Kidney and Cardiovascular Effectiveness of Empagliflozin Compared With Dipeptidyl Peptidase-4 Inhibitors in Patients With Type 2 Diabetes

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Placebo-controlled trials of sodium-glucose co-transporter-2 inhibitors demonstrate kidney and cardiovascular benefits for patients with type 2 diabetes and chronic kidney disease (CKD). We used real-world data to compare the kidney and cardiovascular effectiveness of empagliflozin to dipeptidyl peptidase-4 inhibitors (DPP4is), a commonly prescribed antiglycemic medication, in a diverse population with and without CKD. Using electronic health record data from 20 large US health systems, we leveraged propensity overlap weighting to compare the outcomes for empagliflozin and DPP4i initiators with type 2 diabetes between 2016 and 2020. The primary composite kidney outcome included 40% estimated glomerular filtration rate decrease, incident end-stage kidney disease, or all-cause mortality through 2 years or censoring. We also assessed cardiovascular and safety outcomes. Of 62,197 new users, 20,279 initiated empagliflozin and 41,918 initiated DPP4i. Over a median follow-up of 1.1 years, empagliflozin prescription was associated with a lower risk of the primary outcome (hazard ratio [HR] 0.75, 95% confidence interval [CI] 0.65 to 0.87) than DPP4is. The risks for mortality (HR 0.76, 95% CI 0.62 to 0.92) and a cardiovascular composite of stroke, myocardial infarction, or all-cause mortality (HR 0.81, 95% CI 0.70 to 0.95) were also lower for empagliflozin initiators. No difference in heart failure hospitalization risk between groups was observed. Genital mycotic infections were more common in patients prescribed empagliflozin (HR 1.72, 95% CI 1.58 to 1.88). Empagliflozin was associated with a lower risk of the primary outcome in patients with CKD (HR 0.68, 95% CI 0.53 to 0.88) and those without CKD (HR 0.79, 95% CI 0.67 to 0.94). In conclusion, the initiation of empagliflozin was associated with a significantly lower risk of kidney and cardiovascular outcomes than DPP4is over a median of just over 1 year. The association with a lower risk for clinical outcomes was apparent even for patients without known CKD at baseline. **(Am J Cardiol 2024;221:52−63)**

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Type 2 diabetes mellitus (T2D) increases the risks of kidney and cardiovascular disease.[1−3] Kidney outcomes trials in patients with chronic kidney disease (CKD) demonstrate kidney and cardiovascular benefits for sodium-glucose co-transporter 2 inhibitors (SGLT2is) relative to placebo.[4−8] However, clinical trials have limitations, including the inability to effectiveness in the context of real-world use. Real-world data studies can complement clinical trials and produce generalizable results by including patients, geographical regions, and health care systems with poor representation in clinical trials.[9] Real-world data also allows the examination of active controls. Dipeptidyl peptidase-4 inhibitors (DPP4is) are a commonly prescribed glucose-lowering therapy that have been used as an active control for SGLT2is in real-world data analyses.[10,11] However, the use of real-world data introduces challenges for kidney outcomes. For example, claims-based data sources do not capture sufficient laboratory data to calculate the estimated glomerular filtration rate (eGFR) to identify changes in kidney function and have limited sensitivity to diagnose CKD.[12] The use of electronic health record data overcomes this limitation and allows the assessment of eGFR and other laboratory-based covariates and outcomes. In this study, we analyzed electronic health record−based data from 20 large US health systems participating in the National Patient-Centered Clinical Research Network (PCORnet) to compare the effectiveness of empagliflozin and DPP4is with regards to kidney and cardiovascular outcomes in a population with T2D with and without CKD.

Methods

We collected electronic health record data from 20 US health systems that map clinical data to the PCORnet common data model.[13] The study population included adult (aged ≥18 years) patients with a diagnosis of T2D who were newly prescribed (i.e., no record of prescription in the previous 12 months) empagliflozin or a DPP4i between January 1, 2016 and December 31, 2020. Follow-up data were collected through December 31, 2021. We defined T2D by review of International Classification of Diseases (ICD) codes 9 and 10 in the 12 months before the first prescription of empagliflozin or DPP4i (i.e., the index date) (Supplementary Table 1). We excluded patients without clear engagement in the health system, including <12 months of data available before the index date or an incomplete history of drug dispensations, defined as not having at least 1 ambulatory visit and 1 medication prescription during the 12 months before the index date. Lastly, to avoid contraindications for SGLT2i use during the study period, we excluded patients with a history of type 1 diabetes mellitus, polycystic kidney disease, previous kidney transplant or dialysis requirement, an eGFR <30 ml/min/1.73 m^2, or missing eGFR within the 12 months before the prescription.

The primary exposure was the first prescription for empagliflozin or DPP4is between January 1, 2016 and December 31, 2020 (Supplementary Table 2). The prescriptions for empagliflozin alone or in combination with metformin were included.

The primary outcome was a composite kidney outcome of a sustained 40% decrease in eGFR, incident end-stage kidney disease (ESKD), or all-cause mortality. This composite aligns with the primary outcome for several recent phase 3 kidney outcomes trials.[4−6] A sustained eGFR decrease required 2 eGFR measurements separated by at least 28 days. We defined incident ESKD as kidney transplant, ESKD-related diagnosis or procedure, 2 or more dialysis procedures or diagnoses separated by at least 28 days, or 2 eGFR measurements <15 ml/min/1.73 m^2 separated by at least 28 days. Mortality data were obtained from each site (e.g., in-hospital deaths or deaths recorded from state death registries) and by linking to the Datavant mortality data feed using their privacy-preserving record linkage solution. The Datavant solution contains government (e.g., Social Security Administration Death Master File) and private sources (e.g., private obituary feeds) and is updated on a weekly basis.

We also evaluated cardiovascular and safety outcomes. The cardiovascular outcomes included hospitalization for heart failure, alone or in a composite with all-cause mortality; a composite outcome of myocardial infarction, stroke, or all-cause mortality; and a composite of myocardial infarction, stroke, coronary revascularization, or all-cause mortality. Safety outcomes included diabetic ketoacidosis, severe hypoglycemia (defined as hypoglycemia diagnosis associated with emergency department visit or hospitalization), genital mycotic infection, acute kidney injury requiring hemodialysis, severe urinary tract infection, or urinary tract cancer.

Follow-up began the day after the date of initiation of either empagliflozin or DPP4i (i.e., the index date) and continued until the first occurrence of the outcome of interest, death, study end, 12 months after the last observed prescription, or 2 years after the index date. We limited follow-up to 2 years to prevent any imbalances in the number of prescriptions early in the study period leading to a longer follow-up duration for 1 treatment group. We also censored the follow-up for drug crossover (i.e., patient prescribed empagliflozin started a DPP4i or another SGLT2i or if a DPP4i user started any SGLT2i).

