Reduction of Cardiovascular Risk and Improved Estimated Glomerular Filtration Rate by SGLT2 Inhibitors, Including Dapagliflozin, Is Consistent Across the Class: An Analysis of the Placebo Arm of EXSCEL

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OBJECTIVE

The sodium–glucose cotransporter 2 inhibitors (SGLT2i) empagliflozin and canagliflozin reduce the incidence of major adverse cardiovascular events (MACE), all-cause mortality (ACM), and renal events in cardiovascular outcomes trials, with observational real-world evidence suggesting class effect benefits that include dapagliflozin. We examined the placebo arm of the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) to determine whether the effects of drop-in open-label dapagliflozin on MACE, ACM, and estimated glomerular filtration rate (eGFR) were consistent with the SGLT2i class as a whole.

RESEARCH DESIGN AND METHODS

SGLT2i drop-in therapy occurred in 10.6% of EXSCEL participants, with 5.2% taking dapagliflozin. Propensity-matched cohorts of SGLT2i users and nonusers (*n* = 709 per group) were generated on the basis of their characteristics before open-label SGLT2i drop-in or at baseline for participants taking SGLT2i at enrollment and an equivalent study visit for non-SGLT2i users. Time to first adjudicated MACE and ACM was analyzed using Cox regression. eGFR slopes were compared between matched cohorts using a mixed-model repeated-measures analysis.

RESULTS

In adjusted analyses, SGLT2i users (compared with nonusers) had a numerically lower risk of MACE (adjusted hazard ratio 0.79 [95% CI 0.49–1.28]), as did dapagliflozin users (0.55 [0.26–1.15]). SGLT2i users had a significantly lower ACM risk (0.51 [0.27–0.95]; dapagliflozin: 0.66 [0.25–1.72]). Compared with nonusers, eGFR slope was significantly better for SGLT2i users overall (+1.78 [95% CI 0.87–2.69] mL/min/1.73 m^2 per year) and for dapagliflozin users (+2.28 [1.01–3.54] mL/min/1.73 m^2 per year).

CONCLUSIONS

This post hoc analysis of the placebo arm of EXSCEL supports a beneficial class effect for all SGLT2i, including dapagliflozin, for reduced ACM and less eGFR decline.

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Type 2 diabetes increases the risk of cardiovascular disease (CVD), mortality, and kidney disease, even when blood glucose levels are well controlled (1–4). Starting in 2008, the U.S. Food and Drug Administration mandated cardiovascular outcomes trials (CVOTs) to evaluate the cardiovascular safety of newly approved diabetes treatments (5). The Exenatide Study of Cardiovascular Event Lowering (EXSCEL) CVOT assessed the long-term cardiovascular outcomes of subcutaneous once-weekly 2 mg exenatide, a glucagon-like peptide 1 receptor agonist (GLP-1RA), in 14,752 participants with type 2 diabetes, 73.1% of whom had prior CVD (6–8). EXSCEL was a placebo-controlled, randomized (exenatide:placebo 1:1), pragmatic clinical trial conducted in 35 countries between 2010 and 2017.

Participants in EXSCEL were permitted to receive up to three oral glucose-lowering agents or insulin either alone or in combination with up to two oral glucose-lowering agents for the management of their diabetes (6–8). During the course of EXSCEL, sodium–glucose cotransporter 2 inhibitors (SGLT2i) dapagliflozin, canagliflozin, and empagliflozin were approved and marketed in many of the regions from which the trial recruited participants.

Emerging evidence from CVOTs for empagliflozin (BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients [EMPA-REG OUTCOME]) (9) and canagliflozin (Canagliflozin Cardiovascular Assessment Study [CANVAS]/CANVAS-Renal [R]) (10) and from observational real-world evidence analyses (Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors [CVD-REAL] [11], CVD-REAL 2 [12,13], Evidence for Cardiovascular Outcomes With Sodium Glucose Cotransporter 2 Inhibitors in the Real World [EASEL] [14], and the Birmingham study in The Health Improvement Network [THIN] cohort [15]) suggests that SGLT2i may reduce the incidence of major adverse cardiovascular events (MACE) and provide renal protection (16,17). However, discrepancies among some trial outcomes, differing patient phenotypes, and differences in SGLT1 selectivity on a background of differential safety (namely, amputation and bone health [18]) have raised questions about whether the benefits seen are drug specific or an SGLT2i class effect (13,19,20). This situation also is confounded by the multitude of potential mechanisms beyond glucose control that may contribute to these clinically observed outcomes (21,22). Support for the possible class effect for the cardiorenal benefits observed in the EMPA-REG and CANVAS/CANVAS-R trials may be strengthened by dapagliflozin, another SGLT2i being evaluated in the Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) (23,24) CVOT.

To assess the impact of dapagliflozin compared with other SGLT2i on cardiovascular and renal outcomes within a single trial, this post hoc analysis used data from the placebo group of EXSCEL to assess the impact of SGLT2i overall, and dapagliflozin specifically, on adjudicated MACE, adjudicated all-cause mortality (ACM), and estimated glomerular filtration rate (eGFR) decline in a population spread across multiple regions and with varying cardiovascular risk. The placebo group was selected because some GLP-1RAs have been shown to have cardio- and renal-protective effects (25,26).

RESEARCH DESIGN AND METHODS

Population

The placebo arm of the EXSCEL CVOT (clinical trial reg. no. NCT01144338, ClinicalTrials.gov) included 7,396 participants; 786 (10.6%) of these had a record of open-label SGLT2i use at some point during the trial conduct, of whom 385 (5.2%) used dapagliflozin. All available participants were included in the analysis; 18 participants who never received study treatment were included in the initial assessment for baseline characteristics (Table 1) but were excluded from further analysis because of missing information (Supplementary Fig. 1). All participants provided written informed consent.

