Comparative Effectiveness of SGLT2 Inhibitors, GLP-1 Receptor Agonists, DPP-4 Inhibitors, and Sulfonylureas on Risk of Kidney Outcomes: Emulation of a Target Trial Using Health Care Databases

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OBJECTIVE

To examine the comparative effectiveness of sodium–glucose cotransporter 2 inhibitors (SGLT2is), glucagon-like peptide 1 receptor agonists (GLP-1), dipeptidyl peptidase 4 inhibitors (DPP-4), and sulfonylureas on risk of kidney outcomes among people with type 2 diabetes.

RESEARCH DESIGN AND METHODS

U.S. veterans initiated on SGLT2is (n = 18,544), GLP-1 (n = 23,711), DPP-4 (n = 39,399), or sulfonylureas (n = 134,904) were followed for up to 3 years to evaluate the risk of the composite outcome of estimated glomerular filtration rate (eGFR) decline >50%, end-stage kidney disease (ESKD), or all-cause mortality. Risks were estimated using survival models adjusted for predefined covariates as well as covariates identified by a high-dimensional variable selection algorithm through application of generalized propensity scores.

RESULTS

Compared with those treated with sulfonylureas, treatment with SGLT2is, GLP-1, and DPP-4 was associated with a lower risk of the composite outcome (hazard ratio 0.68 [95% CI 0.63, 0.74], 0.72 [0.67, 0.77], and 0.90 [0.86, 0.95], respectively). While we did not observe a statistically significant difference in risk between the SGLT2i and GLP-1 arms (0.95 [0.87, 1.04]), both SGLT2is and GLP-1 had a lower risk of the composite outcome than DPP-4 (0.76 [0.70, 0.82] and 0.79 [0.74, 0.85], respectively). Analyses by eGFR category suggested that compared with the sulfonylurea arm, those in the SGLT2i and GLP-1 arms exhibited a lower risk of the composite outcome in all eGFR categories, including eGFR <45 mL/min/1.73 m^2. Compared with DPP-4, both SGLT2is and GLP-1 exhibited a reduced risk of the composite outcome in eGFR <90 to ≥60, <60 to ≥45, and <45 mL/min/1.73 m^2.

CONCLUSIONS

In type 2 diabetes, treatment with SGLT2is or GLP-1 compared with DPP-4 or sulfonylureas was associated with a lower risk of adverse kidney outcomes.

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The global and U.S. prevalence of type 2 diabetes and diabetic chronic kidney disease (CKD) is substantial and may be increasing (1–3). Diabetic kidney disease is associated with substantial morbidity and mortality (4,5). Antihyperglycemic agents that reduce risk of CKD among people with diabetes have long been awaited. In the past decade, several randomized clinical trials (RCTs) suggested that compared with placebo, the newest class of antihyperglycemic agents, sodium–glucose cotransporter 2 inhibitors (SGLT2is), reduced the risk of end-stage kidney disease (ESKD) and death (6–9). Several RCTs reported that glucagon-like peptide 1 receptor agonists (GLP-1)—another relatively new antihyperglycemic agent—reduced the risk of adverse kidney outcomes compared with placebo (10–12). However, except for a secondary analysis of one RCT (Canagliflozin Treatment and Trial Analysis-Sulfonylurea [CANTATA-SU]), which showed that compared with glimepiride (a sulfonylurea), the SGLT2i canagliflozin slowed kidney function decline and reduced albuminuria (13), there are no RCTs evaluating the comparative effectiveness of newer SGLT2is and GLP-1 versus older and lower-cost antihyperglycemic therapy, including dipeptidyl peptidase 4 inhibitors (DPP-4) and sulfonylureas, on risk of kidney outcomes (11–21). Furthermore, lack of real-world evidence and concerns about generalizability of evidence generated from RCTs to broader populations may have limited incorporation of recent trial findings into diabetes care (22). Real-world evidence on comparative effectiveness of the four antihyperglycemics would complement RCT evidence to inform clinical care and guide choice of antihyperglycemic therapy.

We aimed to address the unmet need for real-world evidence of the comparative effectiveness of the four classes of antihyperglycemics on risk kidney outcomes. In this work, we use observational real-world data from the Department of Veterans Affairs (VA) to evaluate the comparative effectiveness of incident use of SGLT2is, GLP-1, DPP-4, or sulfonylureas on risk of kidney outcomes defined as a composite end point of estimated glomerular filtration rate (eGFR) decline >50%, ESKD, or all-cause mortality.

RESEARCH DESIGN AND METHODS

Overall Study Design and Specification of a Target Trial

We followed the framework proposed by Hernán and Robins (23) to emulate a four-arm RCT (the target trial) of the comparative effectiveness of SGLT2is, GLP-1, DPP-4, or sulfonylureas on risk of kidney outcomes defined as a composite end point of eGFR decline >50%, ESKD, or all-cause mortality. First, the target trial protocol that would address the research question was specified (Supplementary Table 1). We then emulated the target trial by following the specified protocol to design the cohort, define exposure definitions and outcomes, select confounders, and specify the analytic approach (24,25). The protocol of the target trial, as well as key components of the target trial that was emulated, are specified in Supplementary Table 1.

Cohort Design

Participants were users of the VA Health Care System with a record of use of SGLT2is, GLP-1, DPP-4, or sulfonylureas after 1 October 2016 (N = 605,345), where date of first prescription was designated time 0 (T_0). Participants with no prescription record of the four antihyperglycemics within 1 year before T_0 met the inclusion criteria (n = 269,348). Participants were not included in the cohort if they had a history of type 1 diabetes, eGFR <15 mL/min/1.73 m^2, dialysis, or kidney transplant (selecting n = 243,289). Participants were further excluded if there was no recorded measurement of outpatient eGFR, hemoglobin A_{1c} (HbA_{1c}), height, weight, blood pressure, and LDL within the year before T_0, yielding an analytic cohort n = 216,558 (Supplementary Fig. 1). Participants were followed until the occurrence of an outcome, or administrative end of follow-up (30 November 2019), where participant status was updated every 90 days.

