168 (19.4%)	330 (20.5%)	0.059
2	77 (10.3%)	101 (11.6%)	177 (11.0%)	0.041
3+	107 (14.3%)	115 (13.3%)	222 (13.8%)	0.029
Number of emergency visits due to DM				
0	717 (96.3%)	849 (98.1%)	1,565 (97.3%)	0.106
1	27 (3.6%)	13 (1.5%)	39 (2.4%)	0.134
2+	NTSR	NTSR	NTSR	0.066
Number of outpatient visits				
0	55 (7.4%)	37 (4.2%)	92 (5.7%)	0.136
1	104 (14.0%)	123 (14.2%)	227 (14.1%)	0.007
2	174 (23.3%)	214 (24.7%)	388 (24.1%)	0.032
3	129 (17.3%)	158 (18.3%)	287 (17.8%)	0.025
4	110 (14.8%)	136 (15.7%)	246 (15.3%)	0.025
5+	173 (23.2%)	198 (22.9%)	371 (23.1%)	0.007
Number of outpatient visits due to DM	349 (46.9%)	427 (49.3%)	776 (48.2%)	0.048

SGLT2i – sodium glucose cotransporter 2 inhibitors; GLP-1RA – glucagon like peptide-1 receptor agonist;

SD – standard deviations; DM – diabetes mellitus; ACEI – angiotensin converting enzyme inhibitors; ARB

– angiotensin receptor blockers; BB – beta blockers; CCB – calcium channel blockers; NSAIDs - nonsteroidal

anti-inflammatory drugs; DPP-4i – dipeptidyl peptidase-4 inhibitors; SU – sulphonylureas; TZD -

thiazolidinediones

Table S10. Distribution of baseline characteristics after inverse probability of treatment and censoring weighting among patients with history of atherosclerotic CVDs but no heart failure

Characteristic	SGLT-2i N=10,475	GLP-1RA N=8,827	Total N=19,302	Standardized Absolute Mean Differences
Demographic characteristics				
Age, mean (SD)	73.5(5.53)	73.6(5.56)	73.5(5.54)	0.004
Race				
Whites	8,553 (81.7%)	7,152 (81.0%)	15,705 (81.4%)	0.016
African Americans	802 (7.7%)	695 (7.9%)	1,497 (7.8%)	0.008
Others	1,120 (10.7%)	980 (11.1%)	2,100 (10.9%)	0.013
Sex, Males	4,989 (47.6%)	4,235 (48.0%)	9,225 (47.8%)	0.007
Low-income subsidy, mean (SD)	191.4(420.46)	192.2(412.03)	191.8(416.61)	0.002
Measures of DM severity				
Diabetes retinopathy	1,801 (17.2%)	1,513 (17.1%)	3,314 (17.2%)	0.001
Diabetes nephropathy	1,493 (14.3%)	1,263 (14.3%)	2,756 (14.3%)	0.001
Diabetes neuropathy	3,882 (37.1%)	3,233 (36.6%)	7,114 (36.9%)	0.009
Other diabetes complications	5,114 (48.8%)	4,315 (48.9%)	9,429 (48.8%)	0.001
Number of antihyperglycemic drugs				
0	1,237 (11.8%)	1,018 (11.5%)	2,256 (11.7%)	0.009
1	2,978 (28.4%)	2,512 (28.5%)	5,490 (28.4%)	0.001
2	3,633 (34.7%)	3,098 (35.1%)	6,732 (34.9%)	0.009
3	2,258 (21.6%)	1,879 (21.3%)	4,138 (21.4%)	0.007
4+	368 (3.5%)	320 (3.6%)	687 (3.6%)	0.006
Number of hyperglycemia diagnoses				
0	3,885 (37.1%)	3,307 (37.5%)	7,192 (37.3%)	0.008
1	1,321 (12.6%)	1,096 (12.4%)	2,417 (12.5%)	0.006
2	876 (8.4%)	751 (8.5%)	1,627 (8.4%)	0.005
3	1,333 (12.7%)	1,126 (12.8%)	2,458 (12.7%)	0.001
4+	3,060 (29.2%)	2,548 (28.9%)	5,608 (29.1%)	0.008
Hypoglycemia	374 (3.6%)	300 (3.4%)	674 (3.5%)	0.009
Foot ulcers	568 (5.4%)	448 (5.1%)	1,016 (5.3%)	0.015

Characteristic	SGLT-2i N=10,475	GLP-1RA N=8,827	Total N=19,302	Standardized Absolute Mean Differences
Cardiovascular disorders				
Angina	992 (9.5%)	861 (9.8%)	1,854 (9.6%)	0.010
MI	1,006 (9.6%)	855 (9.7%)	1,861 (9.6%)	0.003
Cardiac revascularization or bypass	301 (2.9%)	249 (2.8%)	550 (2.8%)	0.003
Atherosclerosis	2,457 (23.5%)	2,083 (23.6%)	4,541 (23.5%)	0.003
Ischemic heart diseases	6,462 (61.7%)	5,478 (62.1%)	11,940 (61.9%)	0.007
Cerebrovascular diseases	3,148 (30.1%)	2,636 (29.9%)	5,784 (30.0%)	0.004
Peripheral vascular diseases	3,844 (36.7%)	3,155 (35.7%)	6,999 (36.3%)	0.020
Atrial fibrillation	1,197 (11.4%)	996 (11.3%)	2,193 (11.4%)	0.005
Arrhythmia disorders	1,758 (16.8%)	1,491 (16.9%)	3,249 (16.8%)	0.003
Cardiac arrest	13 (0.1%)	11 (0.1%)	25 (0.1%)	0.001
Comorbid conditions				
Combined comorbidity score, mean (SD)	2.4(2.05)	2.3(2.00)	2.3(2.03)	0.007
Alcohol disorders	86 (0.8%)	78 (0.9%)	165 (0.9%)	0.007
Asthma	1,169 (11.2%)	996 (11.3%)	2,164 (11.2%)	0.004
Brain injury	384 (3.7%)	333 (3.8%)	717 (3.7%)	0.005
Cancer (except for non-melanoma skin)	1,425 (13.6%)	1,173 (13.3%)	2,599 (13.5%)	0.009
Chronic lung disorders	2,839 (27.1%)	2,403 (27.2%)	5,241 (27.2%)	0.003
CKD (stage 1-3)	2,172 (20.7%)	1,844 (20.9%)	4,017 (20.8%)	0.004
Coagulopathy	410 (3.9%)	334 (3.8%)	743 (3.9%)	0.007
Connective tissue disorders	497 (4.7%)	415 (4.7%)	912 (4.7%)	0.002
Dementia	305 (2.9%)	263 (3.0%)	568 (2.9%)	0.004
Deficiency anemia	2,812 (26.8%)	2,362 (26.8%)	5,174 (26.8%)	0.002
Depression	1,969 (18.8%)	1,676 (19.0%)	3,644 (18.9%)	0.005
Difficulty walking	1,922 (18.3%)	1,649 (18.7%)	3,570 (18.5%)	0.008
Dyslipidemia	9,774 (93.3%)	8,242 (93.4%)	18,017 (93.3%)	0.003
Endocrine disorders	4,588 (43.8%)	3,859 (43.7%)	8,447 (43.8%)	0.002
Edema	1,642 (15.7%)	1,371 (15.5%)	3,013 (15.6%)	0.004
Electrolytes disorders	1,481 (14.1%)	1,269 (14.4%)	2,750 (14.2%)	0.007
HIV	24 (0.2%)	23 (0.3%)	46 (0.2%)	0.006
Hematological disorders	3,537 (33.8%)	2,980 (33.8%)	6,516 (33.8%)	0.000

Characteristic	SGLT-2i N=10,475	GLP-1RA N=8,827	Total N=19,302	Standardized Absolute Mean Differences
Hypertension	4,762 (45.5%)	4,051 (45.9%)	8,813 (45.7%)	0.009
Immune disorders	176 (1.7%)	145 (1.6%)	321 (1.7%)	0.003
Metabolic disorders	9,886 (94.4%)	8,334 (94.4%)	18,219 (94.4%)	0.002
Metastatic cancers	107 (1.0%)	86 (1.0%)	192 (1.0%)	0.005
Mild liver disorders	665 (6.3%)	572 (6.5%)	1,237 (6.4%)	0.005
Moderate liver disorders	66 (0.6%)	54 (0.6%)	120 (0.6%)	0.002
Nutritional disorders	3,610 (34.5%)	3,050 (34.6%)	6,660 (34.5%)	0.002
Nervous system disorders	5,891 (56.2%)	4,946 (56.0%)	10,837 (56.1%)	0.004
Paraplegia	163 (1.6%)	132 (1.5%)	295 (1.5%)	0.005
Parkinsonism	141 (1.3%)	120 (1.4%)	261 (1.4%)	0.001
Pneumonia	510 (4.9%)	431 (4.9%)	941 (4.9%)	0.001
Psychosis	614 (5.9%)	540 (6.1%)	1,155 (6.0%)	0.011
Pulmonary circulation disorders	227 (2.2%)	185 (2.1%)	412 (2.1%)	0.005
Rehabilitation	818 (7.8%)	685 (7.8%)	1,504 (7.8%)	0.002
Renal disorders	2,200 (21.0%)	1,868 (21.2%)	4,068 (21.1%)	0.004
Rheumatic disorders	447 (4.3%)	357 (4.0%)	804 (4.2%)	0.011
Smoking and smoking cessation	691 (6.6%)	575 (6.5%)	1,267 (6.6%)	0.003
Thromboembolism	103 (1.0%)	85 (1.0%)	189 (1.0%)	0.002
Vulvular disorders	1,607 (15.3%)	1,355 (15.3%)	2,962 (15.3%)	0.000
Weight loss	91 (0.9%)	78 (0.9%)	168 (0.9%)	0.002
Durable medical equipment claims				
Ambulance	1,261 (12.0%)	1,065 (12.1%)	2,325 (12.0%)	0.001
Hospital beds	60 (0.6%)	52 (0.6%)	112 (0.6%)	0.002
Home oxygen	426 (4.1%)	342 (3.9%)	768 (4.0%)	0.010
Wheelchairs	161 (1.5%)	129 (1.5%)	290 (1.5%)	0.006
History of medications use				
Metformin	7,578 (72.3%)	6,420 (72.7%)	13,998 (72.5%)	0.009
Short acting insulin	1,927 (18.4%)	1,572 (17.8%)	3,499 (18.1%)	0.015
Long acting insulin	4,123 (39.4%)	3,368 (38.2%)	7,491 (38.8%)	0.025
TZD	1,096 (10.5%)	958 (10.9%)	2,054 (10.6%)	0.013
Meglitinide	354 (3.4%)	308 (3.5%)	662 (3.4%)	0.006

Characteristic	SGLT-2i N=10,475	GLP-1RA N=8,827	Total N=19,302	Standardized Absolute Mean Differences
SU	5,163 (49.3%)	4,343 (49.2%)	9,506 (49.2%)	0.002
DPP-4i	4,196 (40.1%)	3,514 (39.8%)	7,710 (39.9%)	0.005
Immunosuppressive drugs	95 (0.9%)	74 (0.8%)	169 (0.9%)	0.007
Steroids	1,914 (18.3%)	1,633 (18.5%)	3,547 (18.4%)	0.006
ACEI	4,764 (45.5%)	4,069 (46.1%)	8,833 (45.8%)	0.012
ARB	4,036 (38.5%)	3,380 (38.3%)	7,416 (38.4%)	0.005
CCB	3,825 (36.5%)	3,252 (36.8%)	7,077 (36.7%)	0.007
BB	6,429 (61.4%)	5,427 (61.5%)	11,856 (61.4%)	0.002
NSAIDS	3,270 (31.2%)	2,761 (31.3%)	6,031 (31.2%)	0.001
Aspirin	622 (5.9%)	530 (6.0%)	1,152 (6.0%)	0.003
Oral contraceptives	201 (1.9%)	170 (1.9%)	370 (1.9%)	0.001
Estrogen	598 (5.7%)	509 (5.8%)	1,107 (5.7%)	0.002
Loop diuretics	2,091 (20.0%)	1,729 (19.6%)	3,820 (19.8%)	0.009
Other diuretics	4,046 (38.6%)	3,400 (38.5%)	7,445 (38.6%)	0.002
Statin	8,340 (79.6%)	7,056 (79.9%)	15,396 (79.8%)	0.008
Measures of healthcare utilization				
HbA1C tests				
0	346 (3.3%)	303 (3.4%)	648 (3.4%)	0.007
1	1,161 (11.1%)	968 (11.0%)	2,128 (11.0%)	0.004
2	2,273 (21.7%)	1,918 (21.7%)	4,191 (21.7%)	0.001
3	2,912 (27.8%)	2,418 (27.4%)	5,330 (27.6%)	0.009
4	2,226 (21.3%)	1,891 (21.4%)	4,117 (21.3%)	0.004
5+	1,558 (14.9%)	1,330 (15.1%)	2,888 (15.0%)	0.006
Flu shots				
0	3,657 (34.9%)	3,115 (35.3%)	6,773 (35.1%)	0.008
1	5,478 (52.3%)	4,585 (51.9%)	10,063 (52.1%)	0.007
2	897 (8.6%)	749 (8.5%)	1,646 (8.5%)	0.003
3+	443 (4.2%)	378 (4.3%)	821 (4.3%)	0.003
Lipid tests				
0	1,052 (10.0%)	890 (10.1%)	1,942 (10.1%)	0.001
1	2,823 (27.0%)	2,336 (26.5%)	5,159 (26.7%)	0.011