To account for potential confounding, a comprehensive set of covariates chosen a priori were included in propensity score (PS) analyses (Supplementary Table 3). These covariates spanned demographic characteristics, medical history, medication use, co-morbidities, and laboratory results assessed at the index date. Clinical variables included blood pressure, body mass index, and smoking history. We also considered medication usage, including antihypertensives, diuretics, lipid-lowering drugs, and antiplatelet agents, among others. The covariates included co-morbidities, such as prevalent cardiovascular disease, diabetes-related complications, mental health conditions, and genitourinary infections, in addition to the Charlson co-morbidity index and diabetes complications severity index.[14,15] Laboratory results included hemoglobin A1c, creatinine, cholesterol levels, and triglycerides. Lastly, we included various measures of health care use in the 12 months before the index date, such as hospitalizations, emergency department visits, office visits, and the number of select laboratory tests ordered.

Several of the listed covariates were also considered for subgroup analyses. These included age (≤65 versus >65

years), gender, previous cardiovascular event, heart failure hospitalization in the previous 12 months, metformin use, and eGFR as a continuous variable among those with CKD. We defined CKD as eGFR <60 ml/min/1.73 m^2.

We used post-LASSO overlap weighting to ensure balance in covariates between the treatment groups. The post-LASSO overlap method involved creating a LASSO penalized regression model with the covariates of interest, subgroup variables, and all pairwise covariate-subgroup interactions.[16] The outcome for this model was treatment group, where empagliflozin was the treatment group of interest and DPP4is served as the reference. The variables chosen by the LASSO model were refit to a logistic model to calculate the PS estimates. The overlap weights were then created such that the weights were equal to the PS for participants prescribed the reference treatment (DPP4is) and 1 PS for participants prescribed empagliflozin. Modeling was performed separately in those with CKD and those without CKD because the clinical rationale for treatment decisions differed between the 2 groups.

We chose the overlap weighting approach rather than matching to retain more participant data. No trimming was required because the overlap weights were bound between 0 and 1. In addition, using this post-LASSO logistic regression modeling approach, we maintained the covariate balance between the subgroups. We confirmed the success of overlap weighting with respect to covariate balance by calculating absolute standardized mean differences between groups; all differences were <0.1.

Baseline characteristics were presented in the unweighted and weighted populations, overall, by treatment group, and by CKD status. Continuous covariates are presented as mean and median (twenty-fifth percentile, seventy-fifth percentile). Categorical covariates are listed as frequencies.

Weighted incidence rates were computed as the number of first events per 1,000 person-years of follow-up. The time to first event was estimated using weighted Cox proportional hazards models. Cause-specific proportional hazards models were used for outcomes where death served as a competing risk, with follow-up censored at the time of death. Because of the potential for glucagon-like peptide-1 receptor agonist (GLP1RA) association with cardiorenal outcomes,[17] we included GLP1RA initiation during the study period in the Cox models as a time-dependent variable. Hazard ratios (HRs) comparing empagliflozin with DPP4is, along with their 95% confidence intervals (CIs) and associated p values, were presented for all outcomes. We confirmed the proportional hazards assumption using weighted Schoenfeld residuals. Kaplan−Meier curves were created for the primary composite outcome in the overall and CKD subgroups. Analyses were performed in the overall cohort and within the CKD stage subgroups.

Several sensitivity analyses were performed. First, we repeated the primary comparison between empagliflozin and DPP4is using PS nearest-neighbor matching (1:1) instead of overlap weighting. In addition, we repeated the comparison of the primary outcome using an intention-to-treat approach whereby participants were not censored after last prescription of empagliflozin or DPP4i. We also applied a more stringent definition for the as-treated analysis by restricting censoring because of discontinuation at 6 months instead of 12 months after their last prescription of empagliflozin or DPP4is. Finally, we excluded data from March 2020 until the end of the study to evaluate the potential impact of COVID-19 on the analyses.

Results

A total of 62,197 people were included in the weighted study cohort (Figure 1). Table 1 lists the baseline characteristics of the study cohort before and after PS weighting. The median age of the unweighted cohort was 62.0 years (interquartile range [IQR] [twenty-fifth to seventy-fifth percentile] 53.0 to 70.0 years). Persons of the Black race comprised 22.2% of the cohort, and women comprised 50% of the cohort. The median eGFR of the unweighted cohort was 78.4 ml/min/1.73 m^2 (IQR 61.1, 93.9 ml/min/1.73 m^2), and CKD was present in 23.7% (14,759 of 62,197) of the cohort (Supplementary Table 4). The median hemoglobin A1c was 8.0% (IQR 7.1% to 9.1%).

Empagliflozin prescription was more common later in the study period, whereas DPP4i prescription slightly decreased over the study period. Empagliflozin initiators were younger (median age 60.0 vs 63.0 years for DPP4i initiators), with higher eGFR (median eGFR 81.2 ml/min/1.73 m^2 vs 76.9 ml/min/1.73 m^2 for DPP4i initiators) and more GLP1RA use (20.1% at the time of empagliflozin initiation vs 4.1% for DPP4i initiators). The standardized mean differences for all covariates decreased to <0.1 for the weighted cohort.

The prescribing information for empagliflozin and DPP4i initiators were overall similar between groups (Supplementary Table 5). For example, 40% of empagliflozin and DPP4i initiators received only 1 prescription, and 23% of empagliflozin initiators and 26% of DPP4i initiators received 4 or more prescriptions. The mean time between the first and last prescription for index drug was 228 days (SD 249 days) for empagliflozin and 220 days (SD 257 days) for DPP4i initiators.

The median follow-up time was 1.08 years (IQR 1.08 to 1.87 years). The primary composite kidney outcome of 40% decrease in eGFR, incident ESKD, or mortality occurred in 3,377 patients (5.4%). Empagliflozin initiators were significantly less likely to experience the primary outcome than DPP4i initiators (HR 0.75, 95% CI 0.65 to 0.86) (Figure 2, Table 2). Of the individual components of the composite primary outcome, empagliflozin initiation was associated with a lower risk of 40% eGFR decrease (HR 0.74, 95% CI 0.60 to 0.91) and all-cause mortality (HR 0.75, 95% CI 0.62 to 0.92). The difference in risk for incident ESKD did not reach statistical significance (HR 0.68, 95% CI 0.46 to 1.00).