Information on concomitant medication use was collected at each 6-month study visit. Textual information was filtered to classify canagliflozin, dapagliflozin, or empagliflozin use, logged by drug name or brand name. No other SGLT2i were used in this study. Because actual start and end dates for concomitant medications were not available, SGLT2i was assumed to have been initiated at the first visit for which its use was recorded. Total SGLT2i exposure was defined as the time from the first to the last recorded use (regardless of gaps or switching type of SGLT2i). No SGLT2i use was conservatively assumed where data were missing (e.g., before collection of SGLT2i information was begun in May 2013). To analyze dapagliflozin use specifically, participants were censored at initiation of treatment with canagliflozin or empagliflozin.

Owing to the pragmatic nature of this trial, only local clinical laboratory values were available. Outliers were capped to constrain measurements to physiologically reasonable ranges using the following cutoffs: BMI >60 kg/m^2, eGFR >250 mL/min/1.73 m^2, HbA_{1c} $>15\%$ (140 mmol/mol), total cholesterol >15 mmol/L, and hemoglobin <75 g/L or >200 g/L.

End Points

This study examined *1*) time to the adjudicated first EXSCEL primary end point (a composite three-point MACE end point of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke), *2*) time to the first adjudicated ACM (a prespecified EXSCEL secondary end point), and *3*) change over time in the local site-reported eGFR calculated using the MDRD equation (27), as specified in the EXSCEL protocol. Exploratory time-to-event analyses also were performed for *1*) cardiovascular death, *2*) nonfatal myocardial infarction, *3*) nonfatal stroke, *4*) hospitalization for heart failure (hHF), *5*) peripheral artery disease (PAD), and *6*) diabetic eye complications.

Statistical Methods

Hazard ratios (HRs) for the time-to-first-event analyses were calculated using a Cox proportional hazards regression model, both with SGLT2i use as the sole exploratory variable (unadjusted) and with adjustment for selected characteristics known to affect cardiovascular risk: duration of diabetes, age, sex, history of CVD, prior heart failure, prior albuminuria (micro- or macroalbuminuria), baseline eGFR, and baseline HbA_{1c}. The number of adjustments was constrained because of the limited size of the data set. Participants missing any of the required covariates were excluded from the adjusted analysis (Supplementary Fig. 1). Prior CVD was defined per EXSCEL protocol as a history of major clinical

Table 1—Clinical characteristics of all participants by SGLT2i use at baseline and propensity-matched cohorts at the time of matching