Characteristic	SGLT-2i N=10,475	GLP-1RA N=8,827	Total N=19,302	Standardized Absolute Mean Differences
2	2,924 (27.9%)	2,481 (28.1%)	5,404 (28.0%)	0.004
3	1,953 (18.6%)	1,649 (18.7%)	3,602 (18.7%)	0.001
4+	1,723 (16.5%)	1,471 (16.7%)	3,195 (16.6%)	0.006
Number of hospital admissions				
0	8,604 (82.1%)	7,232 (81.9%)	15,836 (82.0%)	0.006
1	1,360 (13.0%)	1,174 (13.3%)	2,534 (13.1%)	0.009
2+	511 (4.9%)	422 (4.8%)	933 (4.8%)	0.005
Number of days of hospitalization				
0	8,604 (82.1%)	7,232 (81.9%)	15,836 (82.0%)	0.006
1	937 (8.9%)	809 (9.2%)	1,747 (9.0%)	0.008
2+	934 (8.9%)	786 (8.9%)	1,720 (8.9%)	0.000
Number of emergency visits				
0	6,765 (64.6%)	5,683 (64.4%)	12,448 (64.5%)	0.004
1	1,982 (18.9%)	1,677 (19.0%)	3,659 (19.0%)	0.002
2	906 (8.7%)	746 (8.5%)	1,652 (8.6%)	0.007
3+	822 (7.8%)	720 (8.2%)	1,542 (8.0%)	0.012
Number of emergency visits due to DM				
0	10,253 (97.9%)	8,640 (97.9%)	18,894 (97.9%)	0.000
1	186 (1.8%)	151 (1.7%)	337 (1.7%)	0.005
2+	36 (0.3%)	36 (0.4%)	71 (0.4%)	0.011
Number of outpatient visits				
0	182 (1.7%)	141 (1.6%)	323 (1.7%)	0.011
1	1,088 (10.4%)	932 (10.6%)	2,020 (10.5%)	0.006
2	2,255 (21.5%)	1,918 (21.7%)	4,173 (21.6%)	0.005
3	2,377 (22.7%)	1,986 (22.5%)	4,363 (22.6%)	0.005
4	1,755 (16.8%)	1,503 (17.0%)	3,258 (16.9%)	0.007
5+	2,818 (26.9%)	2,347 (26.6%)	5,166 (26.8%)	0.007
Number of outpatient visits due to DM	5,962 (56.9%)	4,998 (56.6%)	10,960 (56.8%)	0.006

SGLT2i – sodium glucose cotransporter 2 inhibitors; GLP-1RA – glucagon like peptide-1 receptor agonist;

SD – standard deviations; DM – diabetes mellitus; ACEI – angiotensin converting enzyme inhibitors; ARB

– angiotensin receptor blockers; BB – beta blockers; CCB – calcium channel blockers; NSAIDs - nonsteroidal anti-inflammatory drugs; DPP-4i – dipeptidyl peptidase-4 inhibitors; SU – sulphonylureas; TZD - thiazolidinediones

Table S11. Distribution of baseline characteristics after inverse probability of treatment and censoring weighting among patients with history of atherosclerotic CVDs but no heart failure

Characteristic	SGLT-2i N=3,226	GLP-1RA N=3,809	Total N=7,036	Standardized Absolute Mean Differences
Demographic characteristics				
Age, mean (SD)	74.7(6.23)	74.7(6.16)	74.7(6.20)	0.006
Race				
Whites	2,624 (81.3%)	3,080 (80.9%)	5,704 (81.1%)	0.012
African Americans	328 (10.2%)	386 (10.1%)	713 (10.1%)	0.001
Others	275 (8.5%)	344 (9.0%)	619 (8.8%)	0.018
Sex, Males	1,609 (49.9%)	1,917 (50.3%)	3,526 (50.1%)	0.009
Low-income subsidy, mean (SD)	273.8(484.49)	273.8(481.90)	273.8(483.05)	0.000
Measures of DM severity				
Diabetes retinopathy	670 (20.8%)	762 (20.0%)	1,432 (20.4%)	0.019
Diabetes nephropathy	663 (20.5%)	799 (21.0%)	1,462 (20.8%)	0.011
Diabetes neuropathy	1,471 (45.6%)	1,743 (45.8%)	3,214 (45.7%)	0.003
Other diabetes complications	1,731 (53.7%)	2,058 (54.0%)	3,789 (53.9%)	0.007
Number of antihyperglycemic drugs				
0	567 (17.6%)	637 (16.7%)	1,204 (17.1%)	0.023
1	967 (30.0%)	1,151 (30.2%)	2,118 (30.1%)	0.005
2	1,024 (31.7%)	1,227 (32.2%)	2,251 (32.0%)	0.010
3	566 (17.5%)	678 (17.8%)	1,244 (17.7%)	0.007
4+	102 (3.2%)	117 (3.1%)	219 (3.1%)	0.006
Number of hyperglycemia diagnoses				
0	941 (29.2%)	1,116 (29.3%)	2,057 (29.2%)	0.003
1	413 (12.8%)	493 (13.0%)	906 (12.9%)	0.005
2	273 (8.5%)	322 (8.5%)	595 (8.5%)	0.000
3	433 (13.4%)	517 (13.6%)	949 (13.5%)	0.004
4+	1,167 (36.2%)	1,361 (35.7%)	2,528 (35.9%)	0.009
Hypoglycemia	184 (5.7%)	226 (5.9%)	410 (5.8%)	0.011
Foot ulcers	334 (10.3%)	384 (10.1%)	718 (10.2%)	0.008

Characteristic	SGLT-2i N=3,226	GLP-1RA N=3,809	Total N=7,036	Standardized Absolute Mean Differences
Cardiovascular disorders				
Angina	503 (15.6%)	604 (15.9%)	1,107 (15.7%)	0.008
MI	717 (22.2%)	844 (22.2%)	1,562 (22.2%)	0.002
Cardiac revascularization or bypass	224 (6.9%)	258 (6.8%)	482 (6.8%)	0.006
Atherosclerosis	924 (28.6%)	1,100 (28.9%)	2,024 (28.8%)	0.005
Ischemic heart diseases	2,625 (81.4%)	3,097 (81.3%)	5,721 (81.3%)	0.002
Cerebrovascular diseases	1,059 (32.8%)	1,263 (33.2%)	2,323 (33.0%)	0.007
Cardiomyopathy	822 (25.5%)	955 (25.1%)	1,777 (25.3%)	0.009
Congestive heart failure	2,911 (90.2%)	3,438 (90.3%)	6,349 (90.2%)	0.001
Peripheral vascular diseases	1,334 (41.4%)	1,541 (40.4%)	2,875 (40.9%)	0.019
Atrial fibrillation	1,067 (33.1%)	1,212 (31.8%)	2,279 (32.4%)	0.027
Arrhythmia disorders	1,308 (40.5%)	1,548 (40.6%)	2,856 (40.6%)	0.002
Cardiac arrest	18 (0.6%)	22 (0.6%)	40 (0.6%)	0.000
Comorbid conditions				
Combined comorbidity score, mean (SD)	5.6(2.70)	5.6(2.63)	5.6(2.66)	0.001
Alcohol disorders	46 (1.4%)	48 (1.3%)	94 (1.3%)	0.016
Asthma	573 (17.7%)	692 (18.2%)	1,264 (18.0%)	0.011
Brain injury	205 (6.4%)	252 (6.6%)	457 (6.5%)	0.010
Cancer (except for non-melanoma skin)	469 (14.5%)	555 (14.6%)	1,024 (14.6%)	0.000
Chronic lung disorders	1,652 (51.2%)	1,913 (50.2%)	3,565 (50.7%)	0.020
CKD (stage 1-3)	1,159 (35.9%)	1,376 (36.1%)	2,535 (36.0%)	0.004
Coagulopathy	246 (7.6%)	304 (8.0%)	550 (7.8%)	0.013
Connective tissue disorders	255 (7.9%)	309 (8.1%)	565 (8.0%)	0.008
Dementia	192 (5.9%)	226 (5.9%)	417 (5.9%)	0.001
Deficiency anemia	1,394 (43.2%)	1,663 (43.7%)	3,057 (43.5%)	0.009
Depression	849 (26.3%)	1,046 (27.4%)	1,895 (26.9%)	0.025
Difficulty walking	974 (30.2%)	1,148 (30.1%)	2,122 (30.2%)	0.001
Dyslipidemia	3,057 (94.8%)	3,616 (94.9%)	6,673 (94.8%)	0.007
Endocrine disorders	1,705 (52.8%)	2,025 (53.2%)	3,730 (53.0%)	0.006
Edema	998 (30.9%)	1,160 (30.4%)	2,158 (30.7%)	0.011
Electrolytes disorders	1,011 (31.3%)	1,197 (31.4%)	2,207 (31.4%)	0.002

Characteristic	SGLT-2i N=3,226	GLP-1RA N=3,809	Total N=7,036	Standardized Absolute Mean Differences
HIV	NTSR	NTSR	14 (0.2%)	0.014
Hematological disorders	1,703 (52.8%)	2,050 (53.8%)	3,753 (53.3%)	0.020
Hypertension	1,708 (52.9%)	2,068 (54.3%)	3,776 (53.7%)	0.027
Immune disorders	98 (3.0%)	99 (2.6%)	197 (2.8%)	0.027
Metabolic disorders	3,126 (96.9%)	3,690 (96.9%)	6,816 (96.9%)	0.001
Metastatic cancers	42 (1.3%)	51 (1.3%)	93 (1.3%)	0.005
Mild liver disorders	254 (7.9%)	299 (7.8%)	552 (7.8%)	0.001
Moderate liver disorders	34 (1.1%)	42 (1.1%)	76 (1.1%)	0.003
Nutritional disorders	1,305 (40.4%)	1,533 (40.2%)	2,838 (40.3%)	0.004
Nervous system disorders	2,257 (70.0%)	2,672 (70.1%)	4,929 (70.1%)	0.004
Paraplegia	79 (2.5%)	97 (2.6%)	177 (2.5%)	0.006
Parkinsonism	50 (1.5%)	74 (1.9%)	124 (1.8%)	0.031
Pneumonia	460 (14.2%)	554 (14.5%)	1,014 (14.4%)	0.009
Psychosis	306 (9.5%)	352 (9.3%)	658 (9.4%)	0.008
Pulmonary circulation disorders	355 (11.0%)	448 (11.8%)	803 (11.4%)	0.024
Rehabilitation	402 (12.5%)	462 (12.1%)	864 (12.3%)	0.010
Renal disorders	1,169 (36.2%)	1,390 (36.5%)	2,559 (36.4%)	0.006
Rheumatic disorders	347 (10.8%)	408 (10.7%)	755 (10.7%)	0.002
Smoking and smoking cessation	266 (8.3%)	298 (7.8%)	564 (8.0%)	0.016
Thromboembolism	57 (1.8%)	70 (1.8%)	126 (1.8%)	0.005
Vulvular disorders	1,020 (31.6%)	1,219 (32.0%)	2,239 (31.8%)	0.009
Weight loss	67 (2.1%)	84 (2.2%)	152 (2.2%)	0.008
Durable medical equipment claims				
Ambulance	969 (30.0%)	1,134 (29.8%)	2,103 (29.9%)	0.006
Hospital beds	74 (2.3%)	79 (2.1%)	153 (2.2%)	0.014
Home oxygen	457 (14.2%)	562 (14.7%)	1,019 (14.5%)	0.017
Wheelchairs	120 (3.7%)	135 (3.5%)	256 (3.6%)	0.010
History of medications use				
Metformin	1,984 (61.5%)	2,393 (62.8%)	4,377 (62.2%)	0.027
Short acting insulin	932 (28.9%)	1,044 (27.4%)	1,975 (28.1%)	0.033
Long acting insulin	1,625 (50.4%)	1,827 (48.0%)	3,453 (49.1%)	0.048

Characteristic	SGLT-2i N=3,226	GLP-1RA N=3,809	Total N=7,036	Standardized Absolute Mean Differences
TZD	282 (8.7%)	341 (9.0%)	623 (8.9%)	0.008
Meglitinide	137 (4.3%)	152 (4.0%)	289 (4.1%)	0.014
SU	1,430 (44.3%)	1,689 (44.3%)	3,119 (44.3%)	0.000
DPP-4i	1,252 (38.8%)	1,494 (39.2%)	2,745 (39.0%)	0.009
Immunosuppressive drugs	34 (1.0%)	38 (1.0%)	72 (1.0%)	0.005
Steroids	767 (23.8%)	929 (24.4%)	1,696 (24.1%)	0.014
ACEI	1,420 (44.0%)	1,708 (44.8%)	3,128 (44.5%)	0.017
ARB	1,333 (41.3%)	1,559 (40.9%)	2,892 (41.1%)	0.008
CCB	1,252 (38.8%)	1,484 (39.0%)	2,736 (38.9%)	0.003
BB	2,570 (79.7%)	3,041 (79.8%)	5,611 (79.7%)	0.004
NSAIDS	979 (30.4%)	1,163 (30.5%)	2,142 (30.4%)	0.004
Aspirin	324 (10.0%)	365 (9.6%)	689 (9.8%)	0.015
Oral contraceptives	65 (2.0%)	86 (2.3%)	152 (2.2%)	0.016
Estrogen	202 (6.3%)	229 (6.0%)	431 (6.1%)	0.010
Loop diuretics	1,963 (60.9%)	2,310 (60.6%)	4,273 (60.7%)	0.005
Other diuretics	1,325 (41.1%)	1,574 (41.3%)	2,899 (41.2%)	0.005
Statin	2,664 (82.6%)	3,177 (83.4%)	5,841 (83.0%)	0.022
Measures of healthcare utilization				
HbA1C tests				
0	108 (3.3%)	137 (3.6%)	245 (3.5%)	0.014
1	350 (10.8%)	433 (11.4%)	783 (11.1%)	0.017
2	633 (19.6%)	739 (19.4%)	1,372 (19.5%)	0.005
3	825 (25.6%)	999 (26.2%)	1,824 (25.9%)	0.015
4	705 (21.9%)	819 (21.5%)	1,524 (21.7%)	0.009
5+	605 (18.8%)	682 (17.9%)	1,287 (18.3%)	0.022
Flu shots				
0	1,142 (35.4%)	1,343 (35.2%)	2,485 (35.3%)	0.003
1	1,627 (50.4%)	1,909 (50.1%)	3,536 (50.3%)	0.006
2	328 (10.2%)	390 (10.2%)	718 (10.2%)	0.002
3+	129 (4.0%)	167 (4.4%)	296 (4.2%)	0.019
Lipid tests				

