



# Comparative Effectiveness of the Sodium–Glucose Cotransporter 2 Inhibitor Empagliflozin Versus Other Antihyperglycemics on Risk of Major Adverse Kidney Events

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## OBJECTIVE

To examine the comparative effectiveness of the sodium–glucose cotransporter 2 inhibitor (SGLT2i) empagliflozin and other non-SGLT2i antihyperglycemics on the risk of major adverse kidney events (MAKE) of estimated glomerular filtration rate (eGFR) decline >50%, end-stage kidney disease, or all-cause mortality.

## RESEARCH DESIGN AND METHODS

In a cohort study of 379,033 new users of empagliflozin or other non-SGLT2i antihyperglycemics, predefined variables and covariates identified by a high-dimensional variable selection algorithm were used to build propensity scores. Weighted survival analyses were then applied to estimate the risk of MAKE.

## RESULTS

Compared with other antihyperglycemics, empagliflozin use was associated with 0.99 (95% CI 0.51, 1.55) mL/min/1.73 m<sup>2</sup> less annual reduction in eGFR, 0.25 (95% CI 0.16, 0.33) kg/m<sup>2</sup> more annual decrease in BMI, and reduced risk of MAKE (hazard ratio [HR] 0.68 [95% CI 0.64, 0.73]). Empagliflozin use was associated with reduced risk of MAKE in eGFR ≥90, ≥60 to <90, ≥45 to <60, and ≥30 to <45 mL/min/1.73 m<sup>2</sup> (HR 0.70 [95% CI 0.60, 0.82], 0.66 [0.60, 0.73], 0.78 [0.69, 0.89]), and 0.71 [0.55, 0.92], respectively), in participants without albuminuria, with microalbuminuria and macroalbuminuria (HR 0.65 [95% CI 0.57, 0.75], 0.72 [0.66, 0.79], and 0.74 [0.62, 0.88], respectively), and in participants with and without cardiovascular disease (HR 0.67 [95% CI 0.61, 0.74] and 0.76 [0.69, 0.83], respectively). The association was evident in per-protocol analyses, which required continuation of the assigned antihyperglycemic medication (empagliflozin or other antihyperglycemics) during follow-up (HR 0.64 [95% CI 0.60, 0.70]), and in analyses requiring concurrent use of metformin in at least the first 90 days of follow-up (HR 0.63 [0.57–0.69]).

## CONCLUSIONS

Among people with type 2 diabetes, empagliflozin use was associated with eGFR preservation, a greater decline in BMI, and a reduced risk of MAKE compared with other non-SGLT2i antihyperglycemics.

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The global prevalence of type 2 diabetes in 2017 was 462 million (uncertainty interval 423–509 million) (1). Nearly 40% of people with type 2 diabetes develop diabetic kidney disease, making it the leading driver of chronic kidney disease (CKD) burden in the U.S. and globally (1–3). Diabetic kidney disease is associated with substantial morbidity and reduced life expectancy (4,5). While intensive glucose control with conventional antihyperglycemic medications resulted in a reduction in the risk of major kidney outcomes in patients with type 2 diabetes (6), the burden of major adverse kidney events in these patients remains substantially high (7). In the past 5 years, four randomized clinical trials (RCTs) provided evidence that when compared with placebo, the newest class of antihyperglycemic agents, sodium–glucose cotransporter 2 inhibitor (SGLT2i), reduced the risk of end-stage kidney disease (ESKD) and death (8–11). However, these RCTs included mostly participants with established or at high risk of cardiovascular disease and enrolled a limited number of people with reduced kidney function. The only exception is Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDESCENCE), which enrolled patients with albuminuria and an estimated glomerular filtration rate (eGFR) of 30 to <90 mL/min/1.73 m<sup>2</sup> (8–22). Evaluating the comparative effectiveness of SGLT2i versus other active antihyperglycemics in a real-world setting, including people with and without cardiovascular disease and people with a broad spectrum of kidney function, including advanced kidney disease, would address an important knowledge gap to complement evidence from RCTs and help inform the choice of antihyperglycemic therapy among people with type 2 diabetes.

In this work, we used real-world data from the U.S. Department of Veterans Affairs (VA) to examine the comparative effectiveness of incident use of the SGLT2i empagliflozin versus incident use of other non-SGLT2i antihyperglycemics on the risk of major adverse kidney events (MAKE), defined as a composite end point of eGFR decline >50%, ESKD, or all-cause mortality.

## RESEARCH DESIGN AND METHODS

### Cohort Design

Participants who received antihyperglycemic medications from the VA Health Care System between 1 October 2015 and

30 September 2019 were selected as an initial cohort ( $n = 1,406,662$ ). A flowchart of cohort construction is included in Supplementary Fig. 1A. Within these participants, we selected as the empagliflozin group those who received an empagliflozin prescription between 1 October 2016 and 30 September 2019 ( $n = 66,012$ ) and then limited this group to those with no prior history of SGLT2i exposure in past 1 year ( $n = 63,208$ ). Time zero ( $T_0$ ) was defined as time of the first empagliflozin prescription during this period. From the rest of the initial cohort, we then selected those who switched to or added on an antihyperglycemic medication that was not an SGLT2i to build the control group ( $n = 438,127$ ). Change in antihyperglycemic medication was defined by receipt of prescription of a new class of antihyperglycemics that had not been used in the past year. This approach constructs a control group that may be more similar in clinical characteristics to the empagliflozin group by requiring a change in treatment regimen.  $T_0$  in this group was defined as time of this first new antihyperglycemic medication prescription (time of switch or add-on). Participants in the control group were excluded if they received SGLT2i within 1 year before  $T_0$  ( $n = 435,312$ ). To ensure that all participants had a 1-year covariate ascertainment period, we only included those enrolled in the health care system for >1 year at  $T_0$  (empagliflozin  $n = 62,083$ ; control  $n = 419,979$ ). Within them, 59,156 participants in the empagliflozin group and 401,388 participants in the control group did not experience ESKD or have type 1 diabetes. The groups were further selected to only include participants with an eGFR  $\geq 30$  mL/min/1.73 m<sup>2</sup> within 1 year before  $T_0$  (empagliflozin  $n = 56,261$ ; control  $n = 375,037$ ). After excluding participants who did not have glycated hemoglobin (HbA<sub>1c</sub>), LDL, blood pressure, height, or weight measured within 1 year before  $T_0$ , the final cohort included 52,535 participants in the empagliflozin group and 326,498 participants in the control group. Participants were monitored until the occurrence of an outcome or administrative end of follow-up (31 January 2020).