Data Sources

We used VA databases, which have provided high-dimensional electronic health records since 1 October 1999 (26–29). The VA operates an integrated health care system consisting of >1,400 health care facilities, including 143 hospitals and 1,241 outpatient clinics. All veterans who are enrolled for receipt of care have access to medical benefits, including inpatient and outpatient services; preventive, primary, and specialty care; medications; mental health care; home, geriatric, and extended care; and medical equipment and prosthetics. The Corporate Data Warehouse (CDW) Outpatient Encounters domain and Inpatient Encounters domain were used to collect ICD-10 diagnosis codes, Current Procedural Terminology (CPT) codes, ICD-10 procedure codes, and type of health care system from the patients' outpatient and inpatient encounters (30). Pharmacy data and provider information were obtained from the CDW Outpatient Pharmacy domain. The Managerial Cost Accounting data set and CDW Laboratory Results domain were used to collect information about laboratory data (31). Vital measurements were collected from the CDW Vital Signs domain, and demographic information was collected from the CDW Patient domain and VA Vital Status database (32).

Outcomes

The primary study outcome was time until the occurrence of the composite outcome of eGFR decline >50%, ESKD, or all-cause mortality. Time of ESKD was identified by the first record of dialysis, kidney transplant, or eGFR <15 mL/min/1.73 m^2 in inpatient or outpatient laboratory data sets, while date of death was obtained from the VA Vital Status database. eGFR values were estimated on the basis of the four-variable CKD Epidemiology Collaboration creatinine equation (33).

Exposure

Prescriptions of SGLT2is, GLP-1, DPP-4, or sulfonylureas were identified from outpatient pharmacy records; medications are listed in Supplementary Table 2. We defined two causal contrasts of interest: the intention-to-treat effect and the per-protocol effect. The intention-to-treat effect is the effect of being assigned to a treatment strategy at baseline, where treatment was defined by having a record of prescription of the assigned medication class at T_0. The per-protocol effect is the effect of continued use of the medication class assigned at T_0 throughout follow-up. Participants were considered to have discontinued use of the medication (nonadherent to

the protocol) if a prescription was not refilled 90 days after the end of supply.

Covariates

We selected a set of predefined covariates, including predictors of antihyperglycemic treatment assignment on the basis of clinical knowledge and informed by prior RCTs. Predefined covariates were evaluated in the year before T_0 and included demographics, such as age, race (white, black, and other), and sex; clinical measurements, such as HbA_{1c}, eGFR, albuminuria, blood pressure, LDL, and BMI; history of diseases, including 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 history of medication use, including metformin, insulin, thiazolidinediones, other diabetes medications (α-glucosidase inhibitors and amylin analogs), statins, ACE inhibitors or angiotensin receptor blockers, β-blockers, diuretics, and calcium channel blockers. We also included other covariates, such as smoking status (never, former, current), number of outpatient visits, hospitalization length of stay, type of health care system where the antihyperglycemic was prescribed at T_0 (categorized as hospital system or outpatient clinic), and the calendar year of T_0. Medications, excluding insulin, were categorized into two levels on the basis of whether they were used for $>$90 days within 1 year before T_0. Insulin was categorized into a four-level variable on the basis of insulin use within 1 year before T_0: *1*) never used; *2*) used for a total of $>$90 days but not used within 90 days before T_0; *3*) used within 90 days before T_0, but total duration of use was $<$90 days; and *4*) total duration of use was $>$90 days and was used within 90 days before T_0. All laboratory measurements, besides albuminuria, were treated as continuous variables. Albuminuria was categorized as yes or no on the basis of an albumin-to-creatinine ratio $>$30 mg/g. Predefined continuous covariates, including age, eGFR, and HbA_{1c}, were controlled for as restricted cubic spline functions, where knots were set at the 5th, 30th, 60th, and 95th percentiles. Covariates were time updated for per-protocol analyses.

To more closely emulate the random treatment assignment in the target trial, we additionally leveraged the high-dimensional information available in VA electronic databases by using a high-dimensional variable selection algorithm to reduce potential imbalances in patient characteristics that influence treatment and are not captured by the predefined covariates (25,34). Variables within the year before T_0 were selected from outpatient records, inpatient records, pharmacy data, and laboratory data. Data were then organized into seven dimensions: outpatient ICD-10 diagnostic codes, outpatient CPT codes, inpatient ICD-10 diagnostic codes, inpatient CPT codes, and inpatient ICD-10 procedure codes for surgeries, pharmacy records, and laboratory results. For each dimension, the top 300 items (e.g., ICD codes, procedures, medications, laboratory tests) that occurred most frequently within cohort participants were selected. Abnormal laboratory values were categorized as above or below reference ranges. As a proxy of disease severity, for each participant, we evaluated the number of occurrences for each of the top $300 * 7$ dimensions $=$ 2,100 items and then categorized each item's occurrence into a set of three binary values: ever occurred, sometimes occurred (occurred at a frequency higher than that of 50% of cohort participants), and frequently occurred (occurred at a frequency higher than that of 75% of cohort participants), which generated, in total, $300 * 7 * 3 = 6{,}300$ variables from high-dimensional data. In consideration of the positivity assumption, univariate relative risk of the association between these items and treatment assignment in all six treatment pairs were computed only for variables that occurred in $>$50 patients in all treatment arms (35). To ensure efficiency of probability estimation, we then selected the 500 high-dimensional variables with the strongest association with differences in treatment assignment (this was done independently for each treatment pair [SGLT2is vs. GLP-1, SGLT2is vs. DPP-4, SGLT2is vs. sulfonylureas, GLP-1 vs. DPP-4, GLP-1 vs. sulfonylureas, and DPP-4 vs. sulfonylureas] for a total of six comparisons). Among these selected variables, final selection of covariates was based on predictors of differences in treatment assignment between all pairwise comparisons of the four antihyperglycemics (which appeared in all six sets of pairwise comparisons). The final set of high-dimensional variables was used along with predefined variables to predict the probability of receiving each treatment. For estimation of the per-protocol effect, we used the same predefined predictors of treatment assignment as predictors for nonadherence and additionally applied a high-dimensional covariate selection algorithm at each time point. High-dimensional variables were selected on the basis of their relationship with treatment adherence (36). Both predefined and high-dimensional variables were time updated as appropriate and were used to predict the probability of following the protocol at each time point. Supplementary Fig. 2 provides an overview of the high-dimensional variable selection algorithm.