When we restricted the cohort to only patients with CKD (n = 14,759), empagliflozin initiators (n = 3,633), again, experienced a significantly lower risk of the primary outcome (HR 0.67, 95% CI 0.52 to 0.86) (Table 3) than DPP4i initiators (n = 11,126). Within the CKD cohort, eGFR at index did not modify the association with the primary outcome (p value for interaction = 0.80). Notably, the treatment effect on the primary outcome also remained significant in the non-CKD cohort (HR 0.79, 95% CI 0.67

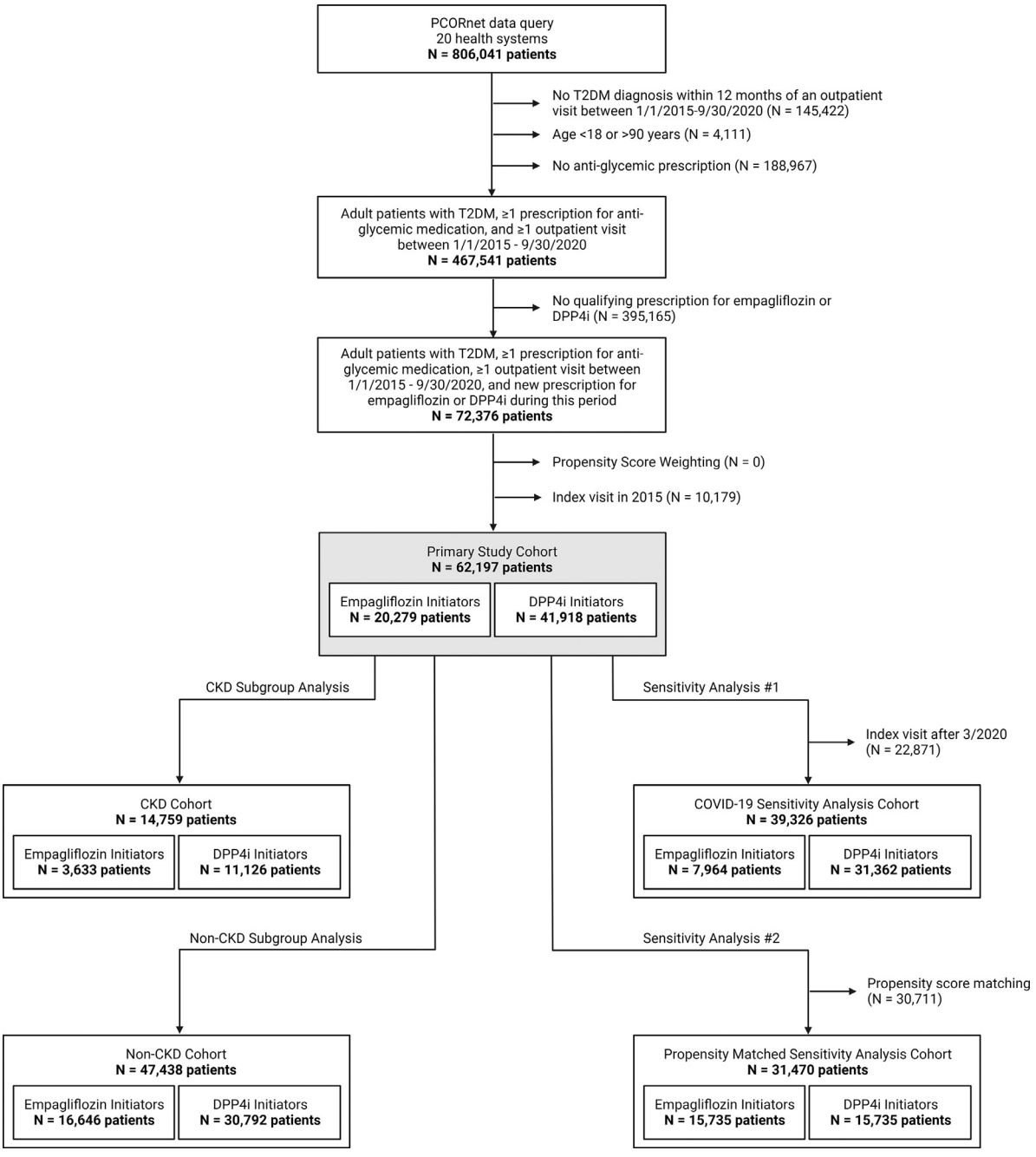

Figure 1. Consort diagram for the primary study cohort, target subgroups, and sensitivity analyses.

to 0.94) (Table 3). In the prespecified subgroup analyses, the relation between the index treatment group and the primary outcome did not differ by age, gender, previous cardiovascular event, recent hospitalization, or metformin use (Figure 3).

The treatment effect on the primary outcome remained significant across a myriad of sensitivity analyses, including propensity matching (n= 31,470, HR 0.75, 95% CI 0.67 to 0.84) (Supplementary Table 6), intention-to-treat analysis (HR 0.78, 95% CI 0.69 to 0.88) (Table 2), stringent discontinuation censoring (HR 0.68, 95% CI 0.57 to 0.80) (Table 2), and the COVID-19 sensitivity analysis (n = 39,326, HR 0.70, 95% CI 0.57 to 0.87) (Supplementary Table 7).

Empagliflozin initiation was associated with a significantly lower risk of a composite cardiovascular outcome consisting of myocardial infarction, stroke, and all-cause death (HR 0.81, 95% CI 0.70 to 0.94) (Table 2). However, the difference in risk was not significant when coronary revascularization was added to the composite (HR 1.03, 95% CI 0.95 to 1.12). The risk for neither a composite of heart failure hospitalization and all-cause mortality (HR 0.90, 95% CI 0.80 to 1.02) or heart failure hospitalization alone (HR 0.96, 95% CI 0.84 to 1.11) differed between the

Table 1
Select baseline characteristics of the study cohort before and after propensity weighting