### Data Sources

Data from VA Corporate Data Warehouse (CDW) were used in this study (23–26). CDW Outpatient and Inpatient Encounters domains were used to collect ICD-10

diagnosis codes, Current Procedural Terminology (CPT) codes, and ICD-10 procedure codes during an outpatient visit or hospitalization (27). The CDW Outpatient Pharmacy domain was used to collect prescription data and provider data. Inpatient and outpatient laboratory results were both obtained from the CDW Laboratory Results domain (28). Vital measurements were collected from the CDW Vital Signs domain, and demographic information, including date of death, was collected from the CDW Patient domain and VA Vital Status Databases (29).

### Outcomes

The outcome of MAKE was defined as time until the first occurrence of eGFR decline >50% from baseline, ESKD, or all-cause mortality. Time of ESKD was identified by first occurrence of eGFR <15 mL/min/1.73 m<sup>2</sup>, chronic dialysis, or kidney transplant, identified in inpatient, outpatient, and laboratory data sets. The Chronic Kidney Disease Epidemiology Collaboration creatinine equation was used to compute eGFR based on serum creatinine, age, race, and sex (30). We also estimated the trajectory of eGFR and BMI during follow-up.

### Exposure

Prescriptions of antihyperglycemic medications were identified from outpatient pharmacy records. Classes of antihyperglycemics included SGLT2i, biguanides (metformin), insulin, sulfonylureas, dipeptidyl peptidase 4 inhibitors (DPP4), glucagon-like peptide 1 receptor agonists (GLP1), thiazolidinediones,  $\alpha$ -glucosidase inhibitors, meglitinides, and amylin analogs (26,31). A list of medications within each class is provided in Supplementary Table 1. A distribution of antihyperglycemic medications at  $T_0$  is presented in Supplementary Table 2.

### Covariates

Predictors of antihyperglycemic prescription were selected as predefined covariates and ascertained in the year before  $T_0$ . Predefined covariates included age, race (White, Black, and other), sex, HbA<sub>1c</sub>, eGFR, systolic blood pressure, diastolic blood pressure, LDL, and BMI computed from weight and height. We also included diseases that may affect the choice of antihyperglycemics, such as congestive heart failure, cardiovascular diseases, cancer, alcoholism, hypoglycemia, diabetic

ketoacidosis, acute kidney injury, bladder and urinary tract infections, venous thromboembolism, pancreatitis, and bone fracture, and albuminuria (32). Acute kidney injury was defined as increased serum creatinine of 0.3 mg/dL or 50% within 30 days, and albuminuria status was categorized into no albuminuria ( $\leq 30$  mg/g), microalbuminuria ( $>30$  to  $\leq 300$  mg/g), and macroalbuminuria ( $>300$  mg/g). Any prescription of GLP1, DPP4, sulfonyleureas, thiazolidinediones, metformin, insulin,  $\alpha$ -glucosidase inhibitors, meglitinides, amylin analogs, statins, ACE inhibitors, or angiotensin receptor blockers (ARBs),  $\beta$ -blockers, diuretics, and calcium channel blockers were also included as predefined covariates (32). Total number of diabetes medications, smoking status (never, former, current), hospital complexity (outpatient clinic or health care system), and the calendar year of  $T_0$  were also included as predefined covariates.

High-dimensional information from VA electronic health records were additionally used to reduce potential biases that were not adjusted for by the predefined covariates (33,34). A high-dimensional variable selection algorithm used all participant records within the 1 year before  $T_0$  from data dimensions, including outpatient ICD-10 diagnostic codes, outpatient CPT, inpatient ICD-10 diagnostic codes, inpatient CPT, and inpatient ICD-10 procedure codes for operations, pharmacy records, and laboratory results. The 300 most frequently occurring items (diagnosis, procedure, abnormal laboratory result, etc.) from each of the seven dimensions were categorized into three binary variables: ever, sometimes, and frequently occurring, which generated in total  $300 \times 7 \times 3 = 6,300$  variables. Variables were further selected based on their association with assignment to the empagliflozin or control group, where the 300 variables with the largest risk ratios were selected. High-dimensional variable selection was conducted independently in the overall cohort and within each subgroup for subgroup analyses.

For estimation of the per-protocol effect, predefined covariates were time updated. High-dimensional variables were selected based on association with adherence to the treatment protocol and were also time updated (35).

### Ethical Approval

The VA St. Louis Health Care System Institutional Review Board (St. Louis,

MO) reviewed and approved this research project.

### Statistical Analyses

Characteristics of the overall cohort and within the SGLT2i empagliflozin and control groups are presented as mean and SD or number and percentage, as appropriate. Kaplan-Meier curves for MAKE in the empagliflozin and control groups are presented.

Supplementary Figure 1B displays the analytic framework used in this study. We used an inverse weighting approach to adjust for confounding. The probability of initiating empagliflozin, in the form of a high-dimensional propensity score, was estimated from logistic regression, where independent variables included both predefined and high-dimensional variables (33). Continuous variables, including age,  $HbA_{1c}$ , eGFR, LDL, systolic and diastolic blood pressure, and BMI, were treated as restricted cubic spline with knots at the 5th, 35th, 65th, and 95th percentiles. Based on the propensity score, we then weighted the control group based on probability of initiating empagliflozin/(1 – probability of initiating empagliflozin) (36). A weighted pseudocohort was then generated where the empagliflozin and control groups had similar baseline characteristics to facilitate comparing the two groups. Weights were truncated at the 0.1th and 99.9th percentile. To demonstrate the reduction of imbalance in baseline characteristics, characteristics in the weighted cohort and the absolute standardized difference between groups were computed. Weighted survival probability in the form of Kaplan-Meier curves for MAKE in the empagliflozin and the control groups are presented.

We applied a weighted linear mixed model to estimate the eGFR and BMI trajectories in the weighted empagliflozin and the control groups. A cubic spline of time was used to capture potential nonlinear trajectories during follow-up, where knots were placed at 0, 90, 365, 730, and 1,095 days. The difference in eGFR trajectory between treatment arms was estimated from the interaction between treatment group and the splined time. eGFR and BMI in the empagliflozin and control groups at 90 days and at 1, 2, and 3 years were plotted. eGFR and BMI changes from baseline ( $T_0$ ) were estimated. The difference between the two trajectories,

where the control group served as the reference, represented the eGFR and BMI changes associated with empagliflozin at each time point.