Statistical Analyses

For the overall cohort and across treatment arms, participant characteristics are presented as means and SDs for continuous variables and frequencies and proportions for categorical variables. Unadjusted survival probabilities across the four treatment arms were estimated by the Kaplan-Meier method.

A flowchart for the overall analytic approach for estimation of intention-to-treat and per-protocol effects is provided in Supplementary Fig. 2. Generalized propensity scores for the probability of treatment assignment were computed by a multinomial logistic regression model that predicted assignment to the four treatment groups where both the predefined variables and the high-dimensional variables were included (37,38). To take into consideration the potential effect modification of relationships with treatment assignment by past history and current use of insulin, we tested interaction terms between insulin and all predefined variables. These terms improved model fit (assessed through Bayesian information criterion) and so were retained.

To test the robustness of our emulation strategy, we applied negative and positive outcome controls to detect the presence of spurious associations and to test whether our approach would reproduce well-established associations (39). These analyses are designed to detect both suspected and unsuspected sources of spurious relationships (39). We used chronic lower respiratory

diseases as a negative outcome control, where there is neither biologic plausibility nor a priori evidence suggesting the presence of a relationship (39). Changes in BMI (increase of >10% and decrease of >10% from baseline) were used as positive outcome controls, where prior evidence suggests that SGLT2is and GLP-1 are associated with weight loss and sulfonylureas are associated with weight gain (19). The associations were estimated through Cox survival models after adjusting for the probability of assignment to SGLT2is, GLP-1, and DPP-4 (the generalized propensity score). The intention-to-treat effects of medications on risk of the composite outcome of eGFR decline >50%, ESKD, or all-cause mortality was estimated through a Cox survival model after adjusting for the generalized propensity score (38). Hazard ratios (HRs) for comparisons between each treatment pair and adjusted survival curves are presented. Estimated number of events per 1,000 person-years and event rate difference were computed on the basis of the survival probability at 3 years obtained from Cox models. To evaluate intention-to-treat effects in different subgroups, subgroup analyses were conducted where subgroups were defined on the basis of baseline eGFR (≥90, <90 to ≥60, <60 to ≥45, and <45 mL/min/1.73 m^2), baseline metformin use (use or non-use of metformin within 90 days before T_0), baseline cardiovascular disease (with and without cardiovascular diseases), BMI category (≤25, >25 to 30, and >30 kg/m^2), and age at T_0 (≥65 and <65 years). For each subgroup analysis, high-dimensional variables were selected independently. We conducted multiple sensitivity analyses to examine the robustness of our results. We *1*) estimated the treatment effect through inverse probability of treatment weighting with 0.1% truncation of stabilized weights (37,40); *2*) estimated the risk of each individual component of the composite outcome, including eGFR decline >50%, ESKD, or all-cause mortality; *3*) adjusted for time-varying HbA_{1c} with restricted cubic spline to investigate antihyperglycemic medication effects independent of glycemic control; *4*) adjusted for time-varying BMI with restricted cubic spline to investigate effects independent of changes in weight; and *5*) adjusted for both time-varying HbA_{1c} and BMI splines.

To offer more patient-centered and clinically relevant treatment effect estimates, we estimated the per-protocol effect of antihyperglycemics on the risk of the composite kidney outcome (41–43). The per-protocol effect in this study is the effect of continuous use of the assigned treatment throughout follow-up. To adjust for differences in probability of treatment assignment across treatment groups and probability of protocol adherence, we applied the approach of inverse weighting by treatment assignment and inverse weighting by the time-dependent probability of nonadherence to the protocol (43–45). Predictors of adherence (nondeviation from the protocol) included time-updated predefined variables as well time-updated high-dimensional variables, which were selected in the pseudocohort at each time point (k) among those who had adhered to the assigned treatment strategy at the prior time point ($k-1$). The stabilized weight for adherence was estimated as follows:

$$SW_k^Z = \prod_{k=1}^{t} \frac{\Pr(Z_k = 1 | \bar{Z}_{k-1} = 1, A, V)}{\Pr(Z_k = 1 | \bar{Z}_{k-1} = 1, A, \bar{Q}_{k-1})}$$

where Z is an indicator of adherence; A is the treatment arm; V is a vector of time-independent predictors, including age, race, sex, type of health care system where the antihyperglycemic medication was initially prescribed, and year of T_0; and $\bar{Q}_{k-1}$ is the history of predefined variables and high-dimensional variables through time $k-1$ (46). The time-dependent probability was estimated from logistic regressions at each time point. The time-dependent high-dimensional variables included the top 500 variables with the strongest univariate relative risk with adherence at time k, further restricted to those variables associated with differences in probability of assignment in all pairwise comparisons of antihyperglycemics (36). Weights were truncated at the 0.1th and 99.9th percentile before estimating the per-protocol effect. The per-protocol effect used pooled logistic regression, with follow-up time treated as a restricted cubic spline and knots placed at 180, 360, 540, 720, and 900 days. A 95% CI that does not cross unity was considered statistically significant. All analyses were done using SAS Enterprise Guide 7.1 software (SAS Institute, Cary, NC). The study was approved by the institutional review board of the VA St. Louis Health Care System.

DATA AND RESOURCE AVAILABILITY

The study protocol and statistical code are available from Z.A.-A. Data are available through the VA.