Characteristic	SGLT-2i N=3,226	GLP-1RA N=3,809	Total N=7,036	Standardized Absolute Mean Differences
0	394 (12.2%)	461 (12.1%)	855 (12.2%)	0.003
1	824 (25.5%)	988 (25.9%)	1,812 (25.8%)	0.010
2	834 (25.9%)	965 (25.3%)	1,800 (25.6%)	0.012
3	550 (17.0%)	660 (17.3%)	1,210 (17.2%)	0.008
4+	625 (19.4%)	734 (19.3%)	1,359 (19.3%)	0.003
Number of hospital admissions				
0	1,861 (57.7%)	2,198 (57.7%)	4,060 (57.7%)	0.000
1	804 (24.9%)	938 (24.6%)	1,742 (24.8%)	0.006
2+	562 (17.4%)	673 (17.7%)	1,234 (17.5%)	0.007
Number of days of hospitalization				
0	1,861 (57.7%)	2,198 (57.7%)	4,060 (57.7%)	0.000
1	441 (13.7%)	512 (13.4%)	953 (13.5%)	0.007
2+	924 (28.6%)	1,099 (28.9%)	2,023 (28.8%)	0.005
Number of emergency visits				
0	1,363 (42.2%)	1,624 (42.6%)	2,986 (42.4%)	0.008
1	732 (22.7%)	844 (22.2%)	1,576 (22.4%)	0.012
2	437 (13.5%)	532 (14.0%)	968 (13.8%)	0.012
3+	695 (21.6%)	810 (21.3%)	1,505 (21.4%)	0.007
Number of emergency visits due to DM				
0	3,106 (96.3%)	3,667 (96.3%)	6,773 (96.3%)	0.000
1	96 (3.0%)	111 (2.9%)	206 (2.9%)	0.004
2+	25 (0.8%)	32 (0.8%)	56 (0.8%)	0.008
Number of outpatient visits				
0	70 (2.2%)	83 (2.2%)	153 (2.2%)	0.002
1	253 (7.8%)	307 (8.1%)	560 (8.0%)	0.008
2	443 (13.7%)	544 (14.3%)	987 (14.0%)	0.016
3	582 (18.1%)	661 (17.3%)	1,243 (17.7%)	0.018
4	537 (16.6%)	637 (16.7%)	1,175 (16.7%)	0.002
5+	1,342 (41.6%)	1,576 (41.4%)	2,918 (41.5%)	0.004
Number of outpatient visits due to DM	1,726 (53.5%)	2,001 (52.5%)	3,727 (53.0%)	0.019

SGLT2i – sodium glucose cotransporter 2 inhibitors; GLP-1RA – glucagon like peptide-1 receptor agonist;

SD – standard deviations; DM – diabetes mellitus; ACEI – angiotensin converting enzyme inhibitors; ARB – angiotensin receptor blockers; BB – beta blockers; CCB – calcium channel blockers; NSAIDs - nonsteroidal anti-inflammatory drugs; DPP-4i – dipeptidyl peptidase-4 inhibitors; SU – sulphonylureas; TZD - thiazolidinediones

Table S12. Risk of hospitalization for heart failure and competing events (mortality prior to heart failure hospitalization)

	No. of events	No. at risk	No. (%) of competing events	Crude RR* (95% CI)	IPTW + IPCW RR* (95% CI)	Aalen Johansen RR*
ITT analyses						
CVD (-) HF (-)						
SGLT-2i	107	11,830	200 (1.7%)	0.60 (0.47, 0.77)	0.83 (0.65, 1.06)	0.84 (0.61, 1.09)
GLP-1RA	153	10,142	178 (1.7%)			
CVD (+) HF (-)						
SGLT-2i	34	609	24 (3.9%)	0.49 (0.33, 0.72)	0.55 (0.38, 0.80)	0.55 (0.30, 0.85)
GLP-1RA	88	771	29 (3.8%)			
CVD (-) HF (+)						
SGLT-2i	180	9,399	317 (3.4%)	0.65 (0.54, 0.79)	0.83 (0.69, 1.00)	0.85 (0.69, 1.04)
GLP-1RA	242	8,205	255 (3.1%)			
CVD (+) HF (+)						
SGLT-2i	333	2,909	159 (5.5%)	0.77 (0.68, 0.87)	0.90 (0.79, 1.02)	0.90 (0.79, 1.02)
GLP-1RA	518	3,478	222 (6.4%)			
As-treated analyses						
CVD (-) HF (-)						
SGLT-2i	57	11,830	110 (0.9%)	0.51 (0.37, 0.71)	0.79 (0.58, 1.06)	0.65 (0.43, 0.96)
GLP-1RA	95	10,142	91 (0.9%)			
CVD (+) HF (-)						
SGLT-2i	23	609	16 (2.6%)	0.47 (0.29, 0.75)	0.47 (0.29, 0.75)	0.48 (0.25, 0.85)
GLP-1RA	62	771	14 (1.8%)			
CVD (-) HF (+)						
SGLT-2i	90	9,399	178 (1.9%)	0.55 (0.42, 0.71)	0.65 (0.51, 0.82)	0.60 (0.42, 0.83)
GLP-1RA	143	8,205	146 (1.8%)			
CVD (+) HF (+)						
SGLT-2i	211	2,909	91 (3.1%)	0.70 (0.60, 0.82)	0.85 (0.73, 0.99)	0.76 (0.60, 0.91)
GLP-1RA	360	3,478	151 (4.3%)			

ITT, intention-to-treat; AT, as treated; CVD, cardiovascular disease; HF, heart failure; MACE, major adverse cardiovascular events; RR, risk ratio; -, without; +, with; IPTW, inverse probability of treatment weighted; IPCW, inverse probability of censoring weighted; CI, confidence intervals.

* Aalen Johansen estimators accounting for competing risk (for HHF outcome) and weighted by inverse probability of treatment and censoring weights that account for confounding and informative censoring.

Table S13. Proportions of patients censored due to treatment non-adherence in as-treated analyses

	No. at risk	Proportion of treatment discontinuation (%)	Proportion of treatment switching to/ augmentation with the comparator (%)
CVD (-) HF (-)			
SGLT-2i	11,830	38.43	5.43
GLP-1RA	10,142	39.58	5.80
CVD (+) HF (-)			
SGLT-2i	609	37.44	5.09
GLP-1RA	771	38.13	3.24
CVD (-) HF (+)			
SGLT-2i	9,399	39.42	5.84
GLP-1RA	8,205	40.72	5.80
CVD (+) HF (+)			
SGLT-2i	2,909	37.74	5.43
GLP-1RA	3,478	37.00	4.26

ITT, intention-to-treat; AT, as treated; CVD, cardiovascular disease; HF, heart failure; MACE, major adverse

cardiovascular events; RR, risk ratio; -, without; +, with; IPTW, inverse probability of treatment weighted;

IPCW, inverse probability of censoring weighted; CI, confidence intervals.

Table S14. RRs and RDs for primary outcomes (HHF, MACE, HHF + MACE, MI, stroke and all-cause mortality) for intent-to-treat analyses

Outcome (ITT/AT)	Baseline subgroups	SGLT2i Events (N)	GLP-1RA Events (N)	Weighted RD/100* (95% CI)	Weighted RR* (95% CI)
HHF (ITT)	CVD - CHF -	107 (11,830)	153/10,142	-0.3 (-0.8, 0.1)	0.8 (0.6, 1.1)
	CVD - CHF +	34 (609)	88 (771)	-7.1 (-11.2, -2.2)	0.6 (0.3, 0.9)
	CVD + CHF -	180 (9,399)	242 (8,205)	-0.6 (-1.3, 1.3)	0.8 (0.7, 1.0)
	CVD + CHF +	333 (2,909)	518 (3,478)	-1.8 (-4.4, 0.4)	0.9 (0.8, 1.0)
MACE (ITT)	CVD - CHF -	411 (11,830)	349 (10,142)	0.4 (-0.1, 0.8)	1.1 (0.9, 1.3)
	CVD - CHF +	48 (609)	58 (771)	0.4 (-2.4, 3.2)	1.1 (0.7, 1.5)
	CVD + CHF -	619 (9,399	513 (8,205)	0.7 (0, 1.5)	1.1 (1.0, 1.3)
	CVD + CHF +	336 (2,909	499 (3,478)	-1.6 (-3.3, 0.0)	0.9 (0.8, 1.00)
HHF+MACE (ITT)	CVD - CHF -	470 (11,830)	455 (10,142)	0.0 (-0.5, 0.6)	1.0 (0.9, 1.1)
	CVD - CHF +	67 (609)	124 (771)	-3.9 (-7.4, -0.4)	0.7 (0.6, 0.9)
	CVD + CHF -	735 (9,399)	677 (8,205)	0.37 (-0.4, 1.2)	1.0 (0.9, 1.2)
	CVD + CHF +	563 (2909	832 (3,478)	-2.2 (-4.2, -0.2)	0.9 (0.8, 0.9)
MI (ITT)	CVD - CHF -	131 (11,830)	102 (10,142)	0.3 (-0.02, 0.5)	1.3 (0.9, 1.6)
	CVD - CHF +	NTS (609)	13 (771)	-0.03 (-1.4, 1.4)	0.9 (0.5, 2.1)
	CVD + CHF -	186 (9,399)	154 (8,205)	0.3 (-0.1, 0.7)	1.2 (0.9, 1.4)
	CVD + CHF +	83 (2909)	126 (3,478)	-0.4 (-1.2, 0.4)	0.9 (0.7, 1.2)
Stroke (ITT)	CVD - CHF -	106 (11,830)	75 (10,142)	0.2 (-0.06, 0.4)	1.2 (0.93, 1.7)
	CVD - CHF +	13 (609)	NTS (771)	1.5 (0.1, 2.9)	2.6 (1.08, 6.1)
	CVD + CHF -	160 (9,399)	137 (8,205)	0.2 (-0.2, 0.6)	1.1 (0.89, 1.4)
	CVD + CHF +	69 (2909)	83 (3,478)	0.2 (-0.6, 0.9)	1.1 (0.80, 1.5)
Mortality (ITT)	CVD - CHF -	217 (11,830)	205 (10,142)	-0.02 (-0.4, 0.4)	0.9 (0.8, 1.2)
	CVD - CHF +	35 (609)	43 (771)	0 (-2.4, 2.4)	1.0 (0.6, 1.6)
	CVD + CHF -	344 (9,399)	290 (8,205)	0.3 (-0.3, 0.8)	1.1 (0.9, 1.3)
	CVD + CHF +	237 (2909)	356 (3,478)	-1.2 (-2.7, 0.2)	0.9 (0.8, 1.0)

ITT, intention-to-treat; AT, as treated; CVD, cardiovascular disease; HF, heart failure; MACE, major adverse cardiovascular events; RR, risk ratio; -, without; +, with; IPTW, inverse probability of treatment weighted; IPCW, inverse probability of censoring weighted; CI, confidence intervals; NTS, number too small (<12) to report according to data user agreement with the Centers for Medicare and Medicaid Services.

* Aalen Johansen estimators accounting for competing risk (for HHF outcome) and weighted by inverse probability of treatment and censoring weights that account for confounding and informative censoring.

Table S15. Effect measure estimates for negative control outcomes

Outcome (ITT/AT)	Baseline subgroups	SGLT2i (Events/N)	GLP-1RA (Events/N)	Weighted RD*/100 (95% CI)	Weighted RR* (95% CI)
Cancer (AT)	CVD - HF -	186/10,543	173/9,118	0.01 (-0.36, 0.39)	1.01 (0.83, 1.22)
	CVD - HF +	NTS/535	15/684	-0.37 (-1.71, 0.97)	0.81 (0.37, 1.75)
	CVD + HF -	150/8,065	135/7,085	-0.19 (-0.62, 0.23)	0.91 (0.73, 1.12)
	CVD + HF +	58/2,442	384/2,981	0.44 (1.24, 0.36)	0.85 (0.62, 1.15)
Cancer (ITT)	CVD - HF -	265/10,543	258/9,118	-0.27 (-0.72, 0.19)	0.91 (0.77, 1.07)
	CVD - HF +	NTS/535	25/684	-1.44 (-3.27, 0.39)	0.59 (0.30, 1.19)
	CVD + HF -	236/8,065	214/7,085	-0.12 (-0.67, 0.43)	0.96 (0.80, 1.15)
	CVD + HF +	89/2,442	123/2,981	-0.62 (-1.65, 0.04)	0.85 (0.65, 1.11)
Cataract (AT)	CVD - HF -	546/11232	500/9673	0.00 (-0.59, 0.60)	1.00 (0.90, 1.12)
	CVD - HF +	23/575	34/741	0.19 (-1.85, 2.24)	1.05 (0.65, 1.67)
	CVD + HF -	440/8868	407/7675	0.04 (-0.70, 0.62)	0.99 (0.88, 1.12)
	CVD + HF +	143/2752	145/3253	0.76 (-0.28, 1.79)	1.17 (0.95, 1.45)
Cataract (ITT)	CVD - HF -	754/11232	735/9673	-0.46 (-1.17, 0.25)	0.94 (0.85, 1.03)
	CVD - HF +	34/575	51/741	0.09 (-2.59, 2.77)	1.01 (0.67, 1.52)
	CVD + HF -	656/8868	591/7675	0.02 (-0.61, 1.01)	1.03 (0.92, 1.14)
	CVD + HF +	197/2752	218/3253	0.25 (-1.03, 1.53)	1.04 (0.86, 1.25)

ITT, intention-to-treat; AT, as treated; CVD, cardiovascular disease; HF, heart failure; MACE, major adverse cardiovascular events; RR, risk ratio; -, without; +, with; IPTW, inverse probability of treatment weighted; IPCW, inverse probability of censoring weighted; CI, confidence intervals.

* Weighted by inverse probability of treatment and censoring weights that account for confounding and informative censoring.