Weighted Cox survival models were built to estimate the intention-to-treat hazard ratio (HR) and risk difference between groups in the weighted cohort. A robust sandwich estimator was applied to account for the influence of weighting on variance. To estimate the effect in different populations of interest to the clinical community, we conducted subgroup analyses according to eGFR category ( $\geq 90$ ,  $\geq 60$  to  $<90$ ,  $\geq 45$  to  $<60$ , and  $\geq 30$  to  $<45$  mL/min/1.73 m<sup>2</sup>), albuminuria status (no albuminuria, microalbuminuria, and macroalbuminuria) at baseline, both albuminuria status and kidney disease status (eGFR  $\geq 60$  and  $<60$  mL/min/1.73 m<sup>2</sup>), in those with and without cardiovascular disease at baseline, according to baseline use of ACE/ARB, metformin, statins, diuretics, and insulin, and according to BMI category ( $>30$ ,  $>25$  to  $\leq 30$ , and  $\leq 25$  kg/m<sup>2</sup>). For each subgroup analysis, the propensity score and the related weighting was estimated independently. We also examined the association between empagliflozin and risk of each component of the composite outcome (MAKE): eGFR decline  $>50\%$ , ESKD, and death, and a composite outcome of eGFR decline  $>50\%$  or ESKD, separately. Event rate differences per 1,000 person-years between the empagliflozin and the control groups in the overall cohort and in subgroups were computed based on the difference in estimated survival probability at 3 years.

Multiple sensitivity analyses were conducted to test robustness of study results.

1. Instead of weighting, variable ratio matching with a maximum of five controls per treatment was conducted to estimate the association in a matched cohort (37).
2. To examine whether the association between empagliflozin and risk of MAKE was independent of change of BMI during follow-up, we controlled for time-dependent BMI in the form of restricted cubic splines.
3. To examine whether the association was independent of change of  $HbA_{1c}$ , we controlled for time-dependent  $HbA_{1c}$  in form of restricted cubic splines.

- We also controlled for both time-dependent BMI and  $HbA_{1c}$  spline terms in the same model.
- Because antihyperglycemic prescribing preferences may have changed over time, we examined the association in two cohort enrollment periods (2016 and 2017) and separately (2018 and 2019).
- To remove events that are less likely related to long-term effects of antihyperglycemics, we excluded participants who experienced events in the first 180 days of the follow-up.
- We tested the association with an alternatively defined outcome of eGFR decline  $>50\%$  based on two eGFR measurements separated by at least 30 days.
- We examined the association with ESKD, defined as receipt of chronic dialysis, kidney transplantation, or eGFR  $<15$  mL/min/1.73 m<sup>2</sup> on two separate occasions at least 30 days apart.

As a means of testing for possible spurious associations, we used the approach outlined by Lipsitch et al. (38) to test the association between empagliflozin and risk of traffic-related injury as a negative outcome control where a priori evidence suggests that an association is not expected. A Cox survival model was used to estimate the association between traffic-related injury and empagliflozin in the weighted cohort.

Per-protocol, analyses were conducted to estimate the effect of empagliflozin when following a defined treatment protocol (39,40). In the weighted cohort, we additionally inverse weighted by the time dependent probability of not following the treatment protocol. Two treatment protocols were specified and examined separately. The first treatment protocol required the continuation of the antihyperglycemic medication initiated at  $T_0$  throughout duration of follow-up. The second treatment protocol required the concurrent use of metformin with empagliflozin or the other antihyperglycemics in the first 90 days of follow-up. For every time interval  $k$  with length of 90 days, the stabilized weight for adherence to treatment protocol was estimated as:  $SW_k^Z = \prod_{k=1}^t \frac{\Pr(Z_k=1 | Z_{k-1}=1, A, V)}{\Pr(Z_k=1 | Z_{k-1}=1, A, Q_{k-1})}$ , where  $Z$  is an indicator of adherence,  $A$  is the treatment group,  $V$  is a vector of time-independent predictors, including age,

race, sex, complexity of hospital where initial prescription occurred, and year of  $T_0$ , and  $Q_{k-1}$  is the history of predefined variables and high-dimensional variables through time  $k-1$ . Stabilized weights were truncated at the 0.1th and 99.9th percentile, and a pooled logistic regression was then used to estimate the per-protocol effect (41,42).

#### Reproducible Research Statement

The study protocol and statistical code are available from Z.A.-A. (email: zalaly@gmail.com). The data in the data set are available through the U.S. Department of Veterans Affairs.

#### RESULTS

There were 379,033 participants in the unweighted cohort corresponding to 644,311.59 person-years of follow-up (details provided in Supplementary Table 3). Survival probabilities in the SGLT2i empagliflozin and the control groups in the unweighted cohort are provided in Supplementary Fig. 2. A weighted cohort was generated based on the probability of initiating empagliflozin, resulting in 52,535 users in the empagliflozin group and 52,850 in the control group. Demographic and health characteristics in the weighted cohort are reported in Table 1.

In the weighted cohort, during 3 years of follow-up, there were 2,305 (4.39%) composite outcomes (MAKE) in the empagliflozin group (34.80 per 1,000 person-years) and 3,642.17 (6.89%) in the control group (51.18 per 1,000 person-years). Weighted survival probabilities in the empagliflozin and the control groups are provided in Fig. 1.

Estimated eGFR trajectories in the empagliflozin and control groups showed decline in eGFR (Fig. 2A). Although the empagliflozin group experienced a rapid drop of eGFR in the first 90 days after treatment initiation, over the span of 3 years, the SGLT2i and control groups exhibited a 5.30 (95% CI 4.62, 5.97) and 8.27 (6.80, 9.92) mL/min/1.73 m<sup>2</sup> decline in eGFR, respectively. Compared with the control group, empagliflozin use was associated with an annual eGFR preservation of 0.99 (0.51, 1.55) mL/min/1.73 m<sup>2</sup>/year and a net 2.97 (1.54, 4.66) mL/min/1.73 m<sup>2</sup> of eGFR preserved in 3 years ( $P < 0.001$ ).