RESULTS

Key baseline demographic and health characteristics of the overall cohort and by antihyperglycemic class are presented in Table 1. Unadjusted survival probability curves by antihyperglycemic class are provided in Supplementary Fig. 3; crude number of events, person-years of follow-up, and crude event rates are presented in Supplementary Table 3. Distributions of key covariates after adjustment by the propensity scores are provided in Supplementary Table 4.

Development of the Target Trial and Testing of Positive and Negative Outcome Controls

First, as a positive outcome control, we tested the association between antihyperglycemic class and risk of weight loss (defined as decrease in BMI of >10%). The results suggest that compared with sulfonylurea users, those on SGLT2is, GLP-1, and DPP-4 had a higher likelihood of a decrease in BMI; both SGLT2is and GLP-1 were associated with a greater likelihood of BMI decrease than DPP-4, with the results reproducing known associations between antihyperglycemic class and weight (Supplementary Table 5 and Supplementary Fig. 4A). Examination of risk of BMI increase >10% also reproduced established associations (Supplementary Table 5 and Supplementary Fig. 4B).

As a negative outcome control, we tested the association between the four classes of antihyperglycemics and the risk of chronic lower respiratory disease, where there is no a priori evidence or biologic plausibility for an association. The results suggest that there was no significant association between any of the antihyperglycemics and risk of chronic lower respiratory diseases (Supplementary Fig. 4C and Supplementary Table 5).

Intention-to-Treat Analyses

The adjusted survival probability in each treatment arm is depicted in Fig. 1*A*. Compared with those in the sulfonylurea arm, those treated with SGLT2is, GLP-1, and DPP-4 had a lower risk of the composite outcome of eGFR decline >50%, ESKD, or all-cause mortality (Figs. 1*A* and

Table 1—Key characteristics of the overall cohort and according to treatment arm

Cohort characteristic	Overall cohort	SGLT2is	GLP-1	DPP-4	Sulfonylureas
Patients	216,558	18,544 (8.56)	23,711 (10.95)	39,399 (18.19)	134,904 (62.29)
Age, years	65.46 (11.05)	65.88 (9.10)	64.87 (10.07)	67.06 (11.07)	65.05 (11.41)
Race					
White	155,829 (71.95)	13,624 (73.47)	17,325 (73.07)	28,465 (72.25)	96,405 (71.46)
Black	38,520 (17.79)	2,803 (15.12)	3,712 (15.66)	6,901 (17.52)	25,104 (18.61)
Other	22,219 (10.26)	2,117 (11.42)	2,674 (11.28)	4,033 (10.24)	13,395 (9.93)
Sex					
Male	204,622 (94.49)	17,794 (95.96)	21,818 (92.02)	37,114 (94.20)	127,896 (94.81)
Female	11,936 (5.51)	750 (4.04)	1,893 (7.98)	2,285 (5.80)	7,008 (5.19)
eGFR (mL/min/1.73 m^2)	75.02 (22.53)	76.49 (18.56)	70.67 (23.72)	72.61 (22.62)	76.29 (22.64)
HbA_{1c} (%)	8.57 (2.50)	8.59 (1.51)	8.68 (1.71)	8.35 (4.34)	8.61 (1.92)
HbA_{1c} (mmol/mol)	70 (20.42)	70 (12.31)	71 (13.99)	68 (35.34)	71 (15.83)
BMI (kg/m^2)	33.14 (6.60)	34.27 (6.47)	36.68 (7.06)	32.61 (6.36)	32.52 (6.38)
LDL (mg/dL)	87.90 (39.52)	81.37 (36.27)	80.95 (36.36)	85.91 (37.35)	90.60 (40.79)
Systolic blood pressure (mmHg)	132.94 (17.17)	132.52 (16.81)	132.55 (17.06)	132.57 (16.79)	133.18 (17.35)
Diastolic blood pressure (mmHg)	76.36 (10.55)	74.54 (10.16)	74.63 (10.22)	75.37 (10.41)	77.20 (10.60)
Congestive heart failure	16,258 (7.51)	2,321 (12.52)	2,975 (12.55)	2,500 (6.35)	8,462 (6.27)
Cardiovascular disease	54,389 (25.12)	7,969 (42.97)	6,915 (29.16)	9,537 (24.21)	29,968 (22.21)
Albuminuria*	57,883 (26.73)	5,762 (31.07)	8,171 (34.46)	10,903 (27.67)	33,047 (24.50)
Metformin use†	103,355 (47.73)	10,348 (55.80)	11,751 (49.56)	18,948 (48.09)	62,308 (46.19)
Insulin use†	56,346 (26.02)	11,224 (60.53)	17,908 (75.53)	12,909 (32.76)	14,305 (10.60)
ACE/ARB use†	91,406 (42.21)	10,084 (54.38)	13,360 (56.35)	17,081 (43.35)	50,881 (37.72)
Calcium channel blocker use†	44,264 (20.44)	4,440 (23.94)	6,211 (26.19)	8,380 (21.27)	25,233 (18.70)
β-Blocker use†	65,903 (30.43)	8,300 (44.76)	10,181 (42.94)	11,755 (29.84)	35,667 (26.44)
Diuretic use†	62,304 (28.77)	6,718 (36.23)	9,957 (41.99)	11,103 (28.18)	34,526 (25.59)
Statin use†	114,032 (52.66)	12,321 (66.44)	16,028 (67.60)	21,720 (55.13)	63,963 (47.41)
Smoking status					
Never	101,461 (46.85)	8,639 (46.59)	11,281 (47.58)	19,134 (48.57)	62,407 (46.26)
Former	67,051 (30.96)	6,167 (33.26)	8,485 (35.79)	12,482 (31.68)	39,917 (29.59)
Current	48,046 (22.19)	3,738 (20.16)	3,945 (16.64)	7,783 (19.75)	32,580 (24.15)
Follow-up time (days)	568 (310, 841)	360 (212, 618)	488 (276, 747)	535 (283, 813)	617 (355, 884)

Data are *n* (%), mean (SD), or median (interquartile range). ARB, angiotensin receptor blocker. *Microalbumin-to-creatinine ratio >30 mg/g. †Use defined as >90 days prescription within 1 year before T_0.