Table S16. Effect measure estimates for primary cardiovascular outcomes among patients with no prevalent cancer diagnosis or cancer-related procedures

Outcome (ITT/AT)	Baseline subgroups	SGLT2i (Events/N)	GLP-1RA (Events/N)	Weighted RR* (95% CI)	Weighted RD*/100 (95% CI)
HHF (ITT)	CVD - HF -	148/14865	234/12626	0.72 (0.59, 0.88)	-0.45 (-0.72, -0.17)
	CVD - HF +	93/1131	182/1430	0.72 (0.57, 0.91)	-3.39 (-5.74, -1.04)
	CVD + HF -	156/6750	186/6065	0.96 (0.78, 1.18)	-0.12 (-0.68, 0.45)
	CVD + HF +	257/2001	399/2475	0.89 (0.77, 1.03)	-1.71 (-3.77, 0.36)
HHF (AT)	CVD - HF -	77/14865	145/12626	0.62 (0.48, 0.79)	-0.41 (-0.62, -0.19)
	CVD - HF +	57/1131	128/1430	0.67 (0.50, 0.90)	-2.49 (-4.23, -0.74)
	CVD + HF -	79/6750	108/6065	0.79 (0.61, 1.02)	-0.38 (-0.80, 0.04)
	CVD + HF +	168/2001	279/2475	0.84 (0.71, 1.00)	-1.68 (-3.33, -0.03)
MACE (ITT)	CVD - HF -	554/14865	478/12626	1.08 (0.96, 1.22)	0.30 (-0.15, 0.76)
	CVD - HF +	106/1131	134/1430	1.05 (0.83, 1.34)	0.49 (-1.77, 2.76)
	CVD + HF -	496/6750	416/6065	1.12 (0.99, 1.27)	0.81 (-0.08, 1.70)
	CVD + HF +	258/2001	391/2475	0.88 (0.76, 1.01)	-1.89 (-3.97, 0.18)
MACE (AT)	CVD - HF -	323/14865	264/12626	1.19 (1.02, 1.38)	0.40 (0.06, 0.74)
	CVD - HF +	65/1131	85/1430	1.20 (0.90, 1.61)	1.07 (-0.63, 2.76)
	CVD + HF -	280/6750	256/6065	0.99 (0.85, 1.17)	-0.02 (-0.69, 0.64)
	CVD + HF +	159/2001	252/2475	0.81 (0.68, 0.96)	-1.94 (-3.53, -0.35)
HHF + MACE (ITT)	CVD - HF -	641/14865	637/12626	0.98 (0.88, 1.09)	-0.08 (-0.58, 0.42)
	CVD - HF +	161/1131	268/1430	0.84 (0.70, 1.00)	-2.90 (-5.76, -0.03)
	CVD + HF -	598/6750	540/6065	1.07 (0.96, 1.20)	0.63 (-0.35, 1.62)
	CVD + HF +	435/2001	643/2475	0.91 (0.82, 1.01)	-2.33 (-4.84, 0.18)
HHF + MACE (AT)	CVD - HF -	377/14865	376/12626	1.03 (0.90, 1.17)	0.08 (-0.30, 0.47)
	CVD - HF +	103/1131	185/1430	0.87 (0.70, 1.08)	-1.46 (-3.67, 0.76)
	CVD + HF -	342/6750	332/6065	0.97 (0.84, 1.12)	-0.17 (-0.91, 0.58)
	CVD + HF +	281/2001	445/2475	0.83 (0.73, 0.95)	-2.83 (-4.86, -0.79)

ITT, intention-to-treat; AT, as treated; CVD, cardiovascular disease; HF, heart failure; MACE, major adverse

cardiovascular events; RR, risk ratio; -, without; +, with; IPTW, inverse probability of treatment weighted; IPCW, inverse probability of censoring weighted; CI, confidence intervals.

* Weighted by inverse probability of treatment and censoring weights that account for confounding and informative censoring.

Table S17. Effect measure estimates for primary cardiovascular outcomes among patients with no

prevalent cataract surgery procedures

Outcome (ITT/AT)	Baseline subgroups	SGLT2i (Events/N)	GLP-1RA (Events/N)	Weighted RR* (95% CI)	Weighted RD*/100 (95% CI)
HHF (ITT)	CVD - HF -	148/14865	234/12626	0.72 (0.59, 0.88)	-0.45 (-0.72, -0.17)
	CVD - HF +	93/1131	182/1430	0.72 (0.57, 0.91)	-3.39 (-5.74, -1.04)
	CVD + HF -	156/6750	186/6065	0.96 (0.78, 1.18)	-0.12 (-0.68, 0.45)
	CVD + HF +	257/2001	399/2475	0.89 (0.77, 1.03)	-1.71 (-3.77, 0.36)
HHF (AT)	CVD - HF -	77/14865	145/12626	0.62 (0.48, 0.79)	-0.41 (-0.62, -0.19)
	CVD - HF +	57/1131	128/1430	0.67 (0.50, 0.90)	-2.49 (-4.23, -0.74)
	CVD + HF -	79/6750	108/6065	0.79 (0.61, 1.02)	-0.38 (-0.80, 0.04)
	CVD + HF +	168/2001	279/2475	0.84 (0.71, 1.00)	-1.68 (-3.33, -0.03)
MACE (ITT)	CVD - HF -	554/14865	478/12626	1.08 (0.96, 1.22)	0.30 (-0.15, 0.76)
	CVD - HF +	106/1131	134/1430	1.05 (0.83, 1.34)	0.49 (-1.77, 2.76)
	CVD + HF -	496/6750	416/6065	1.12 (0.99, 1.27)	0.81 (-0.08, 1.70)
	CVD + HF +	258/2001	391/2475	0.88 (0.76, 1.01)	-1.89 (-3.97, 0.18)
MACE (AT)	CVD - HF -	323/14865	264/12626	1.19 (1.02, 1.38)	0.40 (0.06, 0.74)
	CVD - HF +	65/1131	85/1430	1.20 (0.90, 1.61)	1.07 (-0.63, 2.76)
	CVD + HF -	280/6750	256/6065	0.99 (0.85, 1.17)	-0.02 (-0.69, 0.64)
	CVD + HF +	159/2001	252/2475	0.81 (0.68, 0.96)	-1.94 (-3.53, -0.35)
HHF + MACE (ITT)	CVD - HF -	641/14865	637/12626	0.98 (0.88, 1.09)	-0.08 (-0.58, 0.42)
	CVD - HF +	161/1131	268/1430	0.84 (0.70, 1.00)	-2.90 (-5.76, -0.03)
	CVD + HF -	598/6750	540/6065	1.07 (0.96, 1.20)	0.63 (-0.35, 1.62)
	CVD + HF +	435/2001	643/2475	0.91 (0.82, 1.01)	-2.33 (-4.84, 0.18)
HHF + MACE (AT)	CVD - HF -	377/14865	376/12626	1.03 (0.90, 1.17)	0.08 (-0.30, 0.47)
	CVD - HF +	103/1131	185/1430	0.87 (0.70, 1.08)	-1.46 (-3.67, 0.76)
	CVD + HF -	342/6750	332/6065	0.97 (0.84, 1.12)	-0.17 (-0.91, 0.58)
	CVD + HF +	281/2001	445/2475	0.83 (0.73, 0.95)	-2.83 (-4.86, -0.79)

ITT, intention-to-treat; AT, as treated; CVD, cardiovascular disease; HF, heart failure; MACE, major adverse

cardiovascular events; RR, risk ratio; -, without; +, with; IPTW, inverse probability of treatment weighted; IPCW, inverse probability of censoring weighted; CI, confidence intervals.

* Weighted by inverse probability of treatment and censoring weights that account for confounding and informative censoring.

Table S 18. Risk of cardiovascular outcomes after excluding angina and non-specific atherosclerosis codes from baseline subgroup definitions (CVD = myocardial infarction, stroke, cardiac revascularization, ischemic heart disease, peripheral vascular diseases, HF = heart failure)

Outcome (ITT/AT)	Baseline subgroups	SGLT2i (Events/N)	GLP-1RA (Events/N)	Weighted RR* (95% CI)	Weighted RD*/100 (95% CI)
HHF (ITT)	CVD - HF -	112/12017	163/10319	0.81 (0.64, 1.04)	-0.26 (-0.55, 0.03)
	CVD - HF +	30/542	81/708	0.55 (0.38, 0.80)	-5.13 (-8.08, -2.18)
	CVD + HF -	192/9598	257/8372	0.83 (0.69, 1.00)	-0.42 (-0.88, 0.04)
	CVD + HF +	320/2590	500/3197	0.90 (0.79, 1.02)	-1.54 (-3.34, 0.25)
HHF (AT)	CVD - HF -	60/12017	101/10319	0.78 (0.57, 1.04)	-0.20 (-0.42, 0.02)
	CVD - HF +	21/542	59/708	0.47 (0.29, 0.75)	-3.91 (-6.02, -1.81)
	CVD + HF -	96/9598	152/8372	0.65 (0.51, 0.82)	-0.62 (-0.97, -0.28)
	CVD + HF +	204/2590	348/3197	0.85 (0.73, 0.99)	-1.38 (-2.80, 0.04)
MACE (ITT)	CVD - HF -	421/12017	358/10319	1.10 (0.96, 1.27)	0.35 (-0.14, 0.84)
	CVD - HF +	47/542	56/708	1.06 (0.74, 1.53)	0.03 (-2.94, 3.00)
	CVD + HF -	629/9598	536/8372	1.12 (1.00, 1.25)	0.58 (-0.15, 1.31)
	CVD + HF +	317/2590	469/3197	0.88 (0.78, 1.00)	-1.38 (-3.16, 0.40)
MACE (AT)	CVD - HF -	249/12017	188/10319	1.31 (1.09, 1.56)	0.58 (0.22, 0.94)
	CVD - HF +	28/542	30/708	1.21 (0.74, 1.94)	0.63 (-1.44, 2.70)
	CVD + HF -	354/9598	332/8372	1.03 (0.90, 1.19)	-0.09 (-0.64, 0.45)
	CVD + HF +	196/2590	307/3197	0.83 (0.71, 0.97)	-1.15 (-2.52, 0.21)
HHF + MACE (ITT)	CVD - HF -	484/12017	470/10319	1.01 (0.89, 1.14)	0.04 (-0.49, 0.58)
	CVD - HF +	62/542	117/708	0.69 (0.51, 0.92)	-4.85 (-8.55, -1.15)
	CVD + HF -	755/9598	707/8372	1.03 (0.94, 1.14)	0.28 (-0.52, 1.09)
	CVD + HF +	534/2590	794/3197	0.91 (0.83, 1.00)	-2.17 (-4.34, 0.00)
HHF + MACE (AT)	CVD - HF -	290/12017	270/10319	1.15 (0.98, 1.34)	0.36 (-0.05, 0.77)
	CVD - HF +	42/542	79/708	0.67 (0.47, 0.96)	-3.17 (-5.91, -0.42)
	CVD + HF -	429/9598	438/8372	0.92 (0.82, 1.04)	-0.41 (-1.02, 0.21)
	CVD + HF +	342/2590	551/3197	0.87 (0.78, 0.99)	-1.99 (-3.75, -0.24)

ITT, intention-to-treat; AT, as treated; CVD, cardiovascular disease; HF, heart failure; MACE, major adverse cardiovascular events; RR, risk ratio; -, without; +, with; IPTW, inverse probability of treatment weighted; IPCW, inverse probability of censoring weighted; CI, confidence intervals.

* Aalen Johansen estimators accounting for competing risk (for HHF outcome) and weighted by inverse probability of treatment and censoring weights that account for confounding and informative censoring.

Table S 19. Risk of cardiovascular outcomes after excluding peripheral vascular diseases, angina and atherosclerosis codes from baseline subgroup definitions (CVD = Myocardial infarction, stroke, cardiac revascularization, ischemic heart diseases, HF = heart failure)

Outcome (ITT/AT)	Baseline subgroups	SGLT2i (Events/N)	GLP-1RA (Events/N)	Weighted RR* (95% CI)	Weighted RD*/100 (95% CI)
HHF (ITT)	CVD - HF -	141/13997	203/12085	0.81 (0.65, 1.00)	-0.27 (-0.54, 0.01)
	CVD - HF +	51/765	116/1018	0.66 (0.48, 0.90)	-3.63 (-6.24, -1.02)
	CVD + HF -	163/7618	217/6606	0.86 (0.71, 1.05)	-0.41 (-0.95, 0.13)
	CVD + HF +	299/2367	465/2887	0.89 (0.78, 1.02)	-1.67 (-3.57, 0.24)
HHF (AT)	CVD - HF -	76/13997	126/12085	0.72 (0.55, 0.93)	-0.26 (-0.47, -0.06)
	CVD - HF +	33/765	81/1018	0.53 (0.36, 0.78)	-3.30 (-5.23, -1.37)
	CVD + HF -	80/7618	127/6606	0.69 (0.54, 0.88)	-0.62 (-1.03, -0.21)
	CVD + HF +	192/2367	326/2887	0.86 (0.73, 1.01)	-1.43 (-2.94, 0.08)
MACE (ITT)	CVD - HF -	545/13997	452/12085	1.13 (1.00, 1.27)	0.47 (0.00, 0.94)
	CVD - HF +	68/765	94/1018	0.98 (0.72, 1.32)	-0.21 (-2.83, 2.41)
	CVD + HF -	505/7618	442/6606	1.08 (0.95, 1.22)	0.50 (-0.33, 1.33)
	CVD + HF +	296/2367	431/2887	0.91 (0.80, 1.04)	-1.34 (-3.23, 0.55)
MACE (AT)	CVD - HF -	325/13997	240/12085	1.32 (1.13, 1.55)	0.64 (0.29, 0.99)
	CVD - HF +	39/765	49/1018	1.04 (0.70, 1.56)	0.20 (-1.59, 1.98)
	CVD + HF -	278/7618	280/6606	0.93 (0.79, 1.08)	-0.31 (-0.94, 0.31)
	CVD + HF +	185/2367	288/2887	0.86 (0.73, 1.02)	-1.33 (-2.79, 0.13)
HHF + MACE (ITT)	CVD - HF -	626/13997	593/12085	1.03 (0.93, 1.15)	0.15 (-0.37, 0.66)
	CVD - HF +	98/765	178/1018	0.78 (0.62, 0.99)	-3.53 (-6.79, -0.26)
	CVD + HF -	613/7618	584/6606	1.03 (0.93, 1.15)	0.26 (-0.66, 1.18)
	CVD + HF +	498/2367	733/2887	0.91 (0.83, 1.01)	-2.15 (-4.45, 0.14)
HHF + MACE (AT)	CVD - HF -	379/13997	341/12085	1.15 (1.00, 1.31)	0.39 (0.00, 0.78)
	CVD - HF +	62/765	116/1018	0.69 (0.52, 0.93)	-3.16 (-5.60, -0.72)
	CVD + HF -	340/7618	367/6606	0.89 (0.78, 1.02)	-0.60 (-1.31, 0.10)
	CVD + HF +	322/2367	514/2887	0.87 (0.77, 0.99)	-2.08 (-3.95, -0.22)

ITT, intention-to-treat; AT, as treated; CVD, cardiovascular disease; HF, heart failure; MACE, major adverse cardiovascular events; RR, risk ratio; -, without; +, with; IPTW, inverse probability of treatment weighted; IPCW, inverse probability of censoring weighted; CI, confidence intervals.