	Full population: trial baseline			Propensity matched: time of matching			
	No SGLT2i	SGLT2i	Dapagliflozin	No SGLT2i	SGLT2i	No dapagliflozin†	Dapagliflozin
Participants (*n*)	6,610	786	385	709	709	353	353
Male sex	4,056 (61)	531 (68)	249 (65)	470 (66)	483 (68)	225 (64)	230 (65)
Age (years)	62.2 (9.4)	59.6 (8.9)	59.4 (8.6)	62.7 (9.5)	62.2 (8.6)	63.6 (9.5)	62.0 (8.3)
Race							
White	4,939 (75)	682 (87)	331 (86)	612 (86)	616 (87)	300 (85)	302 (86)
Black	414 (6.3)	22 (2.8)	11 (2.9)	22 (3.1)	19 (2.7)	14 (4.0)	10 (2.8)
Asian	672 (10)	55 (7.0)	32 (8.3)	55 (7.8)	52 (7.3)	26 (7.4)	32 (9.1)
Other/unknown	585 (8.9)	27 (3.4)	11 (2.9)	20 (2.8)	22 (3.1)	13 (3.7)	9 (2.5)
Region							
North America	1,591 (24)	283 (36)	60 (16)	259 (37)	250 (35)	70 (20)	57 (16)
Latin America	1,312 (20)	51 (6.5)	35 (9.1)	48 (6.8)	48 (6.8)	31 (8.8)	32 (9.1)
Asia Pacific	699 (11)	61 (7.8)	43 (11)	54 (7.6)	58 (8.2)	33 (9.3)	43 (12)
Western Europe	1,148 (17)	251 (32)	164 (43)	198 (28)	219 (31)	138 (39)	141 (40)
Eastern Europe	1,860 (28)	140 (18)	83 (22)	150 (21)	134 (19)	81 (23)	80 (23)
Hispanic ethnicity	1,451 (22)	69 (8.8)	38 (9.9)	58 (8.2)	64 (9.0)	37 (10)	36 (10)
Duration of diabetes (years)	13.2 (8.4)	12.8 (7.5)	12.3 (7.4)	15.7 (8.1)	15.5 (7.5)	15.4 (8.3)	14.7 (7.2)
History of CVD (CAD, PAD, or stroke)	4,887 (74)	501 (64)	240 (62)	486 (69)	479 (68)	226 (64)	227 (64)
History of heart failure	1,131 (17)	97 (12)	46 (12)	100 (14)	97 (14)	52 (15)	45 (13)
History of retinopathy	1,137 (17)	109 (14)	52 (14)	132 (19)	122 (17)	59 (17)	57 (16)
History of albuminuria	1,012 (15)	139 (18)	67 (17)	170 (24)	171 (24)	83 (24)	83 (24)
Microalbuminuria	777 (12)	115 (15)	57 (15)	139 (20)	140 (20)	67 (19)	70 (20)
Macroalbuminuria	235 (3.6)	24 (3.1)	10 (2.6)	39 (5.5)	37 (5.2)	19 (5.4)	14 (4.0)
Systolic blood pressure (mmHg)	135.6 (17.0)	134.5 (15.7)	135.0 (16.2)	134.2 (17.1)	134.4 (16.4)	136.5 (16.7)	135.9 (15.6)
Diastolic blood pressure (mmHg)	77.9 (10.2)	78.8 (10.2)	79.5 (10.5)	76.8 (10.9)	77.3 (10.5)	77.8 (10.5)	78.8 (10.1)
BMI (kg/m^2)	32.5 (6.5)	34.4 (6.3)	34.1 (6.2)	34.1 (6.4)	34.3 (6.3)	34.0 (6.8)	34.1 (6.1)
HbA_{1c}							
%	8.1 (1.0)	8.2 (0.9)	8.2 (0.9)	8.3 (1.5)	8.4 (1.3)	8.2 (1.6)	8.3 (1.2)
mmol/mol	65	66	66	67	68	66	67
Cholesterol (mmol/L)	4.6 (3.1)	4.3 (1.1)	4.4 (1.1)	4.2 (1.1)	4.2 (1.1)	4.3 (1.3)	4.3 (1.2)
LDL (mmol/L)	2.5 (1.9)	2.3 (0.8)	2.3 (0.9)	2.3 (0.9)	2.2 (0.9)	2.3 (1.1)	2.3 (0.9)
HDL (mmol/L)	1.1 (0.3)	1.1 (0.3)	1.1 (0.4)	1.4 (7.6)	1.3 (4.0)	1.1 (0.3)	1.6 (5.6)
UACR (g/mol), median (SD)	1.7 (97.3)	1.5 (32.2)	1.7 (29.7)	1.8 (51.4)	1.7 (45.9)	1.7 (38.7)	1.7 (14.7)
Hemoglobin (g/L)	141.4 (75.9)	141.1 (15.4)	142.1 (15.9)	138.5 (43.9)	140.5 (16.9)	136.3 (15.6)	141.6 (17.2)
eGFR (mL/min/1.73 m^2)	75.9 (24.2)	82.6 (21.7)	83.2 (21.6)	79.2 (25.9)	80.1 (21.3)	79.1 (27.1)	81.6 (21.3)
eGFR <60 mL/min/1.73 m^2	1,700 (26)	112 (14)	51 (13)	156 (22)	124 (17)	74 (21)	51 (14)
eGFR <45 mL/min/1.73 m^2	516 (7.8)	17 (2.2)	8 (2.1)	50 (7.1)	18 (2.5)	32 (9.1)	7 (2.0)
Smoking							
Never	766 (12)	91 (12)	45 (12)	84 (12)	84 (12)	39 (11)	43 (12)
Past	2,544 (38)	345 (44)	167 (43)	323 (46)	306 (43)	153 (43)	151 (43)
Current	3,296 (50)	350 (45)	173 (45)	302 (43)	319 (45)	161 (46)	160 (45)
Year of randomization in trial							
2010	209 (3.2)	53 (6.7)	13 (3.4)	52 (7.3)	39 (5.5)	17 (4.8)	13 (3.7)
2011	534 (8.1)	84 (11)	29 (7.5)	108 (15.2)	68 (10)	39 (11)	25 (7.1)
2012	1,697 (26)	201 (26)	120 (31)	242 (34)	179 (25)	133 (38)	111 (31)
2013	1,344 (20)	166 (21)	88 (23)	153 (22)	158 (22)	84 (24)	81 (23)
2014	1,966 (30)	229 (29)	105 (27)	124 (17)	215 (30)	60 (17)	95 (27)
2015	860 (13)	53 (6.7)	30 (7.8)	30 (4.2)	50 (7.1)	20 (5.7)	28 (7.9)
Number of classes of diabetes medications*	1.3 (0.8)	1.6 (0.9)	1.6 (0.9)	1.5 (0.9)	1.6 (0.9)	1.4 (0.9)	1.5 (0.8)
RAASi	5,153 (78)	636 (81)	312 (81)	566 (80)	573 (81)	292 (83)	288 (82)
Other antihypertensive	3,831 (58)	445 (57)	228 (59)	400 (56)	422 (60)	191 (54)	212 (60)
Statin	4,759 (72)	607 (77)	279 (72)	528 (74)	535 (75)	248 (70)	249 (71)
Diuretic	2,893 (44)	325 (41)	153 (40)	336 (47)	315 (44)	156 (44)	144 (41)
Insulin	3,079 (47)	352 (45)	168 (44)	377 (53)	392 (55)	186 (53)	188 (53)
Metformin	4,993 (76)	671 (85)	331 (86)	573 (81)	584 (82)	285 (81)	291 (82)

Continued on p. 321

Table 1—Continued

	Full population: trial baseline			Propensity matched: time of matching			
	No SGLT2i	SGLT2i	Dapagliflozin	No SGLT2i	SGLT2i	No dapagliflozin†	Dapagliflozin
TZD	236 (3.6)	50 (6.4)	19 (4.9)	39 (5.5)	40 (5.6)	15 (4.2)	15 (4.2)
DPP-4i	863 (13)	221 (28)	105 (27)	191 (27)	207 (29)	82 (23)	95 (27)
Sulfonylurea	2,410 (36)	288 (37)	134 (35)	249 (35)	258 (36)	131 (37)	128 (36)

Data are *n* (%) or mean (SD) unless otherwise indicated. Trial baseline metrics calculated for participants with information available at randomization. CAD, coronary artery disease; RAASi, renin-angiotensin-aldosterone system inhibitor; UACR, urinary albumin-to-creatine ratio. †Cohort of non-SGLT2i users matched to dapagliflozin users. *Classes of diabetes medicines included biguanides, sulfonylureas, meglitinides, DPP-4i, and TZDs. Insulin, SGLT2i, and GLP-1RA (excluded by study protocol) are not included.

manifestations of coronary artery disease, atherosclerotic PAD, or ischemic cerebrovascular disease (7). To accommodate for the limited resolution of information about SGLT2i use (interval censored, collected at visits nominally every 6 months), an intention-to-treat–like approach was used; participants remained in the SGLT2i user group from first known use until the end of follow-up (time of event or end of trial follow-up), regardless of SGLT2i discontinuation or switching. A further exploratory subgroup analysis was performed for the MACE and ACM end points in participants with or without prior CVD at trial baseline.