Characteristic	Unweighted				Weighted		
	Overall (N=62,197)	Empa Initiators(N=20,279)	DPP4i Initiators (N=41,918)	AbsoluteSMD	Empa Initiators (N=20,279)	DPP4i Initiators (N=41,918)	AbsoluteSMD
Demographics							
Age (yrs)	62.0 [53.0, 70.0]	60.0 [52.0, 67.0]	63.0 [54.0, 72.0]	0.284	61.0 [52.0 - 68.0]	61.0 [52.0 - 69.0]	0.000
Female sex	50.7%	47.1%	52.5%	0.108	49.6%	49.6%	0.000
Race				0.086			0.000
White	71.6%	74.0%	70.4%		72.3%	72.3%	
Black	22.2%	20.7%	23.0%		21.7%	21.7%	
Other*	6.2%	5.2%	6.6%		6.0%	6.0%	
Hispanic ethnicity	8.8%	7.9%	9.3%	0.048	8.8%	8.8%	0.001
Current smoker	9.5%	9.8%	9.3%	0.017	9.8%	9.8%	0.002
Medical History							
Hypertension	78.2%	78.5%	78.0%	0.011	77.0%	77.0%	0.000
Hyperlipidemia	72.3%	74.1%	71.5%	0.059	71.9%	71.9%	0.000
Heart failure	10.6%	12.0%	9.9%	0.067	9.8%	9.8%	0.000
Myocardial infarction	5.1%	5.9%	4.6%	0.056	4.7%	4.7%	0.000
Coronary artery disease	22.3%	24.7%	21.1%	0.086	21.5%	21.5%	0.000
Ischemic stroke	2.8%	2.5%	3.0%	0.029	2.4%	2.4%	0.000
Hemorrhagic stroke	0.3%	0.2%	0.3%	0.031	0.2%	0.3%	0.024
TIA	1.4%	1.3%	1.5%	0.023	1.3%	1.3%	0.000
Atrial fibrillation	8.7%	7.9%	9.0%	0.040	7.5%	7.5%	0.000
Chronic kidney disease	23.7%	17.9%	26.5%	0.209	19.6%	19.6%	0.000
Acute kidney injury	4.6%	3.8%	5.0%	0.062	3.6%	3.6%	0.000
Urinary tract infections	8.2%	5.7%	9.4%	0.137	6.9%	6.9%	0.000
COPD	9.1%	8.7%	9.3%	0.022	8.4%	8.4%	0.000
Pulmonary hypertension	2.0%	2.3%	1.9%	0.034	1.9%	1.9%	0.000
Osteoarthritis	19.8%	18.6%	20.3%	0.045	18.6%	18.9%	0.007
Dorsopathies	24.8%	24.7%	24.9%	0.004	24.7%	24.7%	0.000
Falls	1.8%	1.5%	2.0%	0.043	1.5%	1.5%	0.000
Osteoporosis	3.9%	2.9%	4.4%	0.082	3.1%	3.1%	0.000
Dementia	2.1%	0.9%	2.6%	0.135	1.0%	1.7%	0.067
Coronary revascularization	9.5%	10.8%	8.8%	0.067	8.7%	8.7%	0.000
PAD	9.3%	8.6%	9.7%	0.037	8.3%	8.3%	0.000
Liver disease	11.3%	12.2%	10.8%	0.046	11.7%	11.7%	0.000
Fractures	1.6%	1.3%	1.7%	0.038	1.3%	1.3%	0.000
Overweight	19.8%	16.4%	21.5%	0.130	18.2%	18.3%	0.003
Obesity	58.3%	63.8%	55.6%	0.168	61.7%	60.4%	0.028
Charlson comorbidity index	4.0 [3.0, 6.0]	4.0 [2.0, 6.0]	4.0 [3.0, 6.0]	0.160	4.0 [2.0 - 6.0]	4.0 [2.0 - 6.0]	0.000
Diabetes complication severity index	1.0 [0.0, 2.0]	1.0 [0.0, 2.0]	1.0 [0.0, 2.0]	0.009	1.0 [0.0 - 2.0]	1.0 [0.0 - 2.0]	0.001
Diabetes Complications							
Diabetic kidney disease	13.9%	14.3%	13.8%	0.014	13.0%	13.0%	0.000
Diabetic retinopathy	5.5%	6.9%	4.9%	0.085	5.4%	5.4%	0.000
Diabetic neuropathy	18.2%	20.4%	17.1%	0.084	17.8%	17.8%	0.000
Diabetes with peripheral circulatory disorders	8.0%	9.1%	7.4%	0.059	8.1%	8.1%	0.000

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Table 1 (***Continued***)

Characteristic	Unweighted				Weighted		
	Overall (N=62,197)	Empa Initiators(N=20,279)	DPP4i Initiators (N=41,918)	AbsoluteSMD	Empa Initiators (N=20,279)	DPP4i Initiators (N=41,918)	AbsoluteSMD
Diabetic foot/foot ulcer	2.3%	2.6%	2.2%	0.027	2.2%	2.2%	0.000
Diabetic ketoacidosis	0.7%	0.7%	0.6%	0.015	0.7%	0.6%	0.018
HHNS	1.2%	1.3%	1.1%	0.012	1.2%	1.2%	0.000
Lower extremity amputation	0.5%	0.5%	0.4%	0.010	0.4%	0.5%	0.004
Vitals/Labs							
Systolic BP (mmHg)	129.0 [120.0, 140.0]	129.0 [120.0, 139.0]	129.0 [120.0, 140.0]	0.006	129.0 [120.0 - 139.0]	129.0 [120.0 - 139.0]	0.000
Diastolic BP (mmHg)	76.0 [68.0, 82.0]	76.0 [70.0, 82.0]	75.5 [68.0, 82.0]	0.094	76.0 [70.0 - 82.0]	76.0 [70.0 - 82.0]	0.000
BMI (kg/m^2)	33.0 [28.7, 38.2]	34.2 [30.0, 39.5]	32.3 [28.1, 37.6]	0.022	33.7 [29.5 - 38.8]	33.5 [29.0 - 39.0]	0.018
Serum creatinine (mg/dL)	0.9 [0.8, 1.1]	0.9 [0.8, 1.1]	0.9 [0.8, 1.1]	0.114	0.9 [0.8 - 1.1]	0.9 [0.8 - 1.1]	0.003
eGFR (ml/min/1.73 m^2)	78.4 [61.1, 93.9]	81.2 [65.5, 95.6]	76.9 [58.8, 93.0]	0.207	80.6 [64.6 - 95.2]	80.4 [64.3 - 95.5]	0.001
BUN (mg/dL)	16.0 [12.0, 20.0]	16.0 [12.0, 20.0]	16.0 [12.0, 20.0]	0.080	15.0 [12.0 - 20.0]	15.0 [12.0 - 20.0]	0.003
HbA1c (%)	8.0 [7.1, 9.1]	8.1 [7.3, 9.3]	7.9 [7.0, 9.0]	0.119	8.1 [7.2 - 9.2]	8.0 [7.2 - 9.3]	0.000
Total Cholesterol (mg/dL)	159.0 [134.0, 190.0]	158.0 [132.0, 189.0]	160.0 [136.0, 191.0]	0.054	160.0 [135.0 - 191.0]	160.0 [135.0 - 191.0]	0.002
LDL (mg/dL)	82.4 [62.6, 107.0]	81.0 [61.0, 106.0]	83.0 [63.4, 108.0]	0.064	83.0 [62.0 - 107.8]	82.6 [62.6 - 108.0]	-0.000
HDL (mg/dL)	43.0 [36.0, 54.0]	42.0 [35.0, 51.0]	44.0 [36.0, 56.0]	0.248	43.0 [35.0 - 52.0]	43.0 [35.0 - 52.0]	0.001
Triglycerides (mg/dL)	149.0 [105.0, 217.0]	155.0 [107.0, 227.0]	146.0 [103.0, 212.0]	0.096	152.0 [106.0 - 223.0]	152.0 [107.0 - 223.0]	0.012
Medications							
ACEi or ARBs	50.1%	52.2%	49.0%	0.062	50.3%	50.3%	0.000
Beta blockers	30.5%	31.2%	30.1%	0.023	29.3%	29.3%	0.000
Calcium-channel blockers	22.4%	21.7%	22.7%	0.025	21.6%	21.6%	0.000
Thiazide diuretics	22.1%	21.8%	22.2%	0.009	22.0%	22.0%	0.000
Loop diuretics	13.5%	14.2%	13.2%	0.028	12.3%	12.3%	0.000
Antiplatelet agents	22.2%	22.8%	21.9%	0.022	21.2%	21.2%	0.000
Oral anticoagulants	7.4%	7.2%	7.6%	0.013	6.9%	6.9%	0.000
Heparin and other low-molecular weight heparins	15.4%	14.9%	15.7%	0.021	13.9%	13.9%	0.000
NSAIDs	37.1%	37.5%	36.8%	0.014	36.3%	37.3%	0.021
Bisphosphonates	1.3%	1.0%	1.5%	0.044	1.1%	1.1%	0.000
ARNi	0.7%	1.4%	0.3%	0.119	0.9%	0.5%	0.053
Statins	52.5%	55.4%	51.1%	0.086	53.2%	53.2%	0.000
sMRAs	4.6%	6.0%	3.9%	0.101	4.5%	4.5%	0.000
Diabetes Medications							
Insulin	30.5%	37.6%	27.1%	0.226	30.8%	30.8%	0.000
Metformin	52.9%	56.6%	51.2%	0.108	55.8%	55.8%	0.000
Sulfonylureas	25.8%	22.9%	27.2%	0.100	24.7%	24.7%	0.000
Glitazones	3.0%	3.2%	2.9%	0.021	3.0%	3.0%	0.000
GLP1RA	9.3%	20.1%	4.1%	0.506	9.8%	9.8%	0.000
Monotherapy	40.6%	38.7%	41.5%	0.058	41.6%	41.8%	0.004
Healthcare Utilization							
Hospitalization within prior 30 days	7.9%	4.8%	9.4%	0.183	5.5%	5.5%	0.000
Hospitalization during prior 31-365 days	12.9%	13.9%	12.5%	0.044	12.5%	12.5%	0.000
N hospitalizations during prior 365 days	0.4, 0.0 [0.0, 0.0]	0.4, 0.0 [0.0, 0.0]	0.4, 0.0 [0.0, 0.0]	0.015	0.3, 0.0 [0.0 - 0.0]	0.3, 0.0 [0.0 - 0.0]	0.000
N hospital days during prior 365 days	1.5, 0.0 [0.0, 0.0]	1.1, 0.0 [0.0, 0.0]	1.7, 0.0 [0.0, 0.0]	0.103	1.1, 0.0 [0.0 - 0.0]	1.1, 0.0 [0.0 - 0.0]	0.000
N emergency department visits during prior 365 days	0.4, 0.0 [0.0, 0.0]	0.4, 0.0 [0.0, 0.0]	0.5, 0.0 [0.0, 0.0]	0.009	0.4, 0.0 [0.0 - 0.0]	0.4, 0.0 [0.0 - 0.0]	0.000