* Aalen Johansen estimators accounting for competing risk (for HHF outcome) and weighted by inverse probability of treatment and censoring weights that account for confounding and informative censoring.

Table S20. Risk of cardiovascular outcomes after excluding angina, non-specific acute/sub-acute ischemic heart diseases and peripheral vascular disease codes from baseline subgroup definitions (CVD = Myocardial infarction, stroke, cardiac revascularization, HF = heart failure)

Outcome (ITT/AT)	Baseline subgroups	SGLT2i (Events/N)	GLP-1RA (Events/N)	Weighted RR* (95% CI)	Weighted RD*/100 (95% CI)
HHF (ITT)	CVD - HF -	148/14865	234/12626	0.72 (0.59, 0.88)	-0.45 (-0.72, -0.17)
	CVD - HF +	93/1131	182/1430	0.72 (0.57, 0.91)	-3.39 (-5.74, -1.04)
	CVD + HF -	156/6750	186/6065	0.96 (0.78, 1.18)	-0.12 (-0.68, 0.45)
	CVD + HF +	257/2001	399/2475	0.89 (0.77, 1.03)	-1.71 (-3.77, 0.36)
HHF (AT)	CVD - HF -	77/14865	145/12626	0.62 (0.48, 0.79)	-0.41 (-0.62, -0.19)
	CVD - HF +	57/1131	128/1430	0.67 (0.50, 0.90)	-2.49 (-4.23, -0.74)
	CVD + HF -	79/6750	108/6065	0.79 (0.61, 1.02)	-0.38 (-0.80, 0.04)
	CVD + HF +	168/2001	279/2475	0.84 (0.71, 1.00)	-1.68 (-3.33, -0.03)
MACE (ITT)	CVD - HF -	554/14865	478/12626	1.08 (0.96, 1.22)	0.30 (-0.15, 0.76)
	CVD - HF +	106/1131	134/1430	1.05 (0.83, 1.34)	0.49 (-1.77, 2.76)
	CVD + HF -	496/6750	416/6065	1.12 (0.99, 1.27)	0.81 (-0.08, 1.70)
	CVD + HF +	258/2001	391/2475	0.88 (0.76, 1.01)	-1.89 (-3.97, 0.18)
MACE (AT)	CVD - HF -	323/14865	264/12626	1.19 (1.02, 1.38)	0.40 (0.06, 0.74)
	CVD - HF +	65/1131	85/1430	1.20 (0.90, 1.61)	1.07 (-0.63, 2.76)
	CVD + HF -	280/6750	256/6065	0.99 (0.85, 1.17)	-0.02 (-0.69, 0.64)
	CVD + HF +	159/2001	252/2475	0.81 (0.68, 0.96)	-1.94 (-3.53, -0.35)
HHF + MACE (ITT)	CVD - HF -	641/14865	637/12626	0.98 (0.88, 1.09)	-0.08 (-0.58, 0.42)
	CVD - HF +	161/1131	268/1430	0.84 (0.70, 1.00)	-2.90 (-5.76, -0.03)
	CVD + HF -	598/6750	540/6065	1.07 (0.96, 1.20)	0.63 (-0.35, 1.62)
	CVD + HF +	435/2001	643/2475	0.91 (0.82, 1.01)	-2.33 (-4.84, 0.18)
HHF + MACE (AT)	CVD - HF -	377/14865	376/12626	1.03 (0.90, 1.17)	0.08 (-0.30, 0.47)
	CVD - HF +	103/1131	185/1430	0.87 (0.70, 1.08)	-1.46 (-3.67, 0.76)
	CVD + HF -	342/6750	332/6065	0.97 (0.84, 1.12)	-0.17 (-0.91, 0.58)
	CVD + HF +	281/2001	445/2475	0.83 (0.73, 0.95)	-2.83 (-4.86, -0.79)

ITT, intention-to-treat; AT, as treated; CVD, cardiovascular disease; HF, heart failure; MACE, major adverse cardiovascular events; RR, risk ratio; -, without; +, with; IPTW, inverse probability of treatment weighted; IPCW, inverse probability of censoring weighted; CI, confidence intervals.

* Aalen Johansen estimators accounting for competing risk (for HHF outcome) and weighted by inverse probability of treatment and censoring weights that account for confounding and informative censoring.

Table S21. Risk of cardiovascular outcomes after limiting baseline cardiovascular conditions to inpatient

setting (all available follow-up)

Outcome (ITT/AT)	Baseline subgroups	Events/N (SGLT2i)	Events/N (GLP-1RA)	HR (95% CI) (weighted)	RD (/100)	RR (/100)
HHF (ITT)	CVD - HF -	153/19602	214/16837	0.88 (0.72, 1.09)	-0.39	0.88
	CVD - HF +	40/207	104/329	0.72 (0.51, 1.01)	-11.18	0.79
	CVD + HF -	247/3089	345/3087	0.86 (0.73, 1.01)	-2.49	0.87
	CVD + HF +	379/1849	613/2347	0.90 (0.79, 1.02)	-3.15	0.92
HHF (AT)	CVD - HF -	67/19602	112/16837	0.70 (0.54, 0.92)	-0.76	0.71
	CVD - HF +	23/207	68/329	0.50 (0.33, 0.78)	-18.76	0.58
	CVD + HF -	112/3089	165/3087	0.72 (0.58, 0.89)	-5.33	0.74
	CVD + HF +	225/1849	380/2347	0.89 (0.76, 1.04)	-3.38	0.91
MACE (ITT)	CVD - HF -	699/19602	631/16837	1.17 (1.05, 1.30)	1.74	1.16
	CVD - HF +	52/207	75/329	1.21 (0.85, 1.73)	6.21	1.15
	CVD + HF -	681/3089	643/3087	1.18 (1.06, 1.31)	5.04	1.13
	CVD + HF +	421/1849	631/2347	0.97 (0.86, 1.10)	-1.03	0.98
MACE (AT)	CVD - HF -	345/19602	281/16837	1.16 (1.01, 1.33)	1.05	1.15
	CVD - HF +	26/207	35/329	1.52 (0.98, 2.38)	12.68	1.39
	CVD + HF -	321/3089	308/3087	1.13 (0.98, 1.31)	3.29	1.11
	CVD + HF +	215/1849	341/2347	0.86 (0.74, 1.00)	-5.17	0.9
HHF+MACE (ITT)	CVD - HF -	779/19602	768/16837	1.09 (0.99, 1.21	1.15	1.09
	CVD - HF +	71/207	144/329	0.86 (0.65, 1.14	-5.54	0.92

	CVD + HF -	819/3089	854/3087	1.07 (0.97, 1.18	2.44	1.05
	CVD + HF +	636/1849	960/2347	0.94 (0.85, 1.04	-2.12	0.97
HHF+MACE (AT)	CVD - HF -	779/19602	768/16837	1.09 (0.99, 1.21	1.15	1.09
	CVD - HF +	71/207	144/329	0.86 (0.65, 1.14	-5.54	0.92
	CVD + HF -	819/3089	854/3087	1.07 (0.97, 1.18	2.44	1.05
	CVD + HF +	636/1849	960/2347	0.94 (0.85, 1.04	-2.12	0.97

Table S22. Risk of cardiovascular outcomes after allowing time varying covariates in censoring weights models

Outcome (ITT/AT)	Baseline subgroups	Weighted risk in % (SGLT2i)	Weighted risk in % (GLP-1RA)	Weighted RR (95% CI)	Weighted RD (per 100) (95% CI)
HHF (AT)	CVD - HF -	1.18	1.76	0.67 (0.42, 0.99)	-0.58 (-1.22, -0.02)
	CVD - HF +	6.88	14.02	0.49 (0.28, 0.99)	-7.14 (-12.07, -0.09)
	CVD + HF -	2.41	4.15	0.58 (0.42, 0.76)	-1.74 (-2.76, -0.88)
	CVD + HF +	14.9	19.64	0.76 (0.61, 0.93)	-4.74 (-8.62, -1.33)
MACE (AT)	CVD - HF -	4.76	4.01	1.19 (0.95, 1.47)	0.75 (-0.22, 1.65)
	CVD - HF +	10.04	7.98	1.26 (0.63, 2.3)	2.06 (-3.87, 7.49)
	CVD + HF -	8.49	8.51	1.00 (0.84, 1.18)	-0.02 (-1.48, 1.44)
	CVD + HF +	16.1	21.53	0.75 (0.61, 0.92)	-5.43 (-9.48, -1.58)
HHF+MACE (ITT)	CVD - HF -	5.51	5.29	1.04 (0.86, 1.25)	0.22 (-0.83, 1.2)
	CVD - HF +	14.71	19.53	0.75 (0.48, 1.27)	-4.82 (-11.81, 3.92)
	CVD + HF -	10.21	10.91	0.94 (0.8, 1.09)	-0.7 (-2.12, 0.99)
	CVD + HF +	25.23	32.76	0.77 (0.65, 0.88)	-7.52 (-12.47, -3.82)

Table S23. Risk of cardiovascular outcomes after allowing all-available years of follow-up

Outcome (ITT/AT)	Baseline subgroups	Events/ N (SGLT2i)	Events/ N (GLP-1RA)	HR	RD (/100)	RR (/100)
HHF (ITT)	CVD - HF -	151/11830	208/10142	0.91 (0.74, 1.13)	-0.43	0.91
	CVD - HF +	42/609	106/771	0.59 (0.41, 0.84)	-10.59	0.63
	CVD + HF -	247/9399	347/8205	0.82 (0.70, 0.97)	-1.64	0.83
	CVD + HF +	379/2909	615/3478	0.89 (0.78, 1.00)	-2.99	0.9
HHF (AT)	CVD - HF -	66/11830	106/10142	0.76 (0.58, 1.00)	-0.93	0.77
	CVD - HF +	24/609	70/771	0.43 (0.27, 0.68)	-13.61	0.47
	CVD + HF -	112/9399	167/8205	0.67 (0.55, 0.82)	-2.81	0.68
	CVD + HF +	225/2909	382/3478	0.88 (0.76, 1.03)	-2.89	0.9
MACE (ITT)	CVD - HF -	550/11830	491/10142	1.21 (1.07, 1.36)	2.57	1.19
	CVD - HF +	63/609	88/771	1.20 (0.86, 1.65)	4.14	1.16
	CVD + HF -	791/9399	731/8205	1.09 (0.99, 1.20)	1.69	1.08
	CVD + HF +	449/2909	670/3478	0.97 (0.86, 1.09)	-1.13	0.97
MACE (AT)	CVD - HF -	271/11830	205/10142	1.28 (1.09, 1.51)	2.41	1.27
	CVD - HF +	30/609	39/771	1.15 (0.74, 1.78)	2.57	1.13
	CVD + HF -	380/9399	356/8205	0.97 (0.85, 1.10)	-0.45	0.97
	CVD + HF +	226/2909	365/3478	0.82 (0.71, 0.96)	-5.79	0.86
HHF+MACE (ITT)	CVD - HF -	629/11830	623/10142	1.12 (1.00, 1.25)	1.77	1.11
	CVD - HF +	83/609	158/771	0.82 (0.63, 1.07)	-5.96	0.86
	CVD + HF -	929/9399	944/8205	1.01 (0.92, 1.11)	0.24	1.01
	CVD + HF +	664/2909	1001/3478	0.93 (0.84, 1.02)	-2.65	0.95
HHF+MACE (AT)	CVD - HF -	629/11830	623/10142	1.12 (1.00, 1.25)	1.77	1.11
	CVD - HF +	83/609	158/771	0.82 (0.63, 1.07)	-5.96	0.86
	CVD + HF -	929/9399	944/8205	1.01 (0.92, 1.11)	0.24	1.01
	CVD + HF +	664/2909	1001/3478	0.93 (0.84, 1.02)	-2.65	0.95

Table S24. Two-year risk of MACE + cardiac revascularization and bypass procedures (risk ratios)

	No. of events	No. at risk	Crude risks (%)	Crude RR* (95% CI)	IPTW RR (95% CI)	IPTW + IPCW RR (95% CI)
ITT analyses						
CVD (-) HF (-)						
SGLT-2i	521	11,830	4.4	0.98 (0.87, 1.11)	1.02 (0.91, 1.16)	1.03 (0.91, 1.16)
GLP-1RA	455	10,142	4.4			
CVD (+) HF (-)						
SGLT-2i	50	609	8.2	0.92 (0.65, 1.30)	0.94 (0.66, 1.33)	0.95 (0.67, 1.36)
GLP-1RA	69	771	8.9			
CVD (-) HF (+)						
SGLT-2i	875	9,399	9.3	1.03 (0.94, 1.13)	1.10 (1.00, 1.20)	1.10 (1.00, 1.20)
GLP-1RA	739	8,205	9.0			
CVD (+) HF (+)						
SGLT-2i	419	2,909	14.4	0.85 (0.76, 0.95)	0.92 (0.82, 1.03)	0.92 (0.82, 1.02)
GLP-1RA	590	3,478	16.9			
As-treated analyses						
CVD (-) HF (-)						
SGLT-2i	324	11,830	2.7	1.07 (0.91, 1.26)	1.17 (0.99, 1.37)	1.18 (1.02, 1.38)
GLP-1RA	259	10,142	2.6			
CVD (+) HF (-)						
SGLT-2i	30	609	4.9	1.12 (0.69, 1.80)	1.18 (0.73, 1.90)	1.11 (0.72, 1.72)
GLP-1RA	34	771	4.4			
CVD (-) HF (+)						
SGLT-2i	517	9,399	5.5	0.99 (0.88, 1.12)	1.04 (0.92, 1.18)	1.03 (0.92, 1.16)
GLP-1RA	454	8,205	5.5			
CVD (+) HF (+)						
SGLT-2i	269	2,909	9.2	0.81 (0.70, 0.94)	0.84 (0.73, 0.97)	0.86 (0.75, 0.98)
GLP-1RA	397	3,478	11.4			

ITT, intention-to-treat; AT, as treated; CVD, cardiovascular disease; HF, heart failure; MACE, major adverse

cardiovascular events; RR, risk ratio; -, without; +, with; IPTW, inverse probability of treatment weighted;

IPCW, inverse probability of censoring weighted; CI, confidence intervals.

* Weighted by inverse probability of treatment and censoring weights that account for confounding and

informative censoring.