Propensity Matching

Participants were propensity matched (28–30) at the time of open-label SGLT2i drop-in or baseline for those taking SGLT2i at enrollment. Covariates were compared at the first visit with recorded use of any SGLT2i and at the same scheduled visit for non-SGLT2i users, starting with baseline and proceeding through each subsequent 6-month visit window. Propensity scores were calculated across all available participants and visits using a generalized linear model. Once non-SGLT2i users were matched to SGLT2i users, they were removed from the pool of available control subjects for matching in future visit windows.

Covariates used for calculation of propensity scores were selected on the basis of observed differences in the baseline populations (Table 1) and other factors relevant to SGLT2i initiation. The covariates included were age, sex, ethnicity (Hispanic or non-Hispanic), smoking status at trial baseline (current, former, or never), race (white, black, Asian, or other), region, duration of diabetes, history of heart failure, history of prior CVD, BMI, eGFR, systolic blood pressure, HbA_{1c}, total cholesterol, and use of renin-angiotensin-aldosterone system inhibitors, thiazolidinediones (TZDs), metformin, dipeptidyl peptidase 4 inhibitors (DPP-4i), and insulin. To account for patient status before SGLT2i initiation, concomitant medication use and laboratory measurements were assessed at the closest available measurement before matching for that covariate or at trial baseline if SGLT2i initiation occurred at or before trial baseline. In the participants who were matched, 11 BMI, 2 eGFR, and 4 HbA_{1c} outliers were capped at any time point. Age and duration of diabetes were updated from trial baseline values by rounding time since randomization to the nearest year. History of prior CVD was updated from baseline using recorded incidence of MACE, PAD/peripheral vascular disease, coronary catheterization, angioplasty or stenting, coronary artery bypass graft, or percutaneous coronary intervention occurring before SGLT2i initiation/matching. History of heart failure was updated on the basis of the hHF interval. Participants who were missing any required covariates at a specific visit after this process were excluded from matching at that visit.

Propensity score matching was performed using a nearest neighbor approach, with a caliper of 0.1 and a matching ratio of 1, with the R software package MatchIt (31). Criteria for accepting a match were *1*) difference between treatment groups after matching of <0.1 standardized difference for every covariate used for matching and *2*) a nonsignificant *P* value for a χ^2 test for matching (28).

Follow-up time began at the time of matching: SGLT2i initiation or the equivalent matched visit for control subjects. The two groups were compared using a Cox proportional hazards regression model as described above. Covariates for model adjustment were evaluated at the time of matching. No multiple test correction was performed; an upper bound <1 on the HR 95% CI was used as the threshold for statistical significance, and nominal *P* values are reported. Propensity score matching between dapagliflozin users and non-SGLT2i users (referred to as the no dapagliflozin cohort for clarity) was repeated using the same protocol.

Sensitivity Analyses

Several sensitivity analyses were performed.

Full Population Time-to-First-Event Analysis

Follow-up time (to an event or censoring) was calculated from trial baseline for non-SGLT2i users and from SGLT2i initiation for SGLT2i users. Time before SGLT2i initiation was excluded. Covariates measured at trial baseline or the first available time point, if missing at baseline, were used for adjustment. Participants with a first event before SGLT2i initiation did not contribute follow-up time or events to the SGLT2i arm.

Time-Dependent Time-to-First-Event Analysis

The full population analysis was repeated by including SGLT2i use as a time-dependent covariate. Participants who never took an SGLT2i contributed follow-up time to the off group, participants taking an SGLT2i at randomization contributed follow-up time to the on group, and participants initiating an SGLT2i during the trial contributed follow-up time to the off group until SGLT2i initiation and then to the on group thereafter. A robust sandwich variance estimator was used (32).

Poisson Multiple Regression

The MACE analyses were repeated using a Poisson multiple regression, including all events occurring during follow-up (as opposed to first event only).

Renal Outcomes

The site-reported eGFR slope versus time was analyzed in the propensity-matched cohorts for both SGLT2i use and dapagliflozin use using a mixed-model repeated-measures (MMRM) analysis, with eGFR as the dependent variable, time (scheduled visit week) and baseline eGFR as linear covariates, SGLT2i use and visit-by-SGLT2i interaction as fixed effects, and patient as a random effect. All available data were used from initiation of SGLT2i (or equivalent time point in matched control subjects) until the end of study follow-up. CIs were calculated using the Wald test.

Software

The data file was created in SAS 9.4 using SAS Studio in an SAS GRID Unix environment. All the source data were received as SAS data sets and provided as a comma-separated value file for analysis. All subsequent analyses were performed in R version 3.4.0 (33).