(*continued on next page*)

Table 1 (*Continued*)

Characteristic	Unweighted				Weighted		
	Overall (N=62,197)	Empa Initiators(N=20,279)	DPP4i Initiators (N=41,918)	AbsoluteSMD	Empa Initiators (N=20,279)	DPP4i Initiators (N=41,918)	AbsoluteSMD
N ambulatory visits during prior 365 days	16.8, 11.0 [6.0, 21.0]	17.0, 12.0 [6.0, 21.0]	16.7, 11.0 [6.0, 21.0]	0.016	16.5, 11.0 [6.0 - 21.0]	16.5, 11.0 [6.0 - 20.0]	0.000
Electrocardiogram during prior 365 days	33.4%	33.1%	33.6%	0.010	31.2%	32.0%	0.018
N distinct medication prescriptions	38.9, 17.0 [8.0, 39.0]	37.7, 18.0 [8.0, 39.0]	39.4, 17.0 [8.0, 38.0]	0.021	35.8, 16.0 [8.0 - 36.0]	37.0, 17.0 [8.0 - 38.0]	0.017
N serum creatinine measurements during prior 365 days	4.0, 2.0 [1.0, 4.0]	3.6, 2.0 [1.0, 4.0]	4.2, 2.0 [1.0, 4.0]	0.082	3.6, 2.0 [1.0 - 4.0]	3.6, 2.0 [1.0 - 4.0]	0.000
N HbA1c measurements during prior 365 days	1.6, 1.0 [1.0, 2.0]	1.7, 2.0 [1.0, 2.0]	1.6, 1.0 [1.0, 2.0]	0.080	1.6, 1.0 [1.0 - 2.0]	1.6, 1.0 [1.0 - 2.0]	0.000

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; ARNi = angiotensin receptor-neprilysin inhibitor; BMI = body mass index; BP = blood pressure; COPD = chronic obstructive pulmonary disease; DPP4i = dipeptidyl-peptidase 4 inhibitor; eGFR = estimated glomerular filtration rate; Empa = empagliflozin; GLP1RA = glucagon-like peptide 1 receptor agonist; HbA1c = glycated hemoglobin; HDL = high-density lipoprotein; HHNS = hyperosmolar hyperglycemic nonketotic syndrome; LDL = low-density lipoprotein; N = number; NSAIDs = nonsteroidal anti-inflammatory drugs; PAD = peripheral artery disease; SMD = standard mean difference; sMRA = selective mineralocorticoid receptor antagonist; TIA = transient ischemic attack; UACR = urine albumin : creatinine ratio.

* Includes people of Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, or other race.

Continuous covariates presented as median [interquartile range] or mean, median [interquartile range].

treatment groups. When we restricted to codes for acute heart failure hospitalization in a post hoc analysis, the risk of the composite of all-cause mortality or heart failure hospitalization was significantly lower for empagliflozin initiators (HR 0.84, 95% CI 0.72 to 0.97), although the individual heart failure outcome did not reach significance (HR 0.90, 95% CI 0.72 to 1.11). These trends were similar, regardless of CKD status (Table 3) and across the sensitivity analyses.

The risk for severe hypoglycemia did not differ by treatment group (HR 0.90, 95% CI 0.71 to 1.16) (Table 2). Diabetic ketoacidosis was nominally more common in empagliflozin initiators, although this difference did not reach statistical significance (HR 1.37, 95% CI 0.89 to 2.10). Acute kidney injury requiring dialysis was also similar between empagliflozin and DPP4i initiators (HR 0.84, 95% CI 0.43 to 1.66). Genital mycotic infections were significantly more common in empagliflozin initiators (incidence of 115.96 per 1,000 person-years, HR 1.72, 95% CI 1.58 to 1.88), although the incidence was also high for DPP4i initiators (65.32 per 1,000 person-years). Severe urinary tract infections did not differ between groups (HR 0.68, 95% CI 0.29 to 1.62). The differences in risk for these safety outcomes remained consistent across the sensitivity analyses.

Discussion

In this study of a large, nationally representative cohort of people with T2D with and without CKD, empagliflozin initiation was significantly associated with superior kidney outcomes compared with the initiation of DPP4i over a median follow-up of 1.1 years. In addition, empagliflozin initiation was associated with a lower risk for mortality and lower incidence of a cardiovascular composite outcome of myocardial infarction, stroke, and all-cause mortality. This real-world evidence supports empagliflozin's kidney, cardiovascular, and mortality benefits compared with common alternative glucose-lowering therapy in T2D, regardless of the presence of CKD.

