Microvascular and Cardiovascular Outcomes According to Renal Function in Patients Treated With Once-Weekly Exenatide: Insights From the EXSCEL Trial

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OBJECTIVE

To evaluate the impact of once-weekly exenatide (EQW) on microvascular and cardiovascular (CV) outcomes by baseline renal function in the Exenatide Study of Cardiovascular Event Lowering (EXSCEL).

RESEARCH DESIGN AND METHODS

Least squares mean difference (LSMD) in estimated glomerular filtration rate (eGFR) from baseline between the EQW and placebo groups was calculated for 13,844 participants. Cox regression models were used to estimate effects by group on incident macroalbuminuria, retinopathy, and major adverse CV events (MACE). Interval-censored time-to-event models estimated effects on renal composite 1 (40% eGFR decline, renal replacement, or renal death) and renal composite 2 (composite 1 variables plus macroalbuminuria).

RESULTS

EQW did not change eGFR significantly (LSMD 0.21 mL/min/1.73 m^2 [95% CI −0.27 to 0.70]). Macroalbuminuria occurred in 2.2% of patients in the EQW group and in 2.5% of those in the placebo group (hazard ratio [HR] 0.87 [95% CI 0.70–1.07]). Neither renal composite was reduced with EQW in unadjusted analyses, but renal composite 2 was reduced after adjustment (HR 0.85 [95% CI 0.74–0.98]). Retinopathy rates did not differ by treatment group or in the HbA_{1c}-lowering or prior retinopathy subgroups. CV outcomes in those with eGFR <60 mL/min/1.73 m^2 did not differ by group. Those with eGFR ≥60 mL/min/1.73 m^2 had nominal risk reductions for MACE, all-cause mortality, and CV death, but interactions by renal function group were significant for only stroke (HR 0.74 [95% CI 0.58–0.93]; *P* for interaction = 0.035) and CV death (HR 1.08 [95% CI 0.85–1.38]; *P* for interaction = 0.031).

CONCLUSIONS

EQW had no impact on unadjusted retinopathy or renal outcomes. CV risk was modestly reduced only in those with eGFR ≥60 mL/min/1.73 m^2 in analyses unadjusted for multiplicity.

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Patients with type 2 diabetes are at increased risk for microvascular complications, including retinopathy and nephropathy. The combination of chronic kidney disease (CKD) and diabetes augments the risk for macrovascular complications, making it higher than that with diabetes alone (1–3). While improved glycemic control reduces microvascular risk (4) and has a modest impact on macrovascular outcomes (5), recent evidence suggests that sodium–glucose cotransporter-2 (SGLT-2) inhibitors and some glucagon-like peptide 1 (GLP-1) receptor agonists (RAs) may exert beneficial effects independent of glucose lowering (6–8).

The Exenatide Study of Cardiovascular Event Lowering (EXSCEL) was a multinational, placebo-controlled, randomized cardiovascular (CV) outcome trial designed to assess the impact of the GLP-1 RA exenatide (2 mg taken once weekly; EQW) versus that of placebo when added to usual care in patients with type 2 diabetes who had a wide range of CV risk (9,10). The study randomized 14,752 participants from 35 countries and demonstrated, over a median 3.2-year follow-up, the noninferiority, but not superiority, of EQW compared with a placebo for the primary major adverse CV event (MACE) outcome—a composite of CV-related death, nonfatal myocardial infarction, or nonfatal stroke (hazard ratio [HR] 0.91 [95% CI 0.83–1.00]; $P = 0.061$)—and a reduced risk for all-cause mortality (HR 0.86 [95% CI 0.77–0.97]; $P = 0.016$) that was nominally significant because of the prespecified hierarchical testing paradigm (10). Although the study excluded participants with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 at baseline, 21.7% had at least CKD stage 3 (eGFR <60 mL/min/1.73 m^2). Here we report key primary and secondary CV outcomes, according to the degree of renal dysfunction, and microvascular outcomes measured among the overall population.

RESEARCH DESIGN AND METHODS

Trial Design

The design and primary results of EXSCEL (clinical trial reg. no. NCT01144338, ClinicalTrials.gov) have been described (9,10). The trial was conducted jointly by the Duke Clinical Research Institute and the University of Oxford Diabetes Trials Unit in an academic collaboration with the sponsor, Amylin Pharmaceuticals, a wholly owned subsidiary of AstraZeneca. The protocol was approved by the ethics committee at each participating site, and all participants provided written informed consent for trial participation. Briefly, 14,752 adult participants with type 2 diabetes (HbA_{1c} 6.5–10.0% [48–96 mmol/mol]) who had either had a prior CV event ($n = 10,782$ [73.1%]) or not had a prior CV event ($n = 3,790$ [26.9%]) were randomized 1:1 to receive EQW or placebo in addition to usual care. EXSCEL was a pragmatic trial in which laboratory data, measured per local clinical care guidelines in local laboratories, were collected opportunistically, with the only exceptions being serum creatinine, which was required to be measured annually to inform possible EQW dose changes, and calcitonin, which was measured annually by a central laboratory. Key exclusion criteria were a history of two or more episodes of severe hypoglycemia (defined as hypoglycemia for which a patient received third-party assistance) during the preceding 12 months, end-stage kidney disease or an eGFR <30 mL/min/1.73 m^2 body surface area, or previous treatment with a GLP-1 RA. The primary outcome was time to the first occurrence of any component of the MACE composite (death from CV causes, nonfatal myocardial infarction, or nonfatal stroke). In time-to-event analyses, key secondary outcomes were death from any cause; death from a CV cause; and the first occurrence of nonfatal or fatal myocardial infarction, nonfatal or fatal stroke, hospitalization for acute coronary syndrome, or hospitalization for heart failure. Information was collected systematically for all events at 1 week; at 2, 6, and 12 months; and every 6 months thereafter. An independent clinical events classification committee blinded to treatment assignment adjudicated all components of the primary and secondary outcomes. Criteria for adjudication are defined in the Clinical Event Definitions section of the Supplementary Data.