RESULTS

Patient Population Characteristics

Trial baseline characteristics of placebo arm participants who did not take an SGLT2i (89.4%, *n* = 6,610 of 7,396), who took an SGLT2i at some point (10.6%, *n* = 786 of 7,396), and who took dapagliflozin (5.2%, *n* = 385 of 7,396) at some point are summarized in Table 1. SGLT2i users were, on average, younger, had less CVD and heart failure, had a higher BMI and eGFR (SGLT2i use not recommended for eGFR $<$45 mL/min/1.73 m^2 [empagliflozin, canagliflozin] or $<$60 mL/min/1.73 m^2 [dapagliflozin]), were more likely to be using a DPP-4i or TZD, and were more likely to be living in Western Europe or North America. Dapagliflozin users were more prevalent in Western Europe.

SGLT2i use by region, drug, and time are shown in Fig. 1 and Supplementary Tables 1 and 2. Canagliflozin was the most prevalent SGLT2i in North America, whereas dapagliflozin had the highest overall usage in this study (Fig. 1). Trends in the year of SGLT2i initiation reflect differences in regulatory approval time for the three SGLT2i and completion of the EMPA-REG OUTCOME trial in 2015 (Supplementary Table 2). Median time of first known SGLT2i use in the trial was 2.4 years (interquartile range 1.5–3.6 years) for all SGLT2i and 2.3 years (1.4–3.4 years) for dapagliflozin.

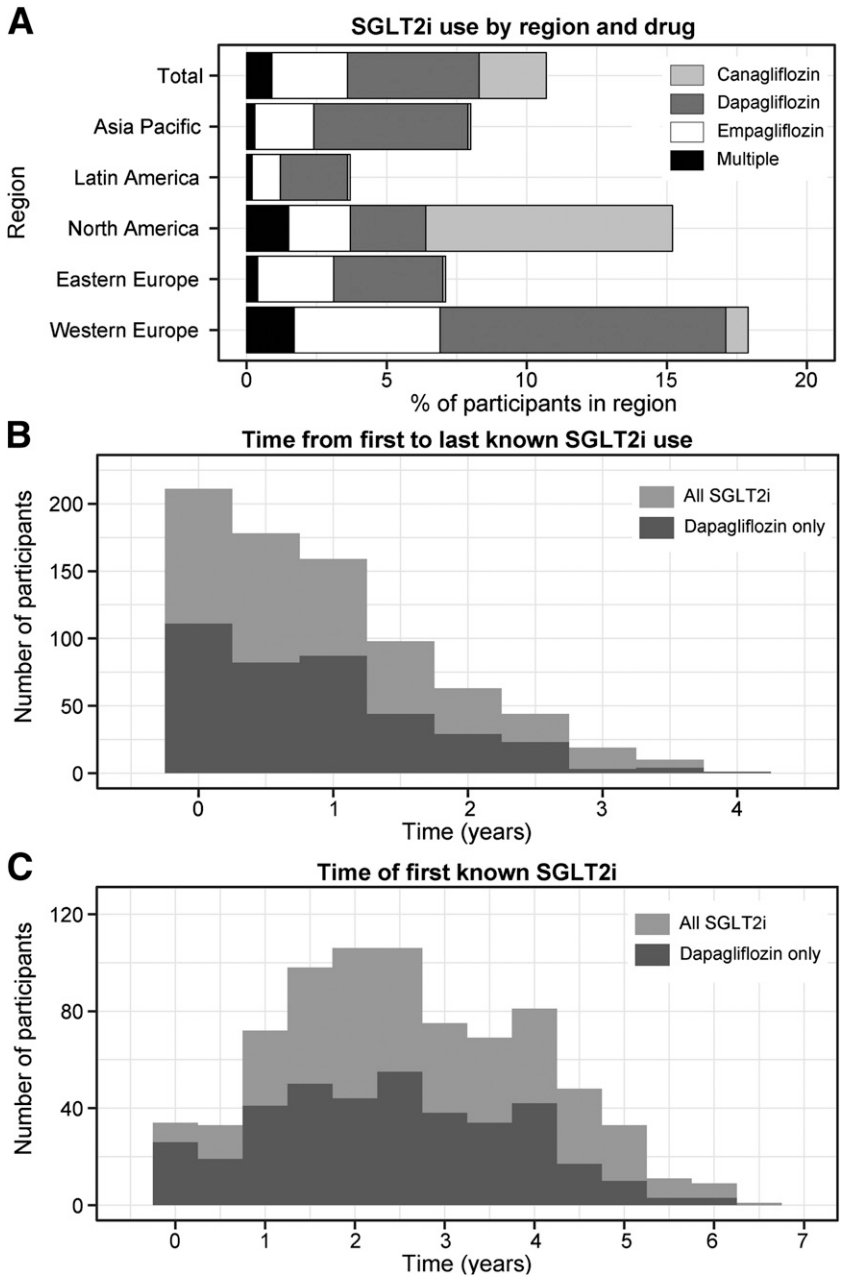

Figure 1—SGLT2i use in the EXSCEL placebo arm. *A*: Percentage of placebo arm participants who took an SGLT2i at some time by region and drug. Multiple indicates use of more than one SGLT2i drug during follow-up. *B*: Time of SGLT2i initiation in the placebo arm relative to trial baseline. *C*: Time from first known SGLT2i use to last known SGLT2i use in the placebo arm.

Median time from first known SGLT2i use to last known use was 9.2 months (2.5–17.9 months) for all SGLT2i and 9.4 months (2.2–16.8 months) specifically for dapagliflozin.