The empagliflozin and control groups both experienced decline in BMI during

the follow up (Fig. 2B). The empagliflozin group was associated with a greater reduction in BMI than the control group. Over the span of 3 years, the empagliflozin and the control groups exhibited 1.68 (95% CI 1.50, 1.83) and 0.95 (0.76, 1.09) kg/m<sup>2</sup> decline in BMI, respectively. Compared with the control group, empagliflozin use was associated with an additional annual decrease in BMI of 0.25 (0.16, 0.33) kg/m<sup>2</sup> in 1 year, and 0.74 (0.480, 0.98) kg/m<sup>2</sup> in 3 years ( $P < 0.001$ ) (Fig. 2B).

Empagliflozin use was associated with reduced risk of MAKE (HR 0.68 [95% CI 0.64, 0.73]), yielding an adjusted rate difference of  $-14.99$  ( $-17.17$ ,  $-12.66$ ) fewer events per 1,000 person-years of empagliflozin use compared with other non-SGLT2i antihyperglycemics (Fig. 3). Analyses by eGFR category suggested that empagliflozin use was associated with reduced risk of MAKE in each of the eGFR categories examined, including eGFR  $\geq 90$ ,  $\geq 60$  to  $<90$ ,  $\geq 45$  to  $<60$ , and  $\geq 30$  to  $<45$  mL/min/1.73 m<sup>2</sup> and in people with no albuminuria, microalbuminuria, and macroalbuminuria. In addition, empagliflozin use was associated with reduced risk of MAKE in participants with eGFR above and below 60 mL/min/1.73 m<sup>2</sup>, regardless of albuminuria status. Empagliflozin use was associated with reduced risk of MAKE in cohort participants with and without cardiovascular disease, and regardless of receipt of ACE/ARB, metformin, statins, diuretics, or insulin, and regardless of BMI category. Compared with other non-SGLT2i antihyperglycemics, empagliflozin use was associated with fewer events per 1,000 person-years in all subgroups examined (Fig. 3A and Supplementary Table 4A).

We also examined the association of empagliflozin with each component of the composite outcome of MAKE. Empagliflozin was associated with reduced risk of each of the three components, including eGFR decline  $>50\%$  (HR 0.72 [95% CI 0.66, 0.79]), ESKD (HR 0.69 [0.57, 0.84]) and death (HR 0.61 [0.56, 0.68]). Analyses that considered the outcome of eGFR decline  $>50\%$  or ESKD yielded consistent results (Fig. 3B and Supplementary Table 4B).

#### Sensitivity Analyses

To examine the robustness of our findings, we conducted multiple sensitivity analyses (Supplementary Table 5).

**Table 1—Demographic and health characteristics of the weighted cohort**

Baseline characteristics	Weighted cohort (n = 105,385)	Empagliflozin (n = 52,535 [49.85%])	Other non-SGLT2i antihyperglycemics (n = 52,850 [50.15%])	Absolute standardized difference
Age, years	65.63 (9.12)	65.35 (9.23)	65.92 (9.00)	0.06
Race, n (%)				
White	77,869 (73.89)	38,697 (73.66)	39,172 (74.12)	0.01
Black	15,534 (14.74)	7,943 (15.12)	7,591 (14.36)	0.02
Other	11,982 (11.37)	5,895 (11.22)	6,087 (11.52)	<0.01
Sex, n (%)				
Male	100,725 (95.58)	50,172 (95.50)	50,553 (95.65)	<0.01
Female	4,660 (4.42)	2,363 (4.50)	2,297 (4.35)	<0.01
eGFR, mL/min/1.73 m <sup>2</sup>	77.41 (18.38)	77.91 (18.40)	76.92 (18.35)	0.05
eGFR category, n (%)				
≥90 mL/min/1.73 m <sup>2</sup>	28,222 (26.78)	14,468 (27.54)	13,794 (26.10)	0.03
≥60 to <90 mL/min/1.73 m <sup>2</sup>	57,077 (54.16)	28,206 (53.69)	28,846 (54.58)	0.02
≥45 to <60 mL/min/1.73 m <sup>2</sup>	17,294 (16.41)	8,515 (16.21)	8,768 (16.59)	0.01
≥30 to <45 mL/min/1.73 m <sup>2</sup>	2,793 (2.65)	1,346 (2.56)	1,443 (2.73)	0.01
HbA <sub>1c</sub> , %	8.70 (1.40)	8.69 (1.40)	8.70 (1.41)	<0.01
HbA <sub>1c</sub> , mmol/mol	72 (11.59)	71 (11.44)	72 (11.59)	<0.01
BMI, kg/m <sup>2</sup>	34.12 (6.43)	34.06 (6.41)	34.17 (6.45)	0.02
LDL, mg/dL	81.04 (34.12)	81.50 (34.37)	80.59 (33.86)	0.03
Blood pressure, mmHg				
Systolic	132.19 (16.33)	132.19 (16.25)	132.19 (16.40)	<0.01
Diastolic	74.84 (9.83)	75.08 (9.83)	74.60 (9.82)	0.05
Congestive heart failure, n (%)	10,951 (10.39)	5,320 (10.13)	5,630 (10.65)	0.01
Alcoholism, n (%)	4,220 (4.00)	2,211 (4.21)	2,009 (3.80)	0.02
Bone fracture, n (%)	1,273 (1.21)	613 (1.17)	660 (1.25)	<0.01
Cancer, n (%)	21,413 (20.32)	10,627 (20.23)	10,786 (20.41)	<0.01
Cardiovascular disease, n (%)	43,395 (41.18)	21,294 (40.53)	22,101 (41.82)	0.03
Diabetic ketoacidosis, n (%)	212 (0.20)	108 (0.21)	104 (0.20)	0.002
Hypoglycemia, n (%)	3,626 (3.44)	1,730 (3.29)	1,896 (3.59)	0.02
Pancreatitis, n (%)	1,192 (1.13)	625 (1.19)	567 (1.07)	0.01
Bladder and urinary tract infections, n (%)	2,233 (2.12)	1,077 (2.05)	1,156 (2.19)	0.01
Venous thromboembolism, n (%)	608 (0.58)	325 (0.62)	283 (0.53)	0.01
Acute kidney injury, n (%)	9,705 (9.01)	4,705 (8.96)	4,789 (9.06)	<0.01
Albuminuria, n (%)				
None (≤30 mg/g)	41,314 (39.20)	20,827 (39.64)	20,487 (38.76)	0.02
Microalbuminuria (>30 to ≤300 mg/g)	52,999 (50.29)	26,371 (50.20)	26,628 (50.38)	<0.01
Macroalbuminuria (>300 mg/g)	11,072 (10.51)	5,337 (10.16)	5,735 (10.85)	0.02
Metformin, n (%)*	84,393 (80.08)	42,156 (80.24)	42,237 (79.92)	<0.01
Insulin, n (%)*	59,402 (56.37)	29,011 (55.22)	30,391 (57.50)	0.05
Sulfonylureas, n (%)*	50,157 (47.59)	24,901 (47.40)	25,256 (47.79)	0.03
DPP4, n (%)*	25,272 (23.98)	12,817 (24.40)	12,455 (23.57)	0.03
GLP1, n (%)*	13,608 (12.91)	6,557 (12.48)	7,051 (13.34)	0.02
Thiazolidinediones, n (%)*	8,150 (7.73)	4,277 (8.14)	3,873 (7.33)	0.03
α-Glucosidase inhibitors, n (%)*	1,841 (1.75)	878 (1.67)	963 (1.82)	0.06
Meglitinides, n (%)*	271 (0.26)	165 (0.31)	106 (0.20)	0.05
Amylin analogs, n (%)*	50 (0.05)	28 (0.05)	22 (0.04)	0.02
Total number of diabetes medications used	2.31 (0.96)	2.30 (0.94)	2.32 (0.99)	0.02
ACE/ARB, n (%)*	73,851 (70.08)	36,566 (69.60)	37,285 (70.55)	0.02
Calcium channel blockers, n (%)*	32,218 (30.57)	15,918 (30.30)	16,300 (30.84)	0.01
β-Blockers, n (%)*	55,122 (52.31)	26,989 (51.37)	28,133 (53.23)	0.04
Diuretics, n (%)*	46,648 (44.26)	23,003 (43.79)	23,645 (44.74)	0.02
Statins, n (%)*	89,615 (85.04)	44,515 (84.73)	45,100 (85.34)	0.02
Hospital complexity, n (%)				
Outpatient clinic	55,543 (52.70)	28,123 (53.53)	27,420 (51.88)	0.03
Health care system	49,842 (47.30)	24,412 (46.47)	25,430 (48.12)	0.03