2 and Table 2). While there was no statistically significant difference in risk between the SGLT2i and GLP-1 arms, both SGLT2is and GLP-1 had a lower risk of the composite outcome than DPP-4 (Figs. 1*A* and 2 and Table 2). Adjusted event rate differences between each pairwise comparison of antihyperglycemic classes per 1,000 person-years are presented in Table 2. The adjusted event rates for each treatment arm per 1,000 person-years are provided in Supplementary Table 6.

Analyses by eGFR category suggested that compared with the sulfonylurea arm, those in the SGLT2i and GLP-1 arms exhibited a lower risk of the composite outcome in all eGFR categories. DPP-4 exhibited a lower risk than sulfonylureas in eGFR categories ≥60 mL/min/1.73 m^2, which became nonsignificant in lower eGFR categories. Compared with DPP-4, both SGLT2is and GLP-1 exhibited a reduced risk of the composite outcome in eGFR ≥90, ≥60 to <90, ≥45 to <60, and <45 mL/min/1.73 m^2 (Fig. 2 and Table 2).

Because the four studied antihyperglycemics are generally used as second-line agents (after metformin), we evaluated their comparative effectiveness among metformin users at baseline. The results were consistent with those in the primary analyses (Fig. 2 and Table 2). Subgroup analyses by history of cardiovascular disease, BMI category, and age-group produced results consistent with the main analyses (Fig. 2 and Table 2).

Sensitivity Analyses

We conducted several sensitivity analyses to test robustness of our main results (Supplementary Table 7). First, application of inverse probability of treatment weighting suggested that the average treatment effects of these antihyperglycemics were consistent with the effects estimated in the primary analyses. Second, we investigated the individual components of the composite end point, and the results suggested that the comparative effectiveness of the four classes of antihyperglycemics on the risk of the individual components of the composite outcome is consistent with the main analyses and were also consistent when the outcome was defined as eGFR decline >50% or ESKD. Third, to evaluate the relationship between antihyperglycemic type and the composite outcome independent of glycemic status, we developed analyses that additionally adjusted for time-dependent HbA_{1c}, and the results were consistent with the primary analyses. Fourth, to evaluate whether the observed relationship between antihyperglycemic class

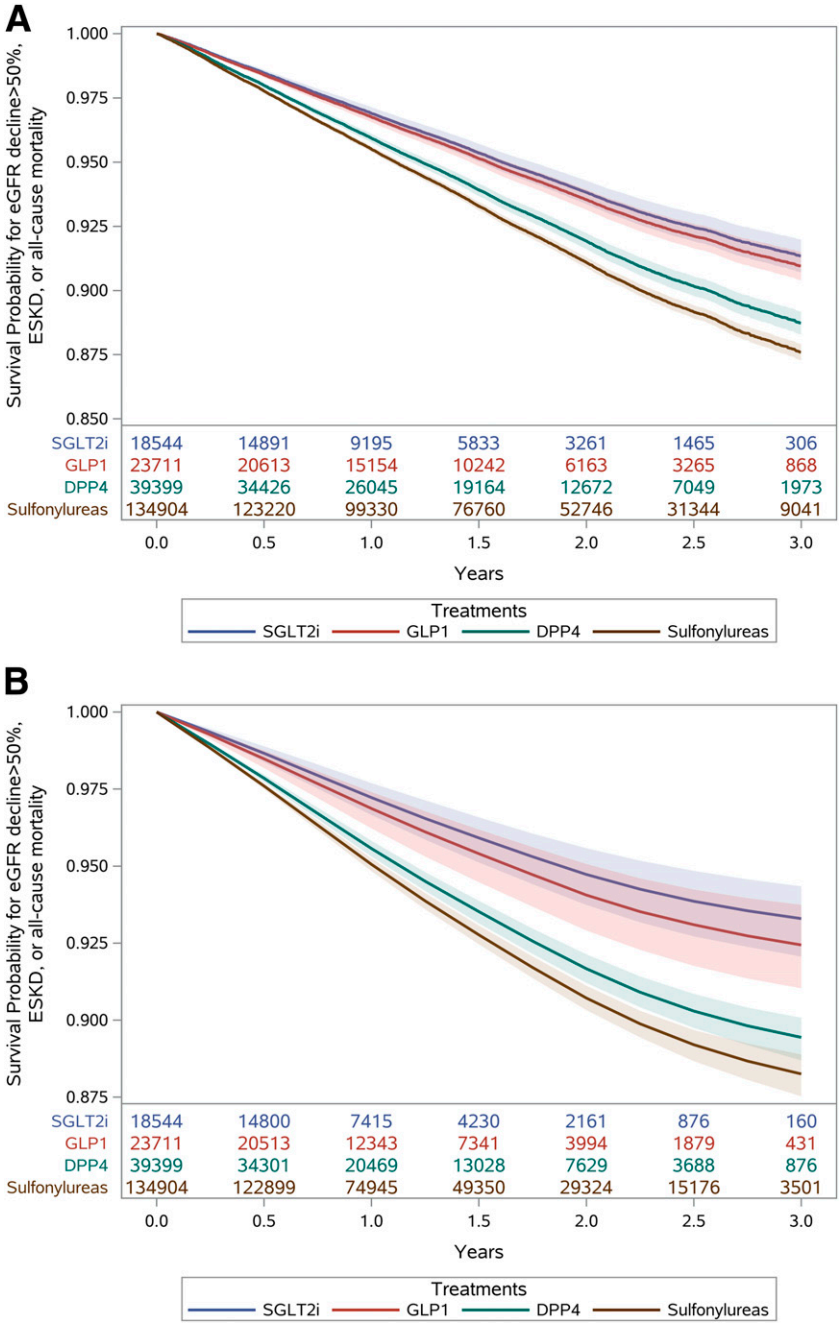

Figure 1—*A*: Adjusted intention-to-treat survival probability for the composite outcome of eGFR decline >50%, ESKD, or all-cause mortality. Survival probability in SGLT2i, GLP-1, DPP-4, and sulfonylureas arms, according to an intention-to-treat analysis. *B*: Adjusted per-protocol survival probability for the composite outcome of eGFR decline >50%, ESKD, or all-cause mortality. Survival probability in SGLT2i, GLP-1, DPP-4, and sulfonylurea arms according to a per-protocol analysis where the protocol was defined as maintaining use of the assigned antihyperglycemic medication throughout duration in the cohort. Light-colored bands represent the 95% CI for each treatment. Number of patients at risk in each arm is indicated.