Randomized, placebo-controlled trials have established the clinical benefits of SGLT2i across a myriad of study populations.[4–8,18,19] However, these landmark trials are often tailored to establish efficacy in a target population and may lead to clinically relevant limitations, such as poor generalizability. For example, the racial composition of many clinical trials often does not mirror the general population, especially for people of Black race, who comprised only 4% to 5% of the study population for the landmark trials of SGLT2is in CKD. In addition, active controls provide clinically relevant comparisons. DPP4is are a commonly used glucose-lowering therapy, which may have pleiotropic benefits that extend beyond changes in hemoglobin A1c,[20] including putative actions that may mitigate podocyte injury.[21] In a comparative effectiveness study, DPP4i initiation was associated with a 10% lower risk of a composite kidney outcome than sulfonylureas.[22] Because of the relatively slow rate of CKD progression, clinical trials powered to detect kidney outcomes typically make the resource-conscious decision to focus on patients with proteinuric CKD, although the Empagliflozin in Patients with Chronic Kidney Disease trial (EMPA-KIDNEY) enrolled

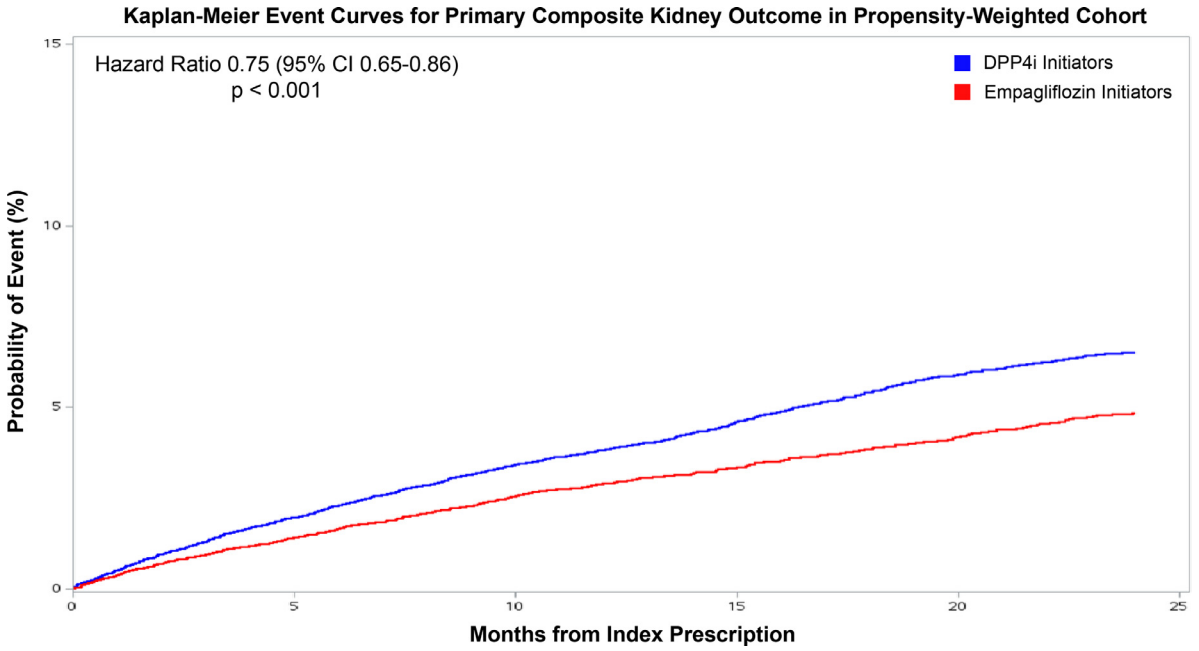

Figure 2. Kaplan−Meier event curve for the primary kidney composite outcome. Number of patients at risk not listed because propensity weighting was applied to compare the treatment cohorts. Rx = prescription.

Table 2
Effectiveness of empagliflozin compared to DPP4i on kidney, cardiovascular, and safety outcomes in the propensity score overlap-weighted cohort

Outcome	Empagliflozin Incidence Rate* (Event/1000 patient-years)	DPP4i Incidence Rate(Event/1000 patient-years)	Hazard Ratio(95% CI)	P-value
Primary Outcome				
40% eGFR decline, incident ESKD, or all-cause death	26.65	36.65	0.75 (0.65 - 0.86)	<0.001
Sensitivity Analyses of the Primary Outcome				
ITT approach	28.30	37.01	0.78 (0.69 - 0.88)	<0.001
Discontinuation censoring at 6 months	23.56	35.60	0.68 (0.57 - 0.80)	<0.001
Secondary Kidney and Outcomes				
40% decline in eGFR	12.10	16.55	0.74 (0.60 - 0.91)	0.005
Incident ESKD	3.34	4.90	0.68 (0.46 - 1.00)	0.05
Incident Dialysis	3.47	4.76	0.73 (0.49 - 1.08)	0.11
Kidney transplant	0.02	0.06	–	–
Secondary Mortality and CV Outcomes				
All-cause death	13.47	18.60	0.75 (0.62 - 0.92)	0.005
HF hospitalization or all-cause death	41.45	46.55	0.90 (0.80 - 1.02)	0.10
HF hospitalization	30.93	32.36	0.96 (0.84 - 1.11)	0.61
Acute HF hospitalization or all-cause death†	24.65	30.24	0.84 (0.72 - 0.97)	0.02
Acute HF hospitalization†	12.74	14.40	0.90 (0.72 - 1.11)	0.32
MACE‡	23.93	30.27	0.81 (0.70 - 0.94)	0.007
MACE or revascularization§	97.31	96.36	1.03 (0.95 - 1.12)	0.46
Safety Outcomes				
Diabetic ketoacidosis	4.06	2.86	1.37 (0.89 - 2.10)	0.15
Severe hypoglycemia	9.43	10.69	0.90 (0.71 - 1.16)	0.43
Urinary tract cancer	4.65	5.14	0.93 (0.65 - 1.33)	0.69
Severe UTI	0.69	1.01	0.68 (0.29 - 1.62)	0.39
AKI requiring dialysis	1.23	1.45	0.84 (0.43 - 1.66)	0.62
Genital mycotic infection	115.96	65.32	1.72 (1.58 - 1.88)	<0.001

AKI = acute kidney injury; CI = confidence interval; CV = cardiovascular; DPP4i = dipeptidyl peptidase-4 inhibitors; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HF = heart failure; ITT = intention to treat; MACE = major adverse cardiovascular event; UTI = urinary tract infection.

* Incidence rate reflects per 1,000 person-years.

† Post hoc analysis.

‡ MACE outcome includes stroke, myocardial infarction, or all-cause death.

§ Coronary revascularization procedure.