Continued on p. 2790

Table 1—Continued

Baseline characteristics	Weighted cohort (n = 105,385)	Empagliflozin (n = 52,535 [49.85%])	Other non-SGLT2i antihyperglycemics (n = 52,850 [50.15%])	Absolute standardized difference
Year of treatment initial, n (%)				
2016	2,025 (1.92)	956 (1.82)	1,067 (2.02)	0.01
2017	17,874 (16.96)	8,439 (16.06)	9,435 (17.85)	0.05
2018	35,078 (33.29)	16,957 (32.28)	18,121 (34.29)	0.04
2019	50,408 (47.83)	26,183 (49.84)	24,225 (45.84)	0.08
Smoking status, n (%)				
Never	48,845 (46.35)	24,389 (46.42)	24,456 (46.27)	<0.01
Former	35,238 (33.44)	17,260 (32.85)	17,978 (34.02)	0.02
Current	21,302 (20.21)	10,886 (20.72)	10,416 (19.71)	0.03

Values are mean (SD) unless specified otherwise. \*Any prescription within 1 year before T<sub>0</sub>.

- We conducted a variable ratio matching analysis, which allows each treatment to be matched with up to five controls, and the results suggested that empagliflozin use was associated with reduced risk of the composite outcome (HR 0.73 [95% CI 0.69, 0.77]).
- To examine whether the observed association was independent of change in BMI, we additionally controlled for time-dependent BMI as a restricted cubic spline, and the result was consistent (HR 0.71 [95% CI 0.66, 0.76]).
- We additionally controlled for time-dependent HbA<sub>1c</sub> as a spline, resulting in a HR of 0.73 (95% CI 0.68, 0.78).
- Results were consistent after controlling for both time-dependent BMI and HbA<sub>1c</sub> (HR 0.72 [95% CI 0.67, 0.77]).
- To examine whether the observed association of empagliflozin with the outcome varied depending on temporal differences in the availability of the medication and prescription criteria, we examined the effect of empagliflozin in years 2016 and 2017 when SGLT2i was less accessible and in years 2018 and 2019 when SGLT2i use became relatively more popular. Compared with the control group, empagliflozin use exhibited a reduced risk of the composite outcome in both time periods examined, HR 0.70 (95% CI 0.64, 0.77) in years 2016 and 2017 and HR 0.65 (0.59, 0.72) in years 2018 and 2019.
- We also conducted analyses where we removed users with an event in the first 180 days of follow-up, because these events may be unlikely related to exposure to the antihyperglycemic medication. Results showed that compared with the control

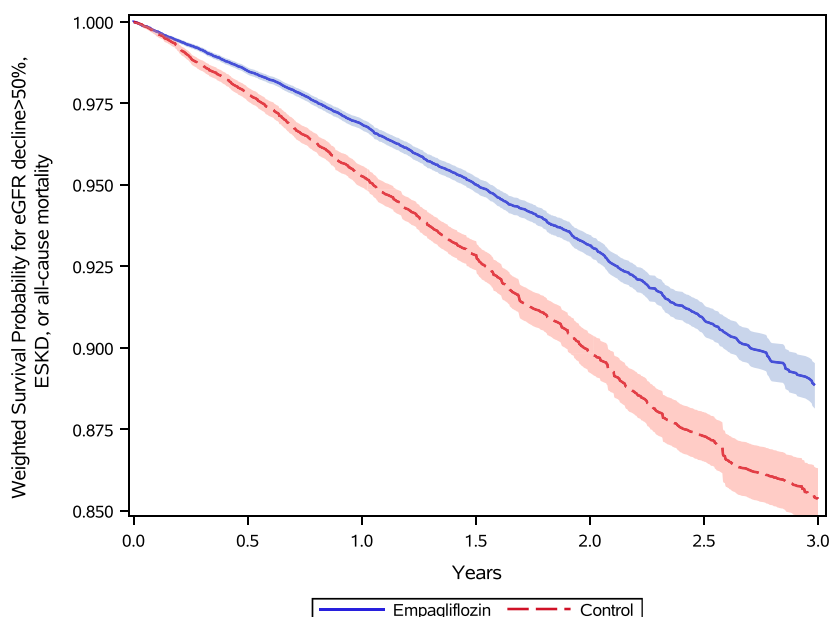
group, empagliflozin use was associated with reduced risk of the composite kidney outcome (HR 0.67 [95% CI 0.62, 0.73]).