and risk of composite outcome is independent of BMI, we developed analyses that additionally adjusted for time-dependent BMI, and the results were consistent with the primary analyses. Finally, results were consistent in analyses adjusting for both time-updated HbA_{1c} and BMI.

Per-Protocol Analyses

In a prespecified protocol requiring participants to maintain use of the assigned antihyperglycemic medication throughout duration in the cohort, 77.07%, 74.74%, 68.36%, and 61.23% in the SGLT2i, GLP-1, DPP-4, and sulfonylurea arms remained adherent to the protocol, respectively. Per-protocol analyses suggested that compared with the sulfonylurea arm, those treated with SGLT2is, GLP-1, and DPP-4 had a lower risk of the composite outcome (HR 0.55 [95% CI 0.46, 0.67], 0.62 [0.52, 0.75], 0.89 [0.84, 0.95], respectively) (Figs. 1*B* and 2). While we did not observe a statistically significant difference in risk between the SGLT2i and GLP-1 arms (0.89 [0.68, 1.15]), both SGLT2is and GLP-1 had a lower risk of the composite outcome than DPP-4 (0.62 [CI 0.51, 0.75], 0.70 [0.58, 0.85], respectively) (Figs. 1*B* and 2). Adjusted event rate differences between each pairwise comparison of antihyperglycemic classes per 1,000 person-years are presented in Table 2. The adjusted event rates for each treatment arm per 1,000 person-years are provided in Supplementary Table 6.

CONCLUSIONS

In this study of 216,558 people with type 2 diabetes (345,029.7 person-years of follow-up), we provide real-world evidence that compared with those with new use of sulfonylureas, new use of SGLT2is, GLP-1, and DPP-4 was associated with a lower risk of the composite outcome of eGFR decline >50%, ESKD, or all-cause mortality. We did not observe a statistically significant difference in risk of the composite outcome between the SGLT2i and GLP-1 groups. Both SGLT2is and GLP-1 had a lower risk of the composite outcome than DPP-4. The findings were consistent in multiple sensitivity analyses.

This study provides real-world evidence of the comparative effectiveness of these four classes of antihyperglycemics and complements evidence of efficacy provided by RCTs (6–9,11–13,18). Our data suggest that compared with sulfonylureas, both SGLT2is and GLP-1 are associated with a lower risk of the composite outcome across all subgroups examined. In particular, the risk reduction in SGLT2is versus sulfonylureas and GLP-1 versus sulfonylureas was evident in all eGFR categories, including those with eGFR <45 mL/min/1.73 m^2, a finding that is consistent with, and extends (by providing evidence on GLP-1), the observations in the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial and recent real-world evidence (of SGLT2is vs. other antihyperglycemics),