Propensity Matching

Matches were obtained for 709 SGLT2i users (93% of available participants) and 353 dapagliflozin users (95%, matched separately). All covariates included in the propensity score had an imbalance of $<$0.1 standardized difference (10%) after matching (Supplementary Fig. 2), and the distributions of the propensity scores were similar between cohorts (Supplementary Fig. 3). Of note, the control populations matched to SGLT2i users and dapagliflozin users specifically were different (Table 1), particularly in regional distribution, leading to different estimated event rates for the control group in some analyses. Median follow-up time in the cohorts was balanced

after matching: 1.3 years for non-SGLT2i users versus 1.1 years for SGLT2i users and 1.1 years for both groups in the dapagliflozin-matched cohorts.

Time-to-First-Event Analyses in Propensity-Matched Cohorts

Table 2 shows the incidence rates and estimated HRs for three-part MACE and ACM in the propensity-matched cohorts, comparing SGLT2i users with nonusers and dapagliflozin users with nonusers. MACE incidence rates were numerically lower for SGLT2i users versus nonusers (3.41 vs. 4.45 events per 100 participant-years) and for dapagliflozin users versus nonusers (2.69 vs. 4.54 events per 100 participant-years). Adjustment had minimal effect on the corresponding HRs, which remained numerically in favor of SGLT2i and dapagliflozin use in both the Cox analysis and the Poisson multiple regression (Supplementary Table 3). Kaplan-Meier curves for MACE are shown in Supplementary Fig. 4.

ACM incidence rates and HRs were lower for SGLT2i users and dapagliflozin users than for the corresponding nonusers (adjusted HR 0.51 [95% CI 0.27–0.95] vs. 0.66 [0.25–1.72], respectively). Kaplan-Meier curves for both matched cohorts showed separation in ACM risk within the first year (Supplementary Fig. 5). For both MACE and ACM, incidence rates in the SGLT2i cohort were similar across users of all three drugs (Supplementary Table 4).

A subanalysis of the participants with and without existing CVD at trial baseline in the propensity-matched cohorts was performed. In participants without prior CVD, the adjusted Cox model shows a significantly lower risk of MACE in SGLT2i users (Supplementary Table 5). A significantly lower risk of ACM also was seen in SGLT2i users in the subgroup without prior CVD in both unadjusted and adjusted models (Supplementary Table 6).

No significant differences were seen in time to first event for any of the exploratory end points in the propensity-matched cohorts (Supplementary Table 7). Similar point estimates were found for the three MACE components and hHF as those reported in the EMPA-REG OUTCOME and CANVAS trials (9,10,34).

Time to First Event in Full Population

To provide context, we report MACE and ACM rates in an unmatched population compared with the propensity-matched cohorts. Event rates and HRs for MACE in the full population were similar to those in the propensity-matched cohorts (3.46 and 2.94 vs. 4.29 events per 100 participant-years for SGLT2i users and dapagliflozin users vs. SGLT2i nonusers, respectively) (Supplementary Table 8), despite the lack of matching. ACM rates also were numerically lower with SGLT2i or dapagliflozin use (1.69 and 1.71 vs. 2.59 events per 100 participant-years for SGLT2i users and dapagliflozin users vs. SGLT2i nonusers, respectively), although the event rate in the full SGLT2i nonuser population was lower than that in the equivalent propensity-matched no SGLT2i cohort (Supplementary Table 9).

To quantify explicitly the impact of potential time bias, SGLT2i use was modeled as a time-dependent covariate and provided similar estimates of event rates and HRs as the full population analysis for MACE (Supplementary Table 8). The estimated HR for ACM was similar to that in the propensity-matched cohort and was statistically significant in the unadjusted analysis, but not after adjustment (Supplementary Table 9).

Effect of SGLT2i on Renal Function

Geometric mean eGFR over time in the propensity-matched cohorts is shown in Fig. 2. The MMRM-estimated increase in eGFR in the SGLT2i users was +0.87 (SE 0.37) mL/min/1.73 m^2 per year compared with an estimated decrease in the nonusers of −0.91 (SE 0.26) mL/min/1.73 m^2 per year, corresponding to a treatment effect of +1.78 (SE 0.47) mL/min/1.73 m^2 per year (95% CI 0.87–2.69; P = 0.00013). eGFR preservation was observed for each drug in the SGLT2i cohort (Supplementary Table 10). The treatment effect was also significant in the full population (Supplementary Table 11 and Supplementary Fig. 6).

The estimated increase in eGFR in dapagliflozin users was +1.24 (SE 0.54) mL/min/1.73 m^2 per year compared with an estimated decrease in the nonusers of −1.04 (SE 0.37) mL/min/1.73 m^2 per year, corresponding to a treatment effect of +2.28 (SE 0.64) mL/min/1.73 m^2 per year (95% CI 1.01–3.54; P = 0.0004). The dapagliflozin treatment effect was also significant in the full population (Supplementary Table 11 and Supplementary Fig. 6).

CONCLUSIONS

The placebo arm of EXSCEL provided a unique opportunity to assess credibly the

Table 2—Events, follow-up duration, incidence rates, and HRs for SGLT2i use on first MACE and ACM in propensity-matched cohorts

Event and propensity-matched cohort	*n*	Events	Participant-years of follow-up	Incidence rate (events/100 participant-years)	Unadjusted HR (95% CI)	Adjusted HR† (95% CI)	Nominal *P* values (adjusted)
MACE							
No SGLT2i	709	44	990	4.45			
SGLT2i	709	28	822	3.41	0.78 (0.48–1.27)	0.79 (0.49–1.28)	0.34
No dapagliflozin*	353	22	484	4.54			
Dapagliflozin	353	11	408	2.69	0.59 (0.28–1.24)	0.55 (0.26–1.15)	0.11
ACM							
No SGLT2i	709	37	1,108	3.34			
SGLT2i	709	14	871	1.61	0.48 (0.26–0.89)	0.51 (0.27–0.95)	0.03
No dapagliflozin*	353	13	538	2.42			
Dapagliflozin	353	7	432	1.62	0.66 (0.25–1.69)	0.66 (0.25–1.72)	0.39

†Adjustment for duration of diabetes, age, sex, history of CVD, prior heart failure, prior microalbuminuria, prior macroalbuminuria, baseline eGFR, and baseline HbA_{1c}. *Cohort of non-SGLT2i users matched to dapagliflozin users.