- We alternatively defined eGFR decline >50% based on two eGFR measurements separated by at least 30 days, and the results were consistent (HR 0.61 [95% CI 0.51, 0.73]).
- We also alternatively defined ESKD as receipt of chronic dialysis, kidney transplantation, or eGFR <15 mL/min/1.73 m<sup>2</sup> on two separate occasions at least 30 days apart, and the results were consistent (HR 0.53 [95% CI 0.36, 0.80]) (Supplementary Table 5).

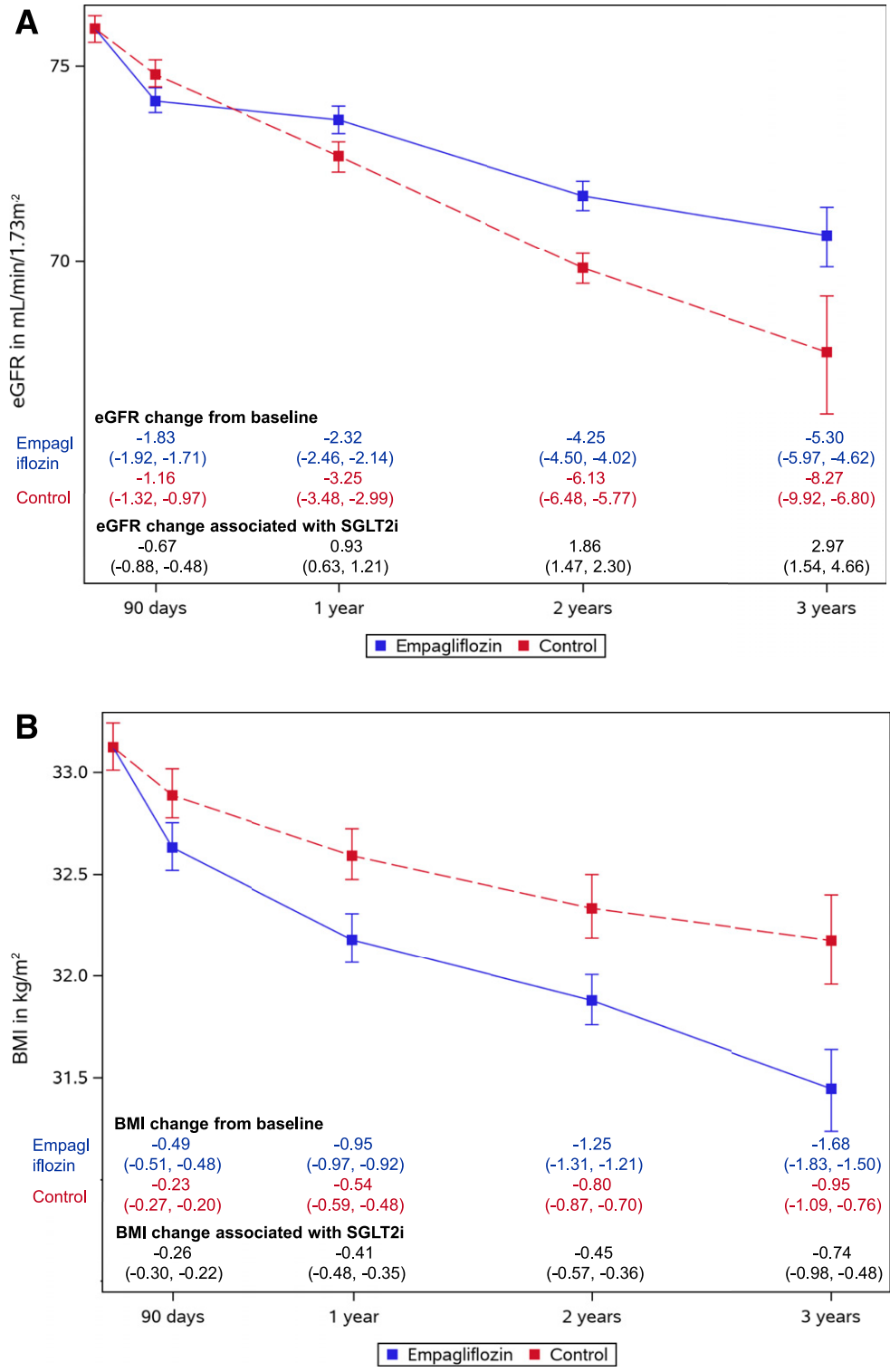
To further test for possible spurious biases, we examined the association between empagliflozin and traffic-related injury as a negative control, where no prior knowledge suggests a causal association exists. No significant association between SGLT2i and traffic-related injury was found (HR 1.10 [95% CI 0.88, 1.38]) (Supplementary Table 5).

#### Per-Protocol Analyses

In a prespecified protocol, which required the continuation of the antihyperglycemic medication initiated at T<sub>0</sub> throughout duration in cohort, 64.12% of the empagliflozin group and 61.66% of the control group adhered to the