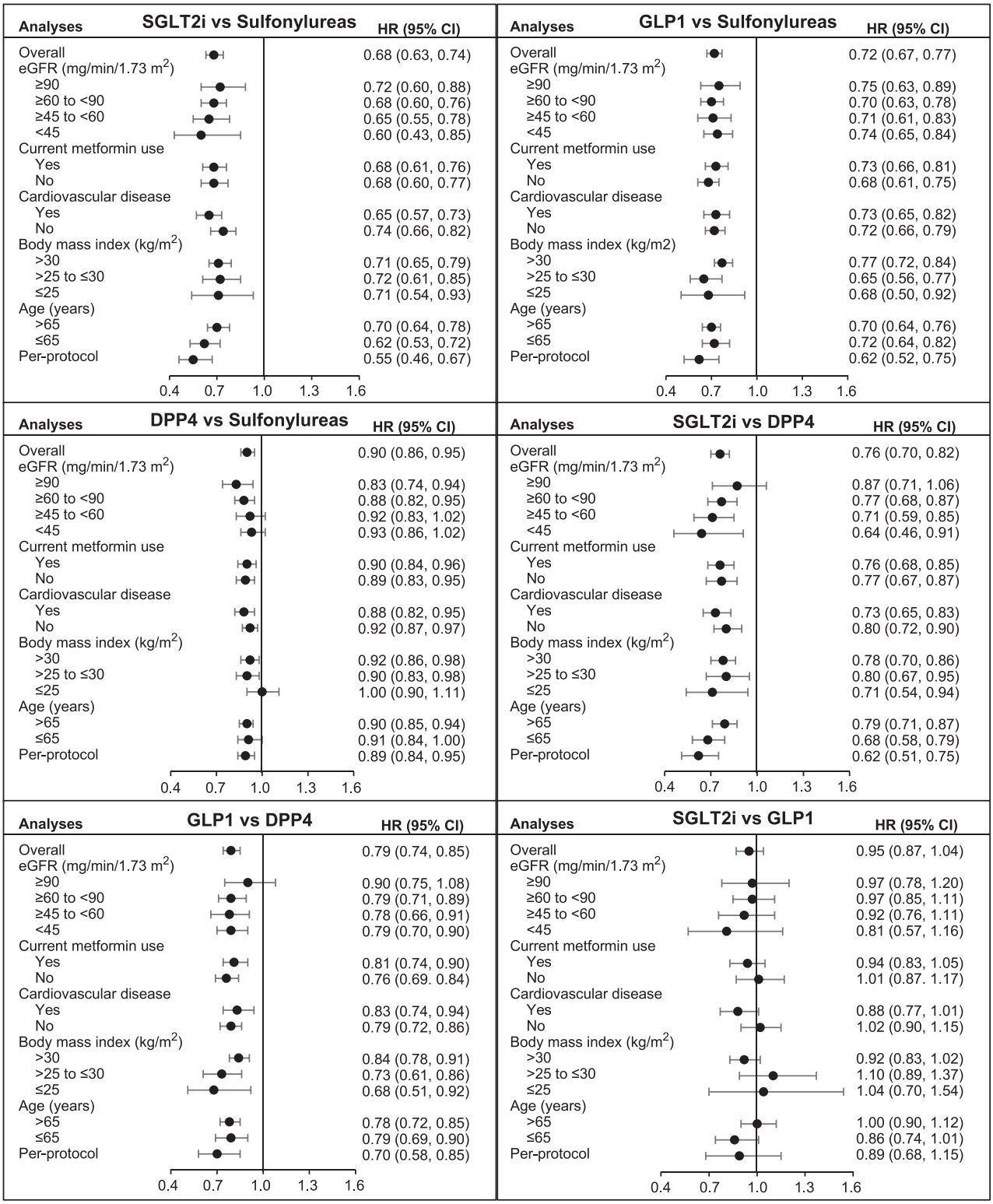

Figure 2—HRs for the composite outcome of eGFR decline >50%, ESKD, or all-cause mortality. Forest plots present the HRs of the composite outcome of eGFR decline >50%, ESKD, or all-cause mortality in the overall cohort and by eGFR category, metformin use status, cardiovascular disease status, BMI category, and age category at T_0 on the basis of intention-to-treat analyses and in the overall cohort on the basis of per-protocol analysis. Comparisons between SGLT2i and sulfonylureas, GLP-1 and sulfonylureas, DPP-4 and sulfonylureas, SGLT2i and DPP-4, GLP-1 and DPP-4, and SGLT2i and GLP-1 are presented, where the latter medication in each pair served as the reference.

Table 2—Pairwise treatment comparisons of the adjusted event rate difference per 1,000 person-years of the composite outcome of eGFR decline >50%, ESKD, or all-cause mortality for the overall cohort and in prespecified subgroups

	SGLT2i vs. SU	GLP-1 vs. SU	DPP-4 vs. SU	SGLT2i vs. DPP-4	GLP-1 vs. DPP-4	SGLT2i vs. GLP-1
Intention-to-treat analyses						
Overall cohort (n = 216,558)	−11.60 (−13.89, −9.37)	−10.42 (−12.28, −8.34)	−3.52 (−4.94, −1.99)	−8.07 (−10.36, −5.66)	−6.88 (−8.74, −4.95)	−1.16 (−3.65, 1.04)
eGFR (mL/min/1.73 m^2)						
≥90 (n = 60,794)	−6.96 (−10.78, −2.98)	−6.52 (−9.74, −2.77)	−4.29 (−6.71, −1.60)	−2.73 (−6.73, 1.68)	−2.20 (−5.58, 1.32)	−0.46 (−4.90, 3.56)
≥60 to <90 (n = 97,748)	−10.54 (−13.47, −7.59)	−9.93 (−12.68, −7.01)	−3.90 (−5.97, −1.65)	−6.68 (−9.76, −3.43)	−6.03 (−8.73, −3.26)	−0.58 (−3.90, 2.30)
≥45 to <60 (n = 34,303)	−16.23 (−22.47, −9.90)	−13.68 (−19.07, −7.68)	−3.91 (−8.02, 0.65)	−12.33 (−18.51, −5.68)	−9.76 (−14.94, −4.32)	−2.48 (−9.38, 3.50)
<45 (n = 23,713)	−28.89 (−44.54, −9.52)	−18.98 (−25.91, −11.03)	−4.75 (−9.97, 0.85)	−23.96 (−39.53, −4.81)	−14.22 (−21.38, −6.91)	−9.64 (−26.09, 9.88)
Current metformin use*						
Yes (n = 142,586)	−10.21 (−12.95, −7.54)	−8.77 (−11.17, −6.09)	−3.30 (−5.06, −1.36)	−6.93 (−9.69, −4.02)	−5.44 (−7.84, −2.97)	−1.43 (−4.33, 1.14)
No (n = 73,972)	−14.30 (−18.60, −9.97)	−14.74 (−17.91, −11.19)	−5.04 (−7.50, −2.42)	−9.24 (−13.49, −4.72)	−9.71 (−12.91, −6.40)	0.54 (−4.30, 5.05)
Cardiovascular disease						
Yes (n = 54,389)	−17.11 (−21.50, −12.83)	−12.98 (−17.13, −8.35)	−5.66 (−8.84, −2.31)	−11.45 (−15.92, −6.81)	−7.25 (−11.46, −2.98)	−4.11 (−9.24, 0.28)
No (n = 162,169)	−8.10 (−10.84, −5.39)	−8.68 (−10.60, −6.48)	−2.55 (−4.02, −0.97)	−5.55 (−8.20, −2.67)	−6.12 (−8.08, −4.06)	0.62 (−2.31, 3.37)
BMI (kg/m^2)						
>30 (n = 142,180)	−9.22 (−1.78, −6.73)	−7.37 (−9.36, −5.21)	−2.66 (−4.38, −0.77)	−6.61 (−9.16, −3.86)	−4.69 (−6.72, −2.62)	−1.84 (−4.47, 0.49)
>25 to ≤30 (n = 57,085)	−10.05 (−14.61, −5.18)	−12.80 (−16.63, −8.19)	−3.64 (−6.13, −0.89)	−6.40 (−11.07, −1.26)	−9.16 (−13.20, −4.78)	2.86 (−3.07, 8.20)
≤25 (n = 17,293)	−17.33 (−29.32, −3.41)	−19.93 (−30.86, −5.35)	−0.19 (−5.72, 6.04)	−17.19 (−29.55, −2.79)	−19.94 (−31.11, −5.57)	2.72 (−15.90, 18.92)
Age (years)						
>65 (n = 124,641)	−12.55 (−15.86, −9.31)	−12.86 (−15.52, −9.93)	−4.44 (−6.37, −2.40)	−8.12 (−11.33, −4.69)	−8.39 (−10.93, −5.72)	0.35 (−3.25, 3.58)
≤65 (n = 91,917)	−10.60 (−13.58, −7.64)	−7.90 (−10.46, −5.02)	−2.41 (−4.53, −0.07)	−8.16 (−11.38, −4.90)	−5.46 (−8.12, −2.66)	−2.69 (−5.86, 0.10)
Per-protocol analysis†						
Overall cohort (n = 216,558)	−17.06 (−21.28, −12.34)	−14.24 (−18.65, −9.08)	−4.00 (−6.29, −1.68)	−13.06 (−17.43, −8.34)	−10.20 (−14.98, −5.01)	−2.80 (−8.78, 3.37)