Table 3
Effectiveness of empagliflozin compared to DPP4i on kidney, cardiovascular, and safety outcomes in the propensity score overlap-weighted cohort stratified by CKD status

Outcome	CKD (N = 14,759)			No CKD (N = 47,438)		
	Empagliflozin Incidence Rate*	DPP4i Incidence Rate	Hazard Ratio (95% CI) P-value	Empagliflozin Incidence Ratea	DPP4i Incidence Rate	Hazard Ratio (95% CI) P-value
Primary Outcome						
40% eGFR decline, incident ESKD, or all-cause death	44.15	67.36	0.67 (0.52 - 0.86) 0.001	22.62	29.33	0.79 (0.67 - 0.94) 0.008
Sensitivity Analyses of the Primary Outcome						
ITT approach	50.84	67.30	0.78 (0.63 - 0.95) 0.01	23.04	30.02	0.78 (0.67 - 0.90) <0.001
Discontinuation censoring at 6 months	41.57	67.82	0.62 (0.46 - 0.83) 0.001	19.56	28.00	0.71 (0.58 - 0.88) 0.001
Secondary Kidney and Outcomes						
40% decline in eGFR	16.46	27.39	0.61 (0.41 - 0.91) 0.02	11.10	13.95	0.80 (0.63 - 1.03) 0.08
Incident ESKD	8.18	12.96	0.61 (0.35 - 1.09) 0.09	2.23	2.97	0.75 (0.43 - 1.29) 0.30
Incident Dialysis	7.86	12.03	0.63 (0.35 - 1.12) 0.12	2.46	3.01	0.84 (0.50 - 1.42) 0.52
Kidney transplant	0.10	0.10	–	0.00	0.05	–
Secondary Mortality and CV Outcomes						
All-cause death	23.75	35.56	0.69 (0.49 - 0.96) 0.03	11.09	14.49	0.80 (0.63 - 1.02) 0.07
Acute HF hospitalization or all-cause death	50.05	61.34	0.82 (0.65 - 1.05) 0.12	18.86	22.83	0.85 (0.70 - 1.03) 0.10
Acute HF hospitalization	29.47	33.08	0.90 (0.65 - 1.24) 0.50	8.92	9.95	0.91 (0.68 - 1.20) 0.50
MACE†	40.65	55.67	0.74 (0.57 - 0.97) 0.03	20.07	24.18	0.85 (0.71 - 1.03) 0.10
MACE or revascularization‡	169.32	164.13	1.04 (0.90 - 1.20) 0.63	81.63	80.89	1.03 (0.94 - 1.14) 0.52
Safety Outcomes						
Diabetic ketoacidosis	3.59	3.46	1.05 (0.40 - 2.72) 0.93	4.17	2.71	1.47 (0.91 - 2.38) 0.113
Severe hypoglycemia	14.90	18.89	0.80 (0.51 - 1.24) 0.32	8.17	8.72	0.96 (0.71 - 1.30) 0.81
Urinary tract cancer	8.62	9.35	0.93 (0.51 - 1.70) 0.82	3.74	4.13	0.93 (0.60 - 1.45) 0.76
Severe UTI	0.90	2.00	0.46 (0.09 - 2.27) 0.34	0.64	0.77	0.82 (0.29 - 2.33) 0.72
AKI requiring dialysis	2.53	4.02	0.59 (0.21 - 1.64) 0.31	0.93	0.83	1.16 (0.46 - 2.92) 0.76
Genital mycotic infection	99.20	52.23	1.84 (1.48 - 2.30) <0.001	119.94	68.52	1.70 (1.54 - 1.87) <0.001

AKI = acute kidney injury; CI = confidence interval; CV = cardiovascular; DPP4i = dipeptidyl peptidase-4 inhibitors; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HF = heart failure; ITT = intention to treat; MACE = major adverse cardiovascular event; UTI = urinary tract infection.

* Incidence rate reflects 1,000 person-years.

† MACE outcome includes stroke, myocardial infarction, or all-cause death.

‡ Coronary revascularization procedure.

patients with less albuminuria, provided that the CKD was sufficiently severe based on the eGFR.[6] In the present investigation, we aimed to compare the effectiveness of empagliflozin with a commonly used antiglycemic treatment in a real-world, representative population of patients with T2D with and without CKD.

In our study, empagliflozin initiation was associated with a 25% lower risk of a composite kidney outcome. This effect size aligns with SGLT2i versus DPP4i comparisons in Veterans Affairs (36%) and UK (24%) clinical populations focused on a comparable kidney composite outcome.[22,23] Our study differs from these previous studies in a few key ways. We partnered with 20 health systems across the United States that contribute electronic health record data into PCORnet to create a large and diverse study population. Previous cohorts consisted almost exclusively of men (i.e., Veterans Affairs data) or contained fewer than 5% of patients who identify as being Black.[22–25] In addition, we demonstrated kidney and other clinical benefits over a shorter time frame. The median follow-up of 1.1 years is approximately

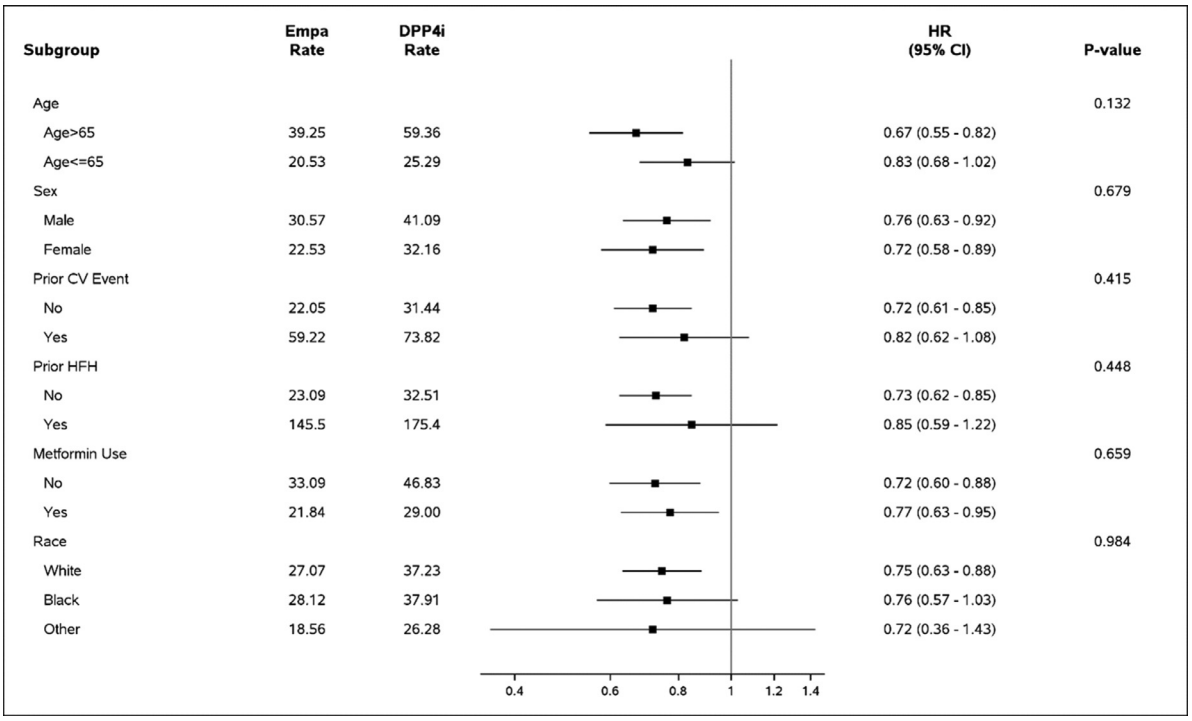

Figure 3. Subgroup analysis for primary kidney composite outcome. Bars represent 95% confidence interval. Heart failure hospitalization denotes hospitalization within 12 months of the study index date. CV = cardiovascular; HFH = heart failure hospitalization.

half of the duration of kidney outcomes trials. Furthermore, we demonstrated a significant clinical benefit for empagliflozin initiation in the non-CKD cohort.