Table S25. Two-year risk of MACE + cardiac revascularization and bypass procedures (risk differences)

	Events	Total N	Crude risks (%)	Crude RD (95% CI)	IPTW RD (95% CI)	IPTW + IPCW RD*
ITT analyses						
CVD (-) HF (-)						
SGLT-2i	521	11,830	4.4	-0.08 (-0.6, 0.5)	0.1 (-0.4, 0.7)	0.1 (-0.4, 0.7)
GLP-1RA	455	10,142	4.4			
CVD (+) HF (-)						
SGLT-2i	50	609	8.2	-0.7 (-3.7, 2.2)	-0.5 (-3.5, 2.4)	-0.6 (-3.5, 2.4)
GLP-1RA	69	771	8.9			
CVD (-) HF (+)						
SGLT-2i	875	9,399	9.3	0.3 (-0.6, 1.2)	0.9 (0, 1.7)	0.9 (0, 1.7)
GLP-1RA	739	8,205	9.0			
CVD (+) HF (+)						
SGLT-2i	419	2,909	14.4	-2.6 (-4.3, -0.8)	-1.4 (-3.2, 0.4)	-1.4 (-3.2, 0.4)
GLP-1RA	590	3,478	16.9			
As-treated analyses						
CVD (-) HF (-)						
SGLT-2i	324	11,830	2.7	0.2 (-0.2, 0.6)	0.4 (-0.02, 0.8)	0.4 (-0.02, 0.8)
GLP-1RA	259	10,142	2.6			
CVD (+) HF (-)						
SGLT-2i	30	609	4.9	0.5 (-1.7, 2.8)	0.8 (-1.5, 3.0)	0.5 (-1.6, 2.6)
GLP-1RA	34	771	4.4			
CVD (-) HF (+)						
SGLT-2i	517	9,399	5.5	-0.03 (-0.7, 0.6)	0.2 (-0.5, 0.9)	0.2 (-0.5, 0.9)
GLP-1RA	454	8,205	5.5			
CVD (+) HF (+)						
SGLT-2i	269	2,909	9.2	-2.2 (-3.7, -0.7)	-2.2 (-3.3, -0.3)	-1.6 (-3.0, -0.2)
GLP-1RA	397	3,478	11.4			

ITT, intention-to-treat; AT, as treated; CVD, cardiovascular disease; HF, heart failure; MACE, major adverse cardiovascular events; RR, risk ratio; -, without; +, with; IPTW, inverse probability of treatment weighted; IPCW, inverse probability of censoring weighted; CI, confidence intervals.

* Weighted by inverse probability of treatment and censoring weights that account for confounding and informative censoring.

Table S26. Risk ratios for hospitalization for heart failure after exclusion of heart failure events during a 2-month pre-index period

Subgroups	IP weighted RR (95% CI)*
ITT – HHF risk	
CHF (-) CVD (-)	0.83 (0.65, 1.05)
CHF (+) CVD (-)	0.54 (0.31, 0.92)
CHF (-) CVD (+)	0.83 (0.69, 1.00)
CHF (+) CVD (+)	0.92 (0.75, 1.13)
As-treated – HHF risk	
CHF (-) CVD (-)	0.79 (0.58, 1.06)
CHF (+) CVD (-)	0.66 (0.35, 1.25)
CHF (-) CVD (+)	0.65 (0.51, 0.82)
CHF (+) CVD (+)	0.93 (0.72, 1.20)

ITT, intention-to-treat; AT, as treated; CVD, cardiovascular disease; HF, heart failure; MACE, major adverse cardiovascular events; RR, risk ratio; -, without; +, with; IPTW, inverse probability of treatment weighted; IPCW, inverse probability of censoring weighted; CI, confidence intervals.

* Weighted by inverse probability of treatment and censoring weights that account for confounding and informative censoring.

Table S27. Risk ratios for MACE outcomes after exclusion of MI and stroke events during a 2-month

pre-index period

Subgroups	IP weighted RR (95% CI)*
ITT – MACE risk	
CHF (-) CVD (-)	1.10 (0.96, 1.27)
CHF (+) CVD (-)	1.06 (0.73, 1.53)
CHF (-) CVD (+)	1.10 (0.98, 1.23)
CHF (+) CVD (+)	0.89 (0.78, 1.02)
As-treated – MACE risk	
CHF (-) CVD (-)	1.31 (1.09, 1.56)
CHF (+) CVD (-)	1.21 (0.75, 1.94)
CHF (-) CVD (+)	1.02 (0.88, 1.18)
CHF (+) CVD (+)	0.85 (0.72, 0.99)

ITT, intention-to-treat; AT, as treated; CVD, cardiovascular disease; HF, heart failure; MACE, major adverse

cardiovascular events; RR, risk ratio; -, without; +, with; IPTW, inverse probability of treatment weighted;

IPCW, inverse probability of censoring weighted; CI, confidence intervals.

* Weighted by inverse probability of treatment and censoring weights that account for confounding and

informative censoring.

Table S28. Health seeking behaviors during the first 6 months after the index date (second prescription date)

	No. at risk	Proportion of flu shot (%)	Proportion of lipid tests (%)
CVD (-) HF (-)			
SGLT-2i	11,830	33.5	50.7
GLP-1RA	10,142	33.7	49.2
CVD (+) HF (-)			
SGLT-2i	609	31.7	47.0
GLP-1RA	771	34.2	47.0
CVD (-) HF (+)			
SGLT-2i	9,399	34.6	53.1
GLP-1RA	8,205	35.6	50.4
CVD (+) HF (+)			
SGLT-2i	2,909	34.5	50.8
GLP-1RA	3,478	36.1	47.0

ITT, intention-to-treat; AT, as treated; CVD, cardiovascular disease; HF, heart failure; MACE, major adverse cardiovascular events; RR, risk ratio; -, without; +, with; IPTW, inverse probability of treatment weighted; IPCW, inverse probability of censoring weighted; CI, confidence intervals.

Table S29. Subdistribution hazard ratios (HR) for hospitalization for heart failure outcome from fine and gray Cox model

	Median follow-up (IQR)	IPTW + IPCW HR (95% CI)	Subdistribution HR* (95% CI)	RR from subdistribution hazard functions*
ITT analyses				
CVD (-) HF (-)				
SGLT-2i	1.32 (0.70, 1.99)	0.82 (0.62, 1.08)	0.82 (0.64, 1.05)	0.82
GLP-1RA	1.31 (0.67, 1.99)			
CVD (+) HF (-)				
SGLT-2i	1.14 (0.55, 1.99)	0.55 (0.35, 0.84)	0.55 (0.37, 0.81)	0.57
GLP-1RA	1.25 (0.58, 1.99)			
CVD (-) HF (+)				
SGLT-2i	1.49 (0.68, 0.99)	0.82 (0.66, 1.02)	0.82 (0.68, 0.99)	0.82
GLP-1RA	1.48 (0.64, 0.99)			
CVD (+) HF (+)				
SGLT-2i	1.21 (0.54, 1.99)	0.90 (0.77, 1.04)	0.90 (0.79, 1.03)	0.91
GLP-1RA	1.16 (0.48, 1.99)			
As-treated analyses				
CVD (-) HF (-)				
SGLT-2i	0.75 (0.42, 1.45)	0.75 (0.52, 1.10)	0.75 (0.56, 1.02)	0.75
GLP-1RA	0.71 (0.40, 1.36)			
CVD (+) HF (-)				
SGLT-2i	0.6 (0.34, 1.18)	0.46 (0.27, 0.78)	0.46 (0.28, 0.75)	0.48
GLP-1RA	0.68 (0.36, 1.20)			
CVD (-) HF (+)				
SGLT-2i	0.71 (0.41, 1.37)	0.64 (0.46, 0.88)	0.64 (0.50, 0.81)	0.64
GLP-1RA	0.66 (0.37, 1.34)			
CVD (+) HF (+)				
SGLT-2i	0.63 (0.35, 1.24)	0.83 (0.68, 1.01)	0.83 (0.71, 0.98)	0.85
GLP-1RA	0.61 (0.33, 1.16)			

ITT, intention-to-treat; AT, as treated; CVD, cardiovascular disease; HF, heart failure; MACE, major adverse cardiovascular events; RR, risk ratio; -, without; +, with; IPTW, inverse probability of treatment weighted; IPCW, inverse probability of censoring weighted; CI, confidence intervals.

* Weighted by inverse probability of treatment and censoring weights that account for confounding and informative censoring.
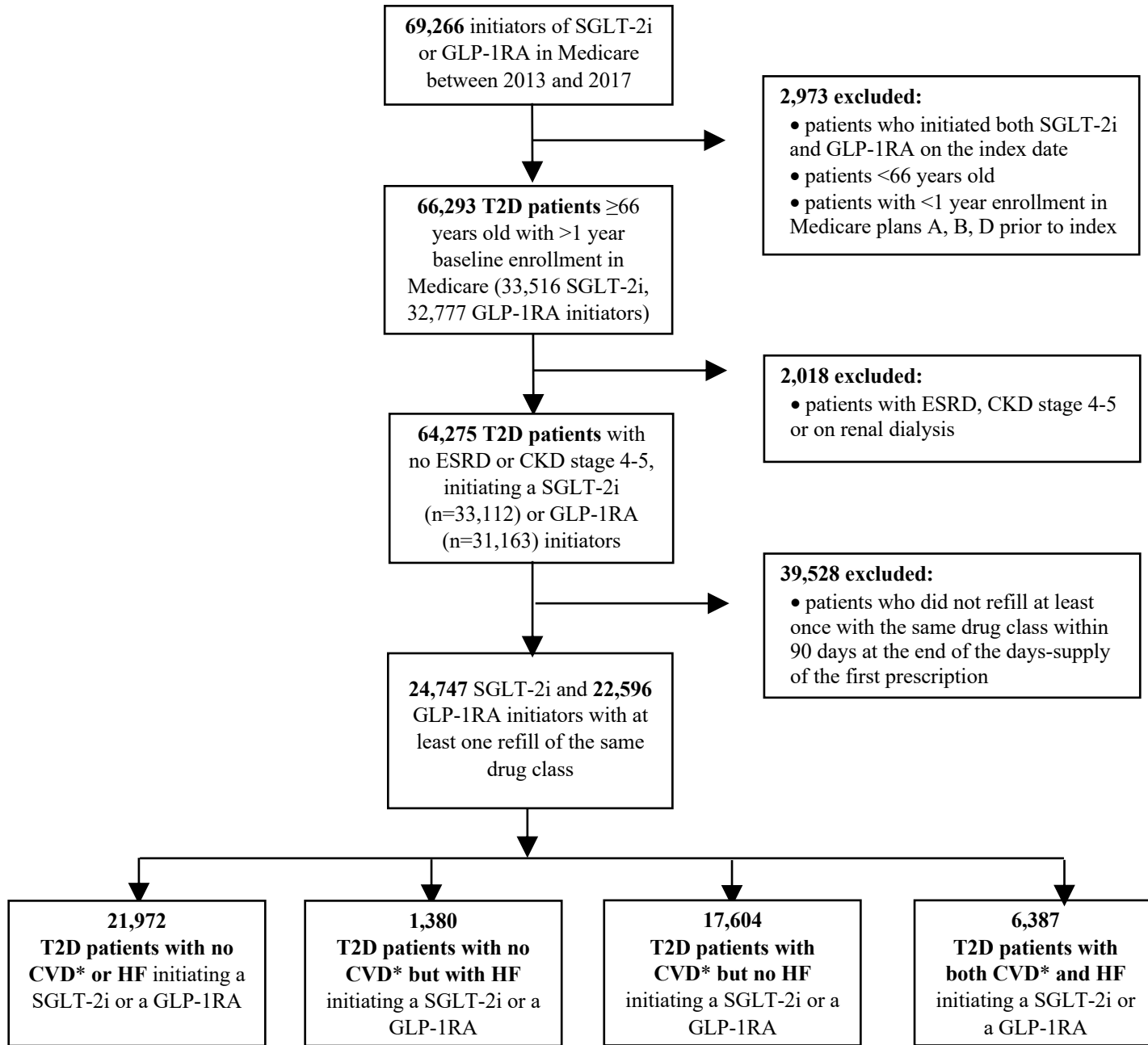
Table S30. Risk of cardiovascular outcomes after excluding exenatide initiators

Outcome (ITT/AT)	Baseline subgroups	Events/N (SGLT2i)	Events/N (GLP-1RA)	HR (95% CI)	RD (per 100)	RR
HHF (ITT)	CVD - HF -	151/11830	164/8174	0.92 (0.74, 1.16	-0.38	0.93
	CVD - HF +	42/609	79/600	0.62 (0.43, 0.90	-8.30	0.65
	CVD + HF -	247/9399	265/6633	0.85 (0.71, 1.01	-1.38	0.86
	CVD + HF +	379/2909	486/2820	0.87 (0.76, 0.99	-3.34	0.89
HHF (AT)	CVD - HF -	66/11830	85/8174	0.79 (0.59, 1.05	-0.88	0.79
	CVD - HF +	24/609	57/600	0.41 (0.26, 0.66	-14.12	0.45
	CVD + HF -	112/9399	125/6633	0.73 (0.59, 0.91	-2.17	0.74
	CVD + HF +	225/2909	307/2820	0.86 (0.73, 1.01	-3.63	0.88
MACE (ITT)	CVD - HF -	550/11830	378/8174	1.23 (1.08, 1.40	2.78	1.21
	CVD - HF +	63/609	67/600	1.19 (0.84, 1.68	3.95	1.16
	CVD + HF -	791/9399	570/6633	1.10 (0.98, 1.22	1.81	1.08
	CVD + HF +	449/2909	532/2820	0.96 (0.84, 1.08	-1.39	0.97
MACE (AT)	CVD - HF -	271/11830	167/8174	1.27 (1.07, 1.51	2.40	1.25
	CVD - HF +	30/609	28/600	1.21 (0.76, 1.93	3.07	1.19
	CVD + HF -	380/9399	286/6633	0.96 (0.84, 1.10	-0.54	0.96
	CVD + HF +	226/2909	303/2820	0.81 (0.69, 0.94	-6.60	0.85
HHF+MACE (ITT)	CVD - HF -	151/11830	164/8174	0.92 (0.74, 1.16	-0.38	0.93
	CVD - HF +	42/609	79/600	0.62 (0.43, 0.90	-8.30	0.65
	CVD + HF -	247/9399	265/6633	0.85 (0.71, 1.01	-1.38	0.86
	CVD + HF +	379/2909	486/2820	0.87 (0.76, 0.99	-3.34	0.89
HHF+MACE (AT)	CVD - HF -	66/11830	85/8174	0.79 (0.59, 1.05	-0.88	0.79
	CVD - HF +	24/609	57/600	0.41 (0.26, 0.66	-14.12	0.45
	CVD + HF -	112/9399	125/6633	0.73 (0.59, 0.91	-2.17	0.74
	CVD + HF +	225/2909	307/2820	0.86 (0.73, 1.01	-3.63	0.88