Results are presented as adjusted event rate difference per 1,000 person-years (95% CI), where the latter medication in each pair served as the reference. SU, sulfonylurea. *Current use defined as having a metformin prescription within 90 days before or at T_0. †Protocol defined as maintaining use of the assigned antihyperglycemic medication throughout duration in the cohort.

suggesting that the benefit of SGLT2is in slowing progression of kidney disease is present regardless of baseline eGFR (9,18,47,48). Compared with DPP-4, both SGLT2is and GLP-1 are also associated with lower risk in all subgroups except those with eGFR ≥90 mL/min/1.73 m^2, which may be explained by the lower event rate in this subgroup. DPP-4 was associated with lower risk than sulfonylureas in people with eGFR ≥60 mL/min/1.73 m^2; the observed risk difference was small and may possibly explain the lack of statistical significance in subgroups with fewer participants; the alternative explanation is that salutary properties of DPP-4 on hard kidney outcomes may not be manifest in people with high renal risk (15). The four antihyperglycemics are commonly used as second-line agents after metformin; our results suggest that the observed associations were consistent regardless of metformin use at baseline. Our per-protocol analyses, which required prescription of the assigned antihyperglycemic to be maintained throughout duration in the cohort, were consistent with the primary results and might more closely reflect the true strength of the association between antihyperglycemic class and the composite outcome. Overall, the findings provide a greater understanding of the comparative effectiveness of these four antihyperglycemics in a real-world setting according to eGFR category and other clinically relevant prespecified subgroups.

In our sensitivity analyses, examination of the individual components of the composite end point yielded results consistent with those of the primary analyses of the composite end point (Supplementary Table 7), suggesting that the observed association between the antihyperglycemics and the composite outcome is also likely driven by risk reduction from each component. Analyses that additionally adjusted for time-updated HbA_{1c} and BMI reproduced the observations made in the primary analyses, suggesting that the observed associations may be independent of the drug effect on glycemic control and changes in weight. These findings are consistent with an evolving understanding of a putative glucose-independent effect of SGLT2i, GLP-1, and DPP-4 on cardiovascular and kidney outcomes (13,49,50).

RCTs provide foundational evidence on safety and efficacy in the populations examined; however, because of their highly selective criteria, results from RCTs leave significant gaps in understanding the benefits and risks applied to broader populations in real-world settings. This concern about generalizability (51–53) and lack of real-world evidence may partially explain the observation that despite RCT evidence showing reduction in risk of kidney disease end points with SGLT2i and GLP-1, incorporation of recent trial findings into diabetes care pathways and utilization of the newer antihyperglycemics have been tepid (22). Furthermore, except for the ongoing Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) (54), which aims to evaluate glycemic control (and does not include an SGLT2i arm) (24), there are no registered clinical trials (finished or ongoing) addressing the comparative effectiveness of newer vis-à-vis older antihyperglycemic agents. A recent white paper suggested that leveraging large, high-quality health care databases and robust methodologies may be useful in addressing knowledge gaps regarding comparative effectiveness of newer (SGLT2is, GLP-1) versus older (DPP-4, sulfonylureas) antihyperglycemics (24). In this study, we used high-dimensional data captured during routine medical care and applied robust methodologies to provide real-world evidence of the comparative effectiveness of the four antihyperglycemics. This complements evidence from RCTs to better inform choice of antihyperglycemic therapy for type 2 diabetes (22).

This study has limitations. We used observational, real-world data from the VA, and our cohort included U.S. veterans who were mostly older, white, and male, which may limit the generalizability of study findings. Although our analytic approach included active comparators (comparison among four classes of 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. Our analyses did not examine risk of incident albuminuria or its progression, did not consider within-antihyperglycemic class differences, and did not examine the risk of adverse events. Because of the low number of people with eGFR <30 mL/min/1.73 m^2 in the SGLT2i arm, comparative effectiveness of SGLT2i vis-à-vis the other antihyperglycemics in this eGFR category could not be undertaken.

The study has several strengths, we designed it to emulate a four-arm target trial by first specifying the trial protocol and then emulating it. We tested the rigor of our approach by applying negative controls to detect spurious associations (39) and positive controls to reproduce a priori knowledge. 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 used a new user design with active comparators and applied advanced statistical methodologies, including high-dimensional variable selection algorithms and per-protocol analyses. We examined the comparative effectiveness in prespecified subgroups of interest to the clinical community and tested robustness of results in multiple sensitivity analyses. Finally, we oriented our research question, study design, and execution to specifically address knowledge gaps that have not been and are unlikely to be addressed by RCTs (comparative effectiveness of the four classes [older and newer] of antihyperglycemics) (24).

In sum, in this real-world study of 345,029.7 person-years, we provide evidence of the comparative effectiveness of four antihyperglycemics. The evidence complements and extends knowledge gained in clinical trials and suggests that in people with type 2 diabetes, both SGLT2is and GLP-1 are associated with a reduced risk of composite kidney outcomes compared with DPP-4 and sulfonylureas.

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manuscript drafting or revision. Z.A.-A. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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