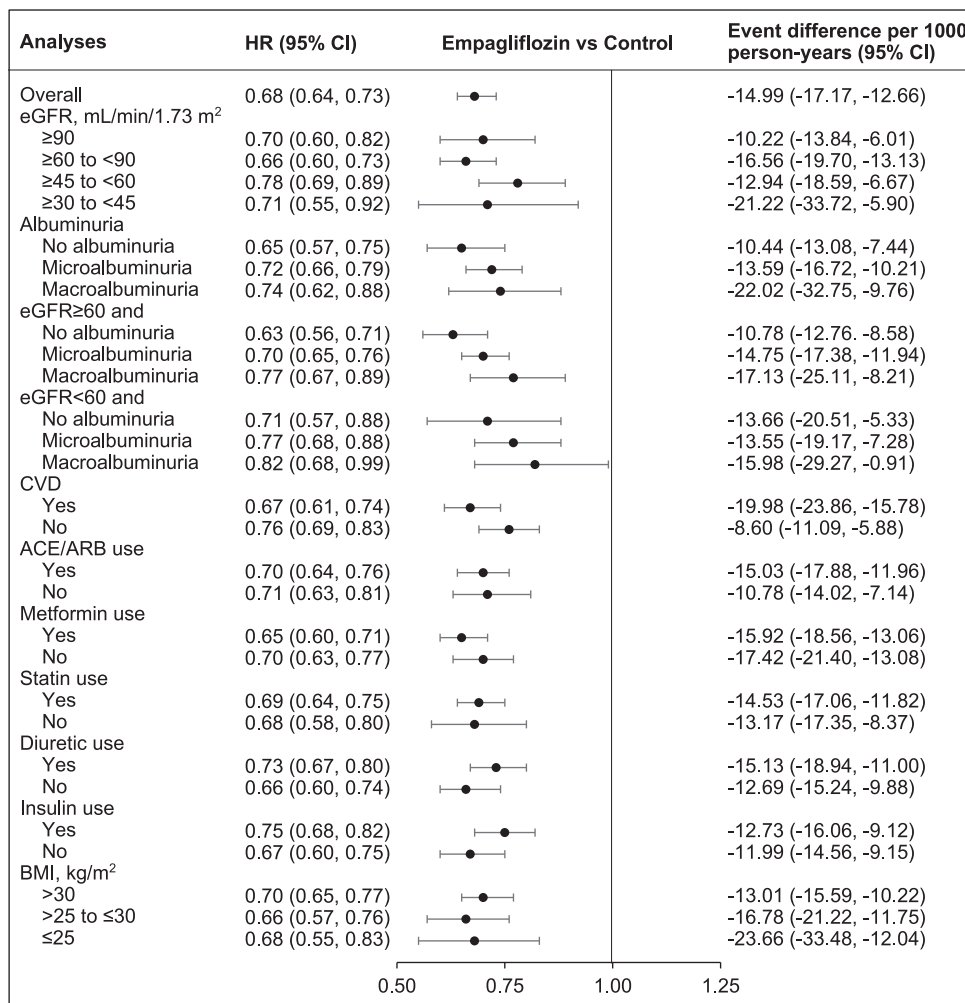


**Figure 1**—Survival probability for MAKE of eGFR decline >50%, ESKD, or all-cause mortality in the empagliflozin group (blue) and the control group of other non-SGLT2i antihyperglycemics (red) in the weighted cohort.

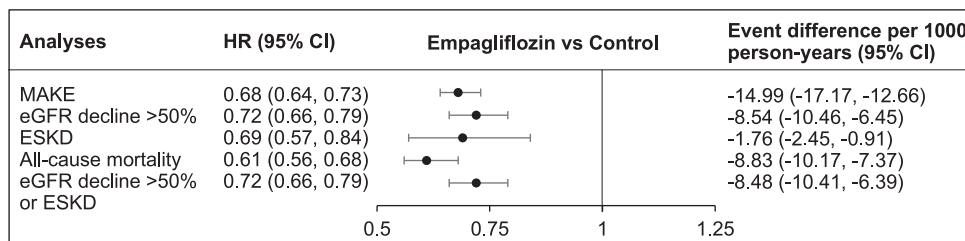


**Figure 2**—A: eGFR trajectory during follow-up. Estimated eGFR values and 95% CIs at 90 days and at 1, 2, and 3 years were plotted for the empagliflozin group (blue) and the control group of other non-SGLT2i antihyperglycemics (red). eGFR change associated with empagliflozin at each time point represents the difference between the two trajectories where the control group served as the reference. B: BMI trajectory during follow-up. Estimated BMI values and 95% CIs at 90 days and at 1, 2, and 3 years were plotted for the empagliflozin group (blue) and the control group of other non-SGLT2i antihyperglycemics (red). BMI change associated with empagliflozin at each time point represents the difference between the two trajectories where the control group served as the reference.

**A**



**B**



**Figure 3—A:** HRs and event rate differences for the MAKE of eGFR decline >50%, ESKD, or all-cause mortality in the overall cohort and in subgroups. **B:** HRs and event rate differences for individual components of the MAKE of eGFR decline >50%, ESKD, or all-cause mortality. Albuminuria status defined as no albuminuria (albumin-to-creatinine ratio ≤30 mg/g), microalbuminuria (>30 to ≤300 mg/g), and macroalbuminuria (>300 mg/g).

protocol in the weighted cohort. Empagliflozin use was associated with reduced risk of MAKE compared with the control group of other non-SGLT2i antihyperglycemics (HR 0.64 [95% CI 0.60, 0.70]).

In analyses of an additional prespecified protocol, which required participants to have concurrent use of metformin

with empagliflozin or other non-SGLT2i antihyperglycemics in the first 90 days of follow-up, 46.54% of the empagliflozin group and 56.11% of the control group adhered to this protocol in the weighted cohort. Empagliflozin use was associated with reduced risk of MAKE compared with the control group (HR 0.63 [95% CI 0.57, 0.69]).

**CONCLUSIONS**

In this real-world study of people with type 2 diabetes and eGFR ≥30 mL/min/1.73 m<sup>2</sup> corresponding to 644,311.59 person-years, incident use of the SGLT2i empagliflozin versus other non-SGLT2i antihyperglycemics was associated with eGFR preservation, a greater decline in BMI, and a reduced risk of MAKE, a



composite of eGFR decline >50%, ESKD, or death. The salutary association was observed regardless of baseline eGFR, regardless of albuminuria status, in people with and without cardiovascular disease, and in several other prespecified subgroups. The association was also observed in two prespecified per-protocol analyses 1) requiring adherence to empagliflozin or the other non-SGLT2i antihyperglycemic medication throughout duration of follow-up, and 2) requiring concomitant use of metformin for the first 90 days. The results were robust to challenge in multiple sensitivity analyses.

Our results suggest that empagliflozin use is associated with eGFR preservation of 0.99 (95% CI 0.51, 1.55) mL/min/1.73 m<sup>2</sup>/year and BMI reduction of 0.25 (95% CI 0.16, 0.33) kg/m<sup>2</sup>/year, an observation that is consistent with results from RCTs and prior real-world evidence (8–11,17,43,44).