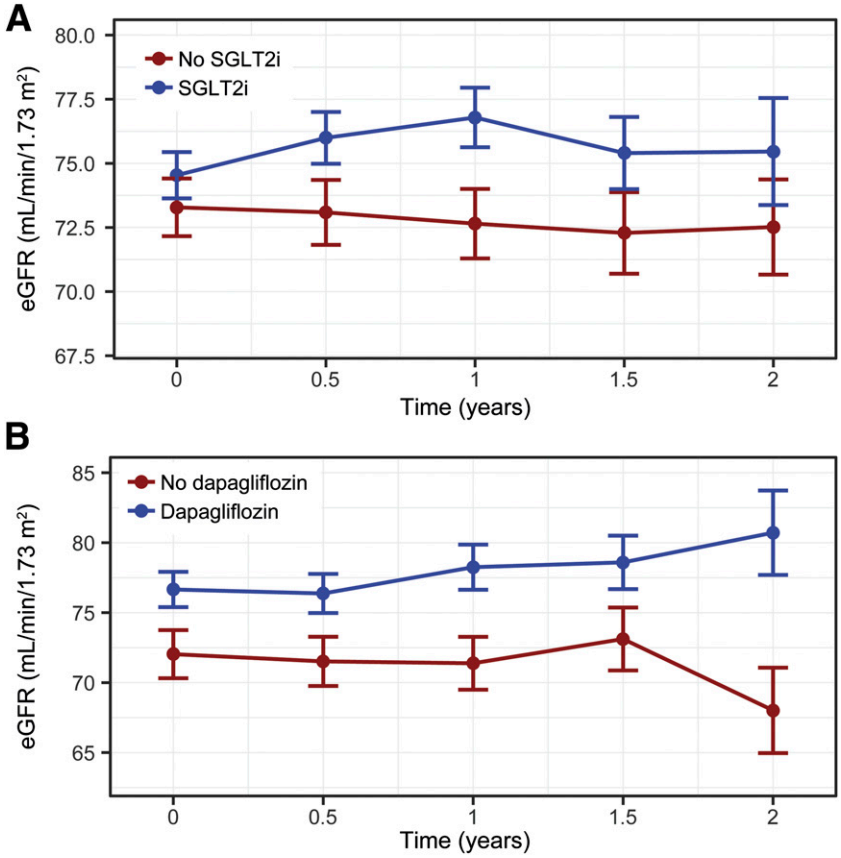

Figure 2—Geometric mean (± SE) eGFR in propensity-matched cohorts for SGLT2i use (*A*) and dapagliflozin use (*B*).

cardiovascular and renal effects of multiple SGLT2i in a type 2 diabetes population that was spread across multiple regions and health care delivery systems and had varying CVD risk (Table 3). Although the propensity-matched cohorts were much smaller than those typically seen in observational real-world evidence studies, these rigorously collected randomized controlled trial data showed statistically significant SGLT2i benefits on ACM and eGFR slope and a numerically lower MACE incidence rate. Dapagliflozin treatment effects on MACE, ACM, and eGFR were numerically consistent with the SGLT2i analyses, supporting a class effect for all three outcomes.

The MACE HRs for SGLT2i users in EXSCEL (Table 2) are similar to those seen in the previous SGLT2i CVOTs (EMPA-REG OUTCOME 0.86 [95% CI 0.74–0.99], CANVAS/CANVAS-R 0.86 [0.75–0.97]) and in the observational CVD-REAL Nordic study (0.78 [0.69–0.87]) (35), providing confidence that the EXSCEL cohorts are representative of SGLT2i use in larger cohorts. The ACM HRs for SGLT2i users were also similar to the estimates in the CVD-REAL and CVD-REAL 2 observational real-world evidence trials (0.49 [0.41–0.57] and 0.51 [0.37–0.70], respectively) and the observational CVD-REAL Nordic comparison between dapagliflozin and DPP-4i (0.59 [0.49–0.72]) (36). The EXSCEL ACM HRs were directionally consistent with EMPA-REG OUTCOME (0.68 [0.57–0.82]) and CANVAS (0.87 [0.74–1.01]). Although ACM curves separated early in this analysis, the MACE curves began to separate at approximately 1 year, consistent with CANVAS but later than in EMPA-REG OUTCOME (9,10,13). Event rates for MACE and ACM in EXSCEL were also similar to EMPA-REG OUTCOME and CANVAS (9,10), although the ACM rates in the control cohorts for all SGLT2i and dapagliflozin were somewhat different.

The MMRM analysis showed significant improvement in eGFR slope with both SGLT2i and dapagliflozin treatment, supporting a similar renal benefit for dapagliflozin as shown for empagliflozin and canagliflozin in their CVOTs. A majority of participants in this analysis did not have micro- or macroalbuminuria, supporting a renal-protective role for SGLT2i in a population with early chronic kidney disease. An initial drop in eGFR upon SGLT2i initiation was not observed because of the 6-month spacing in eGFR measurements and SGLT2i use records. The sensitivity analyses yielded comparable results for MACE, ACM, and eGFR, supporting the robustness of this analysis.