Table S31. Risk of cardiovascular outcomes among canagliflozin vs. liraglutide initiators

Outcome (ITT/AT)	Baseline subgroups	Events/N (SGLT2i)	Events/N (GLP-1RA)	HR (95% CI)	RD (per 100)	RR
HHF (ITT)	CVD - HF -	115/7884	136/5685	0.90 (0.70, 1.17	-0.48	0.91
	CVD - HF +	30/397	65/412	0.50 (0.32, 0.79	-10.96	0.54
	CVD + HF -	199/6153	228/4434	0.84 (0.69, 1.02	-1.49	0.85
	CVD + HF +	304/1848	390/1875	0.95 (0.82, 1.10	-1.27	0.96
HHF (AT)	CVD - HF -	45/7884	66/5685	0.72 (0.51, 1.00	-1.15	0.72
	CVD - HF +	15/397	44/412	0.40 (0.22, 0.72	-12.94	0.43
	CVD + HF -	86/6153	102/4434	0.68 (0.52, 0.88	-2.76	0.69
	CVD + HF +	173/1848	236/1875	0.90 (0.74, 1.08	-2.55	0.91
MACE (ITT)	CVD - HF -	426/7884	313/5685	1.23 (1.06, 1.42	2.72	1.21
	CVD - HF +	50/397	57/412	1.18 (0.80, 1.74	3.72	1.15
	CVD + HF -	619/6153	470/4434	1.08 (0.96, 1.22	1.60	1.07
	CVD + HF +	350/1848	423/1875	1.04 (0.90, 1.19	1.09	1.03
MACE (AT)	CVD - HF -	192/7884	134/5685	1.18 (0.96, 1.44	1.60	1.17
	CVD - HF +	24/397	23/412	1.44 (0.83, 2.50	6.17	1.39
	CVD + HF -	275/6153	218/4434	0.88 (0.75, 1.04	-1.69	0.89
	CVD + HF +	159/1848	227/1875	0.83 (0.69, 1.00	-5.69	0.86
HHF+MACE (ITT)	CVD - HF -	487/7884	395/5685	1.14 (1.00, 1.30	2.04	1.13
	CVD - HF +	62/397	99/412	0.75 (0.54, 1.03	-8.08	0.79
	CVD + HF -	725/6153	609/4434	1.01 (0.91, 1.13	0.24	1.01
	CVD + HF +	518/1848	623/1875	0.99 (0.88, 1.11	-0.43	0.99
HHF+MACE (AT)	CVD - HF -	487/7884	395/5685	1.14 (1.00, 1.30	2.04	1.13
	CVD - HF +	62/397	99/412	0.75 (0.54, 1.03	-8.08	0.79
	CVD + HF -	725/6153	609/4434	1.01 (0.91, 1.13	0.24	1.01
	CVD + HF +	518/1848	623/1875	0.99 (0.88, 1.11	-0.43	0.99

Figure S1. Cohort flowchart of patients initiating a SGLT-2i or a GLP-1RA

69,266 initiators of SGLT-2i or GLP-1RA in Medicare between 2013 and 2017

2,973 excluded:
- patients who initiated both SGLT-2i and GLP-1RA on the index date
- patients <66 years old
- patients with <1 year enrollment in Medicare plans A, B, D prior to index

66,293 T2D patients ≥66 years old with >1 year baseline enrollment in Medicare (33,516 SGLT-2i, 32,777 GLP-1RA initiators)

2,018 excluded:
- patients with ESRD, CKD stage 4-5 or on renal dialysis

64,275 T2D patients with no ESRD or CKD stage 4-5, initiating a SGLT-2i (n=33,112) or GLP-1RA (n=31,163) initiators

39,528 excluded:
- patients who did not refill at least once with the same drug class within 90 days at the end of the days-supply of the first prescription

24,747 SGLT-2i and **22,596** GLP-1RA initiators with at least one refill of the same drug class

21,972 T2D patients with no CVD* or HF initiating a SGLT-2i or a GLP-1RA

1,380 T2D patients with no CVD* but with HF initiating a SGLT-2i or a GLP-1RA

17,604 T2D patients with CVD* but no HF initiating a SGLT-2i or a GLP-1RA

6,387 T2D patients with both CVD* and HF initiating a SGLT-2i or a GLP-1RA

T2D: type 2 diabetes; SGLT2i: sodium-glucose cotransporter-2 inhibitors; GLP-1RA: glucagon-like peptide-1 receptor agonists; CVD: cardiovascular disease; PS: propensity score; HF: heart failure
* Defined as history of myocardial infarction, angina, coronary atherosclerosis and other forms of chronic ischemic heart disease, coronary procedure, heart failure, ischemic stroke, peripheral arterial disease or surgery, lower extremity amputation

Figure S2. Causal diagram to depict relations between exposure, outcome, censoring and competing events (L = a set of confounders, X = SGLT2i vs. GLP-1RA, Y_k = outcome Y at time k, Y_{k+1} = outcome Y at time k+1, D_k = competing event, i.e., death at time k, D_{k+1} = competing event, i.e., death at time k+1, C_k = censoring event, i.e., treatment changes at time k, C_{k+1} = censoring event, i.e., treatment changes at time k+1
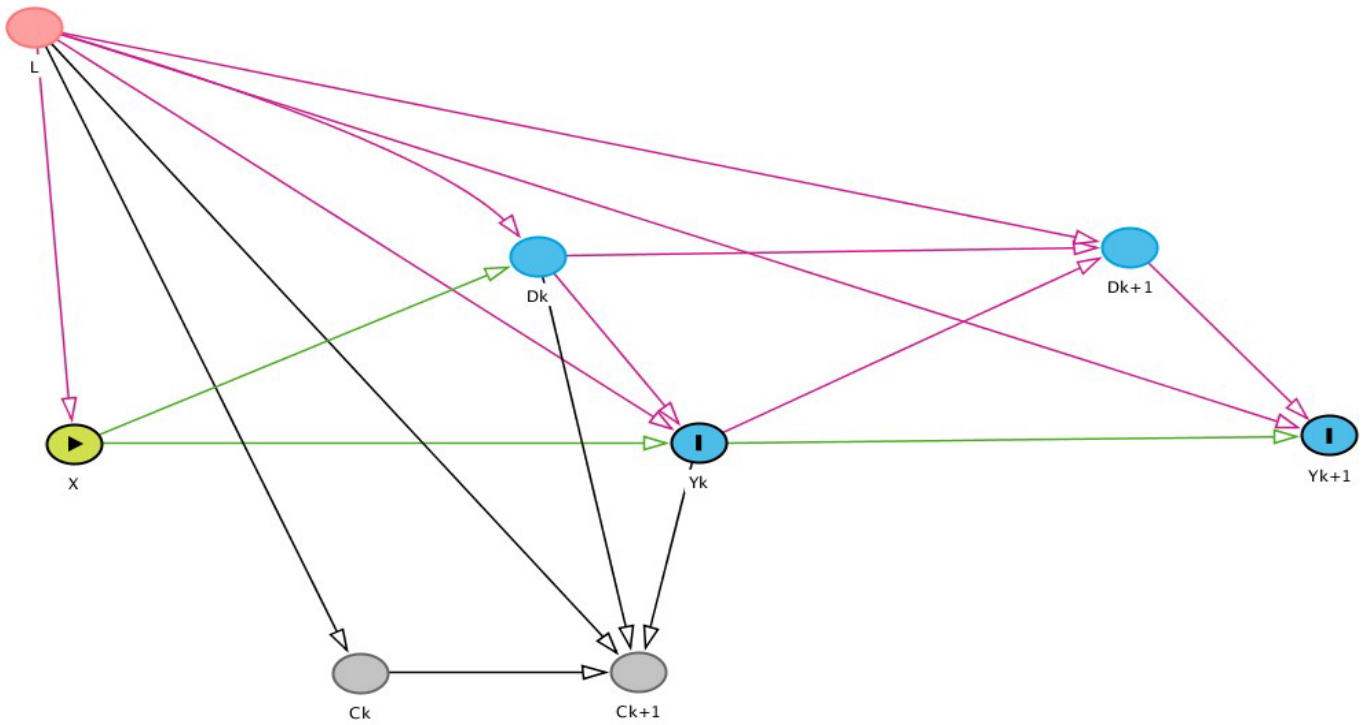
Figure S3. Cumulative risk of hospitalization for heart failure stratified by baseline atherosclerotic cardiovascular diseases (CVD) and heart failure (HF) (intent-to-treat analyses adjusted for baseline confounding and informative censoring)
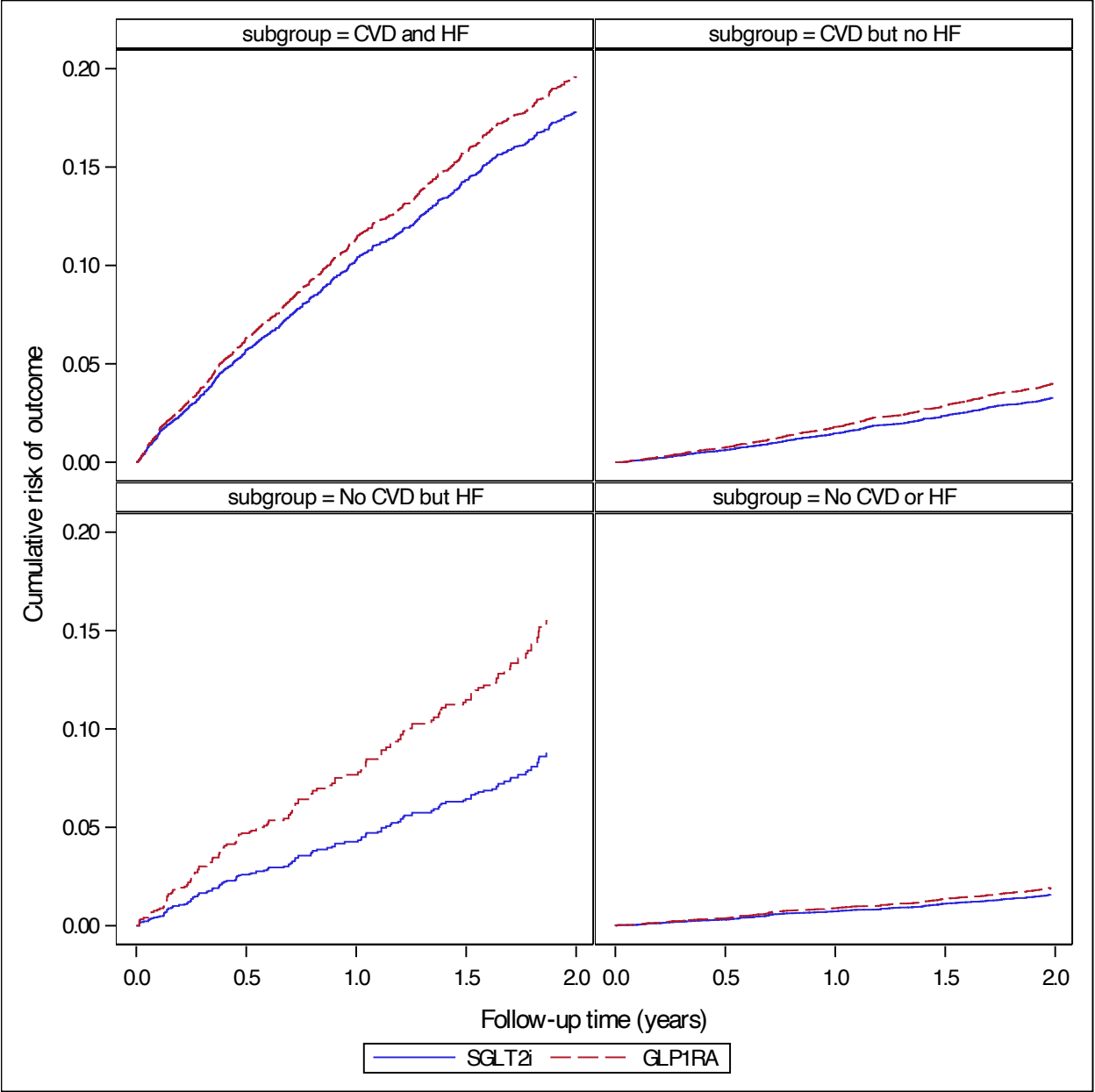
Figure S4. Cumulative risk of major adverse cardiovascular outcomes (myocardial infarction, stroke, mortality) stratified by baseline atherosclerotic cardiovascular diseases (CVD) and heart failure (HF) (intent-to-treat analyses adjusted for baseline confounding and informative censoring)