In addition to a much larger sample size, analysis of real-world data, and inclusion of patients without CKD, our study cohort differs from these clinical trial populations in a few potentially meaningful ways that could explain some of the early evidence of kidney benefit. Compared with participants in the EMPA-KIDNEY trial,[6] the present study population contains more patients of the Black race (22% vs 4%) and fewer persons of the Asian race (<6% vs 36%). In addition, our study cohort was more obese (median body mass index 33 kg/m^2 vs mean 29.9 kg/m^2) and less likely to receive renin-angiotensin-aldosterone system inhibitors (50% vs 85%).

Similar to previous interventional and real-world studies,[10,11,26] we also assessed the comparative cardiovascular effectiveness of empagliflozin and DPP4is. Empagliflozin was associated with a significant 19% lower risk of a composite cardiovascular outcome of myocardial infarction, stroke, and all-cause mortality relative to initiation of DPP4i. This finding aligns with the associations demonstrated in other comparative effectiveness studies focused on major adverse cardiovascular events.[27,28] However, the difference in risk for heart failure hospitalization between initiators of empagliflozin and DPP4is did not reach significance in our study. The risk difference was nominally similar between the CKD and non-CKD cohorts. This lack of a significant difference in heart failure outcomes differs from previous studies that report a difference ranging from 14% to 57%.[10,27–33] A few factors may contribute to this discrepancy. First, our study cohort had a short median follow-up. In addition, the heart failure outcome definition (i.e., ICD code selection) differed across select studies. The incidence rate of heart failure hospitalization also varied significantly, which could reflect different outcome definitions or population risks. Lastly, our composite of acute heart failure hospitalization and all-cause mortality mirrored the difference reported between empagliflozin and placebo in the EMPA-KIDNEY trial.[6] In summary, empagliflozin was associated with significant reductions in some but not all cardiovascular events in our study. This finding differs from other cohorts for select outcomes, such as heart failure hospitalization, and likely highlights the limitations in the unadjudicated outcome definitions and variability in population risks for this outcome.

Safety outcomes reflected the risk profile of empagliflozin and other SGLT2is demonstrated in placebo-controlled trials.[4–8,18,19] Most notably, empagliflozin initiation was associated with a significantly higher risk of genital mycotic infection than DPP4is. Although SGLT2 inhibitors increase the risk of diabetic ketoacidosis compared with placebo,[34] the numerically higher incidence of diabetic ketoacidosis for empagliflozin initiators in our study cohort did not reach statistical significance. Other safety outcomes, such as severe hypoglycemia, urinary tract cancer, severe urinary tract infection, or acute kidney injury requiring dialysis, did not differ between the groups. Importantly, because we analyzed prescriptions rather than confirmed use of empagliflozin or DPP4is, the magnitude of these differences in safety outcomes is likely biased toward the null and should be interpreted with this caveat.

We acknowledge limitations of the study design. Despite PS weighting based on an extensive list of covariates assessed at treatment initiation, residual confounding may remain between the comparator groups. Because prescription was used as the indicator for treatment exposure, we

could not assess medication fills or adherence. However, we applied various sensitivity analyses that provided a wide range of stringency concerning medication discontinuation censoring. Patients may receive select care outside of the contributing health system; however, we minimized this risk by requiring a provider visit and medication prescription in the 12 months before the index date. We also circumvented this limitation for mortality through linkage with the Datavant death index. We applied a clinical trial definition to assess sustained eGFR decrease. Without standardized intervals of creatinine measurement, this can introduce bias between the comparator groups. However, we did not observe a substantial difference in this kidney outcome when we removed the requirement for a repeat creatinine measurement to confirm the eGFR decrease. We also could not define CKD by albuminuria. ICD code−based definitions for outcomes may differ between studies and not perform as well as adjudicated outcomes. Lastly, we focused on empagliflozin; however, we expect these findings to apply to other SGLT2is.

In summary, in a representative US-based cohort with T2D, the initiation of empagliflozin was significantly associated with superior kidney outcomes after a median of just over 1 year compared with the initiation of DPP4is, regardless of the presence of CKD. In addition, empagliflozin initiation was associated with reduced mortality and a lower incidence of a cardiovascular composite outcome of myocardial infarction, stroke, and all-cause mortality. Finally, the risk for examined safety outcomes was consistent with the known safety profile of empagliflozin.

Declaration of competing interest

Boehringer Ingelheim was given the opportunity to review the manuscript for medical and scientific accuracy as well as intellectual property considerations. Dr. Butler reports consultant honoraria from Abbott, American Regent, Amgen, Applied Therapeutic, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardiac Dimension, Cardior, CVRx, cytokinetics, Edwards, Element Science, Innolife, Impulse Dynamics, Imbria, Inventiva, Lexicon, Eli Lilly, LivaNova, Janssen, Medtronics, Merck, Occlutech, Novartis, Novo Nordisk, Pfizer, Pharmacosmos, Pharmain, Roche, Sequana, SQ Innovation, and Vifor. Dr. Pagidipati reports research support from Alnylam, Amgen, Boehringer Ingelheim, Eggland's Best, Eli Lilly, Novartis, Novo Nordisk, and Verily Life Sciences; consultation/advisory panels for Bayer, Boehringer Ingelheim, CRISPR Therapeutics, Eli Lilly, Esperion, AstraZeneca, Merck, Novartis, and Novo Nordisk; executive committee member for trials sponsored by Novo Nordisk and Amgen; data safety monitor board for trials sponsored by Johnson and Johnson and Novartis; medical advisory board for Miga Health. The remaining authors have no competing interests to declare.

CRediT authorship contribution statement

Daniel Edmonston: Writing − original draft, Conceptualization. **Hillary Mulder:** Writing − review & editing, Formal analysis, Conceptualization. **Elizabeth Lydon:** Writing − review & editing, Formal analysis, Conceptualization. **Karen Chiswell:** Writing − review & editing, Supervision, Formal analysis, Conceptualization. **Zachary Lampron:** Writing − review & editing, Project administration. **Christina Shay:** Conceptualization, Project administration. **Keith Marsolo:** Conceptualization, Data curation, Writing − review & editing. **William Schuyler Jones:** Conceptualization, Data curation, Writing − review & editing. **Javed Butler:** Data curation, Writing − review & editing. **Raj C. Shah:** Data curation, Writing − review & editing. **Alanna M. Chamberlain:** Data curation, Writing − review & editing. **Daniel E. Ford:** Data curation, Writing − review & editing. **Howard S. Gordon:** Data curation, Writing − review & editing. **Wenke Hwang:** Data curation, Writing − review & editing. **Alexander Chang:** Data curation, Writing − review & editing. **Ajaykumar Rao:** Data curation, Writing − review & editing. **Hayden B. Bosworth:** Conceptualization, Supervision, Writing − review & editing. **Neha Pagidipati:** Conceptualization, Supervision, Writing − review & editing.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2024.04.011.

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