Although the number of MACE and ACM events in participants without prior CVD at trial baseline was small in this analysis, the trend to protection by SGLT2i in the primary prevention population suggests that SGLT2i could provide clinical benefit to patients with a wide range of CVD risk. This result is important because limited data are available on participants without preexisting CVD; all participants in EMPA-REG OUTCOME and most in CANVAS had established CVD. The observational real-world CVD-REAL studies included larger primary prevention populations in which significant benefit with SGLT2i use was seen (11,12), and DECLARE-TIMI 58 includes a large primary prevention population (23).

The mechanisms underlying this cardiovascular and renal protection by SGLT2i are not fully understood but are key to optimize SGLT2i use in clinical practice. Hypothesized hemodynamic effects include *1*) induction of natriuresis and osmotic diuresis, thus reducing glomerular hyperfiltration and blood pressure, and *2*) increasing water clearance, thus reducing volume load (37–39). Other hypotheses include changes in cardiac energetics, inflammation, or fibrosis (39), although the early onset of benefit observed, particularly in EMPA-REG (9), is more consistent with the hypothesized hemodynamic changes. Further insight into these potential mechanisms will be provided by the ongoing DAPASALT (Natriuretic Effect of 2-Week Dapagliflozin Treatment in Type 2 Diabetes Mellitus Patients With Either Preserved or Impaired Renal Function and Non-Diabetics With Impaired Renal Function) mechanistic trial (clinical trial reg. no. NCT03152084, ClinicalTrials.gov).

This analysis was designed to address appropriately several limitations of this data set, which should be considered when interpreting the results. First, to

Table 3—Summary of key results

Previous knowledge in the field

- Empagliflozin and canagliflozin reduce risk of MACE, but whether this is a class effect remains to be established.
- The CVOTs for empagliflozin, canagliflozin, and dapagliflozin enrolled populations with different cardiovascular risks; whether patients without existing CVD will receive cardiovascular benefit from SGLT2i remains unclear.
- SGLT2i are known to improve eGFR and albuminuria, but differences in end point definition make between-trial and between-drug comparisons difficult.

New insights from this study

- This study examined users of three different SGLT2i within the same rigorously collected global clinical trial with adjudicated MACE and ACM, providing new support for a class effect.
- Although event numbers were low, this analysis suggests that SGLT2i may also reduce cardiovascular risk in subjects without diagnosed CVD.
- SGLT2i as a class, including dapagliflozin, have a positive effect on eGFR slope in a population with preserved eGFR and predominantly normoalbuminuria at baseline.

address the imbalance in demographic and clinical characteristics resulting from nonrandomized SGLT2i use in the EXSCEL placebo arm, propensity matching was performed. The large pool of non-SGLT2i users allowed for a high level of matching with SGLT2i users. Although the possibility of residual confounding cannot be ruled out, the matching procedure succeeded in matching >90% of SGLT2i and dapagliflozin users and included several metrics of disease state, medical history, access to care (duration of diabetes and use of newer diabetes medicines including DPP-4i and TZD), and laboratory measurements not often available in real-world analyses (eGFR, HbA_{1c}, systolic blood pressure, and cholesterol); other socioeconomic data were not available. The characteristics of these populations (Table 1) are similar to those of SGLT2i users in clinical practice (11,12,35), although the applicability of these results beyond the examined cohorts remains to be confirmed. Of note, there is a random element to participant matching order with the nearest neighbor approach; rematching would lead to small changes in event numbers and HR CIs. As such, trends and consistency with results in the literature were the focus of this analysis as opposed to specific HR estimates. Furthermore, the estimated HRs in the matched cohorts were similar to those in the full population in many instances. Although the relatively small sizes of the matched cohorts make achieving significant HRs challenging, the consistency of point estimates and drug usage patterns with data in the literature provide confidence that the results are realistic.

Second, the pragmatic nature of EXSCEL led to several limitations in the resolution of available data. Many participants had missing data as a result of skipped study visits or incomplete panels of measurements at some visits. As such, a last-observation-carried-forward approach was used for matching, using the last available measures before SGLT2i initiation to match participants with an equal likelihood of initiating treatment with an SGLT2i. Information on concomitant medication was collected only at 6-month visits. Therefore, the actual dates of SGLT2i initiation and cessation were not known. To address this in a conservative manner, an intention-to-treat–like approach was applied, starting follow-up for SGLT2i use at the first visit with known usage and continuing follow-up beyond the end of SGLT2i treatment.

Immortal time bias and imbalance in participant follow-up are common challenges in observational studies (40), and two approaches were used to address the former. In the propensity-matching procedure, participant characteristics at the time of SGLT2i initiation were matched to those of control subjects at the same study visit as well as on metrics of disease severity and medical history. This approach does not introduce the time lag bias that arises when matching participants upon initiation of diabetes medicines that may be used as different lines of therapy (40), although confounding bias in early prescribing patterns because of market availability and the impact of the completion of EMPA-REG OUTCOME during EXSCEL cannot be excluded. Furthermore, by starting follow-up at the time of matching for SGLT2i users and control subjects, the follow-up time between arms also was balanced. To explicitly address time bias in the full population, time to event for MACE and ACM also was analyzed by incorporating SGLT2i use as a time-dependent covariate (Supplementary Tables 8 and 9); this had a large impact on the estimated HR for ACM, producing an estimate more in line with the propensity-matched cohorts and literature and emphasizing the importance of balancing follow-up time.

In summary, this post hoc analysis provides a novel, credible source of evidence to support the benefit of the SGLT2i class as a whole, including dapagliflozin, on adjudicated MACE, adjudicated ACM, and eGFR preservation in a global type 2 diabetes population with open-label use of multiple SGLT2i (Table 3).

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