Until recently, SGLT2i use has been limited to people with eGFR >45 mL/min/1.73 m<sup>2</sup>. Except for the CREDENCE trial, which enrolled people with albuminuria and eGFR 30 to <90 mL/min/1.73 m<sup>2</sup>, all of the other RCTs of SGLT2i and kidney outcomes included a minority of patients with reduced kidney function or albuminuria. One real-world study included people with eGFR <60 mL/min/1.73 m<sup>2</sup> ( $n = 2,747$  [7.7%]), but did not report outcomes in those with eGFR <45 mL/min/1.73 m<sup>2</sup> (43). Our data capture the recent increase in empagliflozin use in people with low eGFR and provide evidence of effectiveness that empagliflozin use was associated with a reduced risk of MAKE in people with eGFR 45 to <60 and  $\geq 30$  to <45 mL/min/1.73 m<sup>2</sup>—extending evidence of efficacy of canagliflozin in eGFR 45 to <60 and  $\geq 30$  to <45 mL/min/1.73 m<sup>2</sup> from the CREDENCE trial and also providing plausibility to the notion of a salutary class effect of SGLT2i on kidney outcomes. Furthermore, the risk reduction associated with empagliflozin was observed regardless of albuminuria status at baseline, an observation congruent with analyses of the four major RCTs (Dapagliflozin Effect on Cardiovascular Events trial [DECLARE-TIMI 58], Canagliflozin Cardiovascular Assessment Study [CANVAS] Program, BI 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients [EMPA-REG OUTCOME], and CREDENCE) (8–11,17). In addition, the reduced risk

observed in patients with eGFR <60 mL/min/1.73 m<sup>2</sup> and without albuminuria extends observations from CREDENCE and suggest that the beneficial effect of SGLT2i in patients with reduced kidney function is present regardless of albuminuria status. Taken together, the results from this analysis complement observations from prior RCTs by providing real-world evidence of effectiveness in several eGFR groups (including lower eGFR categories) and regardless of albuminuria status.

The observation that the SGLT2i empagliflozin use was associated with a reduced risk of MAKE in people with and without cardiovascular disease adds to known evidence from RCTs that mostly included people with established cardiovascular disease or at high risk of cardiovascular disease. In other subgroup analyses, empagliflozin use was associated with a reduced risk of MAKE regardless of baseline metformin, insulin, statin, or diuretic use and regardless of baseline BMI category. Overall, the results suggest that the salutary association of empagliflozin with MAKE is evident in clinically relevant subgroups and support the assessment that results from RCTs extend to broader populations with different characteristics.

Our analyses also provide supportive evidence that the risk reduction seen with the SGLT2i empagliflozin is evident regardless of baseline use of ACE/ARB. Most participants in EMPA-REG OUTCOME (80.7%), CANVAS Program (80%), DECLARE-TIMI 58 (81.3%), and CREDENCE (99.9%) received ACE/ARB (8–11,17). A meta-analysis of the effects of SGLT2i on substantial loss of kidney function, ESKD, and death due to kidney disease suggested a protective effect in participants who were on ACE/ARB at baseline and a trend toward a protective effect that was not statistically significant—likely due to the low number of trial participants—in those who were not on ACE/ARB at baseline (17). Our results complement and extend these observations by providing evidence that the salutary association of SGLT2i on the risk of kidney outcomes is present regardless of ACE/ARB use.

The association of empagliflozin with kidney outcomes was independent of glycemic control (HbA<sub>1c</sub>) and BMI, an observation consistent with prior studies that also suggests a glucose-independent mechanism likely involving reduced glomerular hyperfiltration, which may also

explain the acute early reduction in eGFR in the SGLT2i group, which then stabilized to yield less annual reduction in eGFR (eGFR preservation) compared with the control arm (13,45,46). The results were robust to challenge in other sensitivity analyses, including variable ratio propensity score matching analysis, evaluation of the association when SGLT2i was starting to be used (2016 and 2017) and the most recent years (2018 and 2019), and evaluation of the individual components of the composite end point; the latter analysis also suggests that the association observed in the overall cohort was driven by the reduction in risk in each of the components of the composite outcome.

This study has several limitations. We relied on observational real-world data from the VA to build our cohort, which was mostly composed of older, White, and male participants, and therefore this may limit the generalizability of study findings. Although our analytic approach evaluated empagliflozin versus other active non-SGLT2i antihyperglycemics, considered known confounders, and applied a high-dimensional variable selection algorithm to more comprehensively capture potential confounding, we cannot completely rule out the possibility of residual confounding. We estimated the intention-to-treat effect, which may be limited by variable nonadherence among study participants; however, we also evaluated the study question in two prespecified per-protocol analyses that accounted for nonadherence. Our analyses did not examine risk of incident albuminuria or its progression, and we did not examine risk of adverse events.

The study has several strengths. We used large scale real-world data from the VA, which operates the largest integrated health care system in the U.S.; VA data are captured during routine clinical care, which might more closely recapitulate real-world experiences. We developed our research aim, study design, and execution to specifically address a knowledge gap of the comparative effectiveness of the SGLT2i empagliflozin versus an active comparator control on risk of kidney outcomes in people with type 2 diabetes who switched or added on an antihyperglycemic medication. In addition to reporting relative risk, we reported absolute risk differences in the overall cohort and in subgroups with different baseline risks, which may be clinically

meaningful in informing choice of antihyperglycemic medication. We used a new user design with an active comparator, applied advanced statistical methodologies, including high-dimensional variable selection algorithms and inverse probability of treatment weighting, and reported both an intention-to-treat effect, which estimates the effectiveness of empagliflozin at the level of observed adherence in our cohort, and the per-protocol effect, which accounts for nonadherence and offers estimates of effectiveness that may be more generalizable across different settings (40). We examined the comparative effectiveness in prespecified subgroups, including those with low eGFR ( $\geq 45$  to  $< 60$ , and  $\geq 30$  to  $< 45$  mL/min/1.73 m<sup>2</sup>) and in subgroups based on albuminuria and cardiovascular disease. We tested robustness of results in multiple sensitivity analyses and applied a negative control to detect spurious associations.

In sum, real-world data suggest that compared with other antihyperglycemics, the SGLT2i empagliflozin was associated with eGFR preservation, a greater decline in BMI, and a significant reduction in the risk of MAKE of eGFR decline  $> 50\%$ , ESKD, or all-cause mortality among people with type 2 diabetes. The risk reduction was evident regardless of baseline eGFR, regardless of albuminuria status, and in several other prespecified clinically relevant subgroups. Overall, our results suggest that the salutary kidney effect of SGLT2i observed in RCTs likely extends to broader populations in real-world settings.

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