Figure S5. Cumulative risk of a composite of hospitalization for heart failure or major adverse cardiovascular outcomes (myocardial infarction, stroke, mortality) stratified by baseline atherosclerotic cardiovascular diseases (CVD) and heart failure (HF) (intent-to-treat analyses adjusted for baseline confounding and informative censoring)
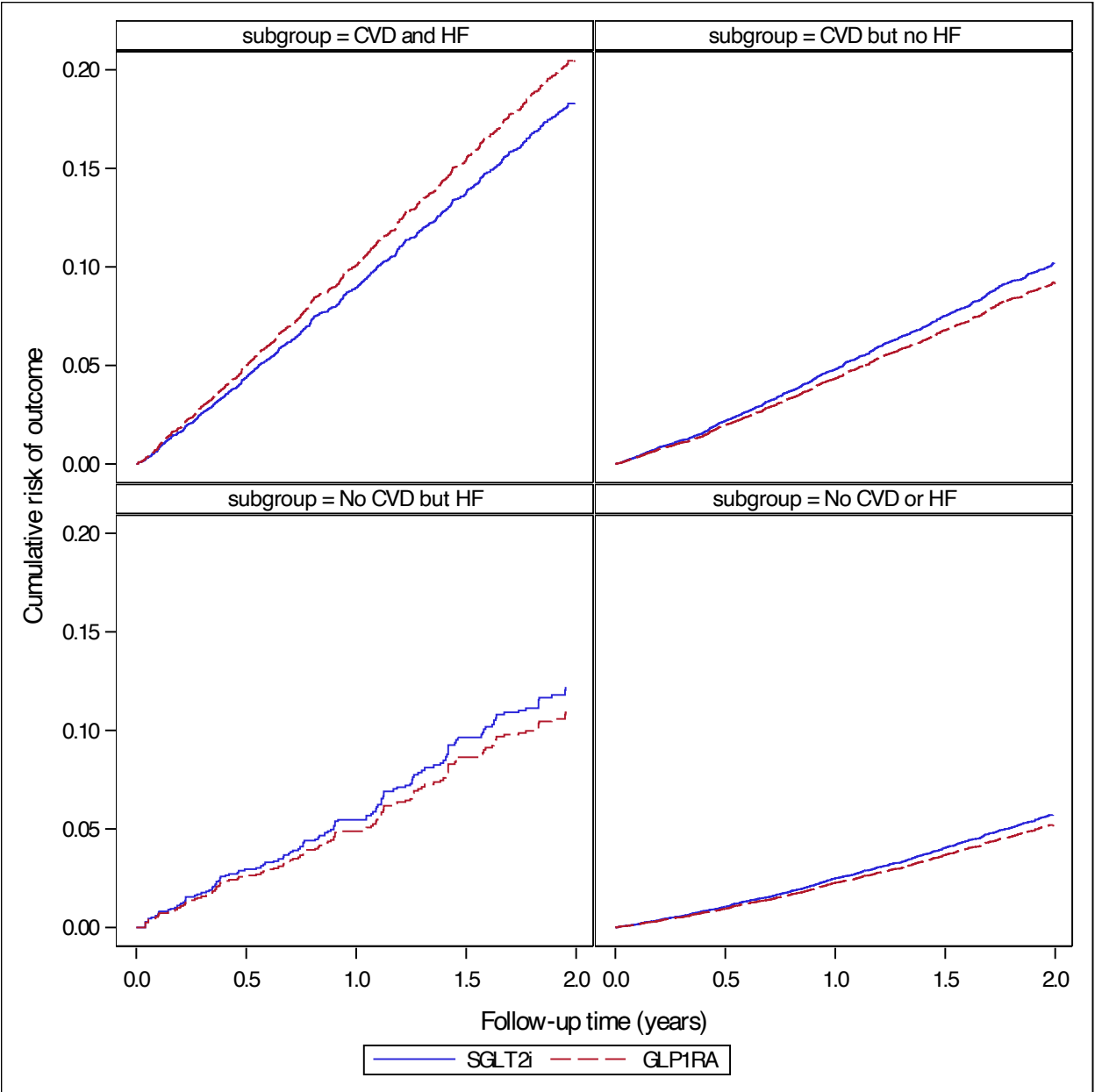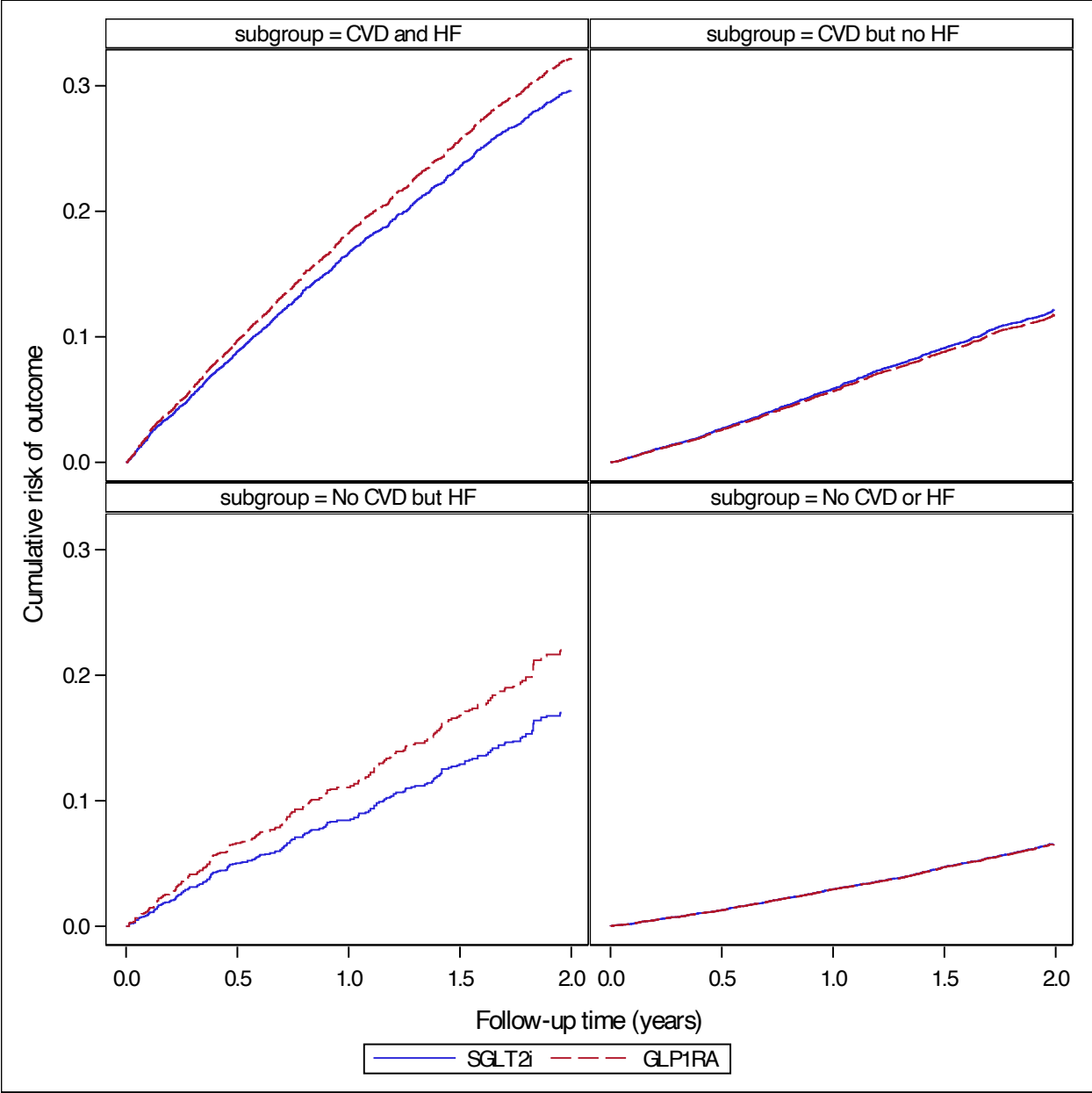
Figure S 6. Inverse probability of treatment and censoring weighted risk ratios (RR) and differences (RD) for hospitalization for heart failure for intent-to-treat (ITT) and as-treated (AT) analyses (secondary definition which includes rhematic and hypertensive heart failure codes in addition to congestive heart failure codes)

Cohort	RR			RD/100	
ITT					
CVD - CHF -	0.87			-0.19	
CVD + CHF -	0.48			-6.68	
CVD - CHF +	0.88			-0.36	
CVD + CHF +	0.91			-1.41	
AT					
CVD - CHF -	0.81			-0.18	
CVD + CHF -	0.43			-4.48	
CVD - CHF +	0.69			-0.58	
CVD + CHF +	0.86			-1.44	

Figure S 7. Inverse probability of treatment and censoring weighted risk ratios (RR) and differences (RD) for MACE outcomes for intent-to-treat (ITT) and as-treated (AT) analyses (with only ischemic stroke)

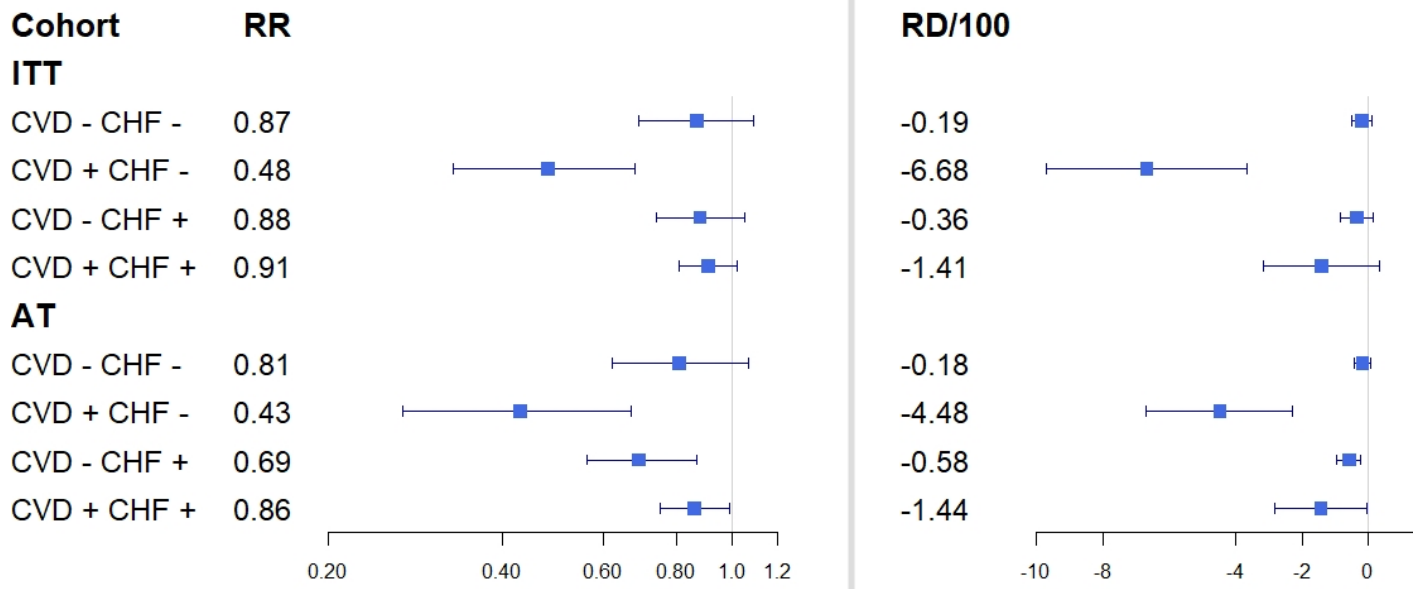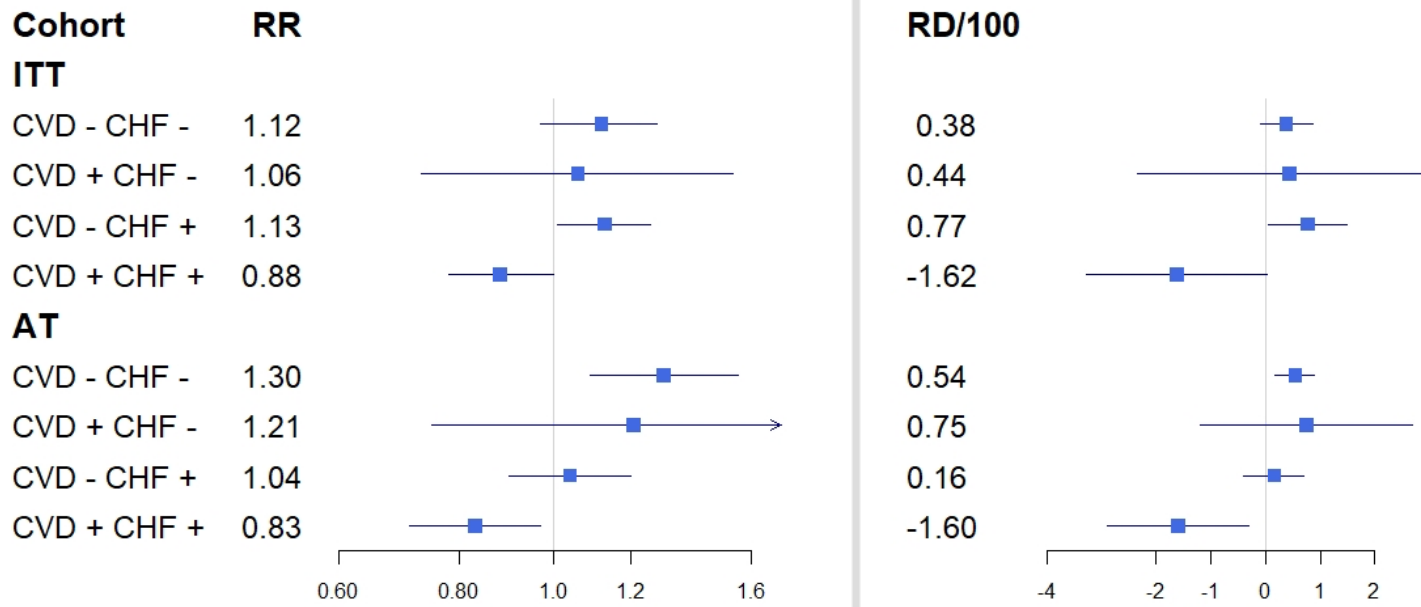| Cohort	RR		RD/100	
ITT				
CVD - CHF -	1.12		0.38	
CVD + CHF -	1.06		0.44	
CVD - CHF +	1.13		0.77	
CVD + CHF +	0.88		-1.62	
AT				
CVD - CHF -	1.30		0.54	
CVD + CHF -	1.21		0.75	
CVD - CHF +	1.04		0.16	
CVD + CHF +	0.83		-1.60	

Figure S 8. Inverse probability of treatment and censoring weighted risk ratios (RR) and differences (RD) for MACE outcomes with cardiac revascularization procedures for intent-to-treat (ITT) and as-treated (AT) analyses (with only ischemic stroke)

Cohort	RR		RD/100	
ITT				
CVD - CHF -	1.03		0.15	
CVD + CHF -	0.94		-0.56	
CVD - CHF +	1.10		0.91	
CVD + CHF +	0.92		-1.39	
AT				
CVD - CHF -	1.18		0.45	
CVD + CHF -	1.11		0.53	
CVD - CHF +	1.04		0.24	
CVD + CHF +	0.86		-1.61	

RR axis: 0.60　0.80　1.0　1.2　1.6

RD/100 axis: -4　-2　-1　0　1　2