Prespecified additional microvascular outcomes reported here comprise renal composite 1 (time to first event of a 40% decline in eGFR [11], renal replacement, or renal death), renal composite 2 (renal composite 1 variables plus incident macroalbuminuria), and incident retinopathy. Also analyzed were progression to a 30% or 40% decline in eGFR as well as progression to CKD stage 3, 4, or 5. Results for progression end points were not meaningfully different from those reflected in the renal composites and are not presented here. Laboratory values for eGFR were obtained from blood sampling during usual care, consistent with the pragmatic trial design. Progression to micro- or macroalbuminuria was classified as an expected diabetes complication and was assessed at each visit via a yes-or-no answer to the question, "Since the previous visit, did the patient experience any new or worsening occurrences of albuminuria?" An affirmative response indicated classification of the event as either micro- or macroalbuminuria. Additional clinical data (e.g., urine albumin-to-creatinine ratio) were neither collected nor adjudicated.

Retinopathy events were classified as an expected diabetes complication and subject to pragmatic prospective data collection at each visit via a yes-or-no answer to the following question: "Since the previous visit, did the patient experience any new or worsening occurrences of retinopathy?" Additional clinical data (e.g., retinal exam results) for this end point were neither collected nor adjudicated.

Statistical Analysis

The intention-to-treat population was used for all analyses. Baseline characteristics were summarized, using mean (±1 SD), median (25th, 75th percentile), or number (proportion), as appropriate, for continuous and categorical variables. The overall least squares mean difference (LSMD) in eGFR between the EQW and placebo treatment groups was calculated for participants with a baseline value and at least one follow-up value. Changes in HbA_{1c} early after randomization were calculated for patients with baseline and follow-up values within the 1st year, for use in the retinopathy subgroup analyses; the value closest to 6 months after baseline (capped at 1 year) was chosen. Subgroups according to baseline renal function were eGFR <60 and ≥60 mL/min/1.73 m^2, CKD stage 1 (eGFR ≥90 mL/min/1.73 m^2), CKD stage 2 (eGFR 60–89 mL/min/1.73 m^2), CKD stage 3a (eGFR 45–59 mL/min/1.73 m^2), CKD stage 3b (eGFR 30–44 mL/min/1.73 m^2), CKD stage 4 (eGFR 15–29 mL/min/1.73 m^2), and CKD stage

Table 1—Baseline characteristics of participants by CKD stage

	Stage 1 (n = 4,268)	Stage 2 (n = 7,246)	Stage 3a (n = 2,288)	Stage 3b (n = 889)
Age (years)	57.7 (9.3)	62.3 (8.7)	65.9 (8.4)	68.0 (8.5)
<65	3,260/4,268 (76.4)	4,278/7,246 (59.0)	945/2,288 (41.3)	300/889 (33.7)
≥65	1,008/4,268 (23.6)	2,968/7,246 (41.0)	1,343/2,288 (58.7)	589/889 (66.3)
≥75	125/4,268 (2.9)	547/7,246 (7.5)	353/2,288 (15.4)	215/889 (24.2)
Sex				
Male	2,814/4,268 (65.9)	4,487/7,246 (61.9)	1,330/2,288 (58.1)	485/889 (54.6)
Female	1,454/4,268 (34.1)	2,759/7,246 (38.1)	958/2,288 (41.9)	404/889 (45.4)
Race				
White	3,093/4,267 (72.5)	5,578/7,243 (77.0)	1,777/2,287 (77.7)	678/889 (76.3)
Asian	493/4,267 (11.6)	653/7,243 (9.0)	211/2,287 (9.2)	90/889 (10.1)
Black	318/4,267 (7.5)	398/7,243 (5.5)	107/2,287 (4.7)	51/889 (5.7)
Hispanic	333/4,267 (7.8)	554/7,243 (7.6)	178/2,287 (7.8)	66/889 (7.4)
Other	30/4,267 (0.7)	60/7,243 (0.8)	14/2,287 (0.6)	4/889 (0.5)
Region				
Europe	2,172/4,268 (50.9)	3,342/7,246 (46.1)	923/2,288 (40.3)	325/889 (36.6)
North America	973/4,268 (22.8)	1,753/7,246 (24.2)	678/2,288 (29.6)	288/889 (32.4)
Latin America	628/4,268 (14.7)	1,438/7,246 (19.8)	473/2,288 (20.7)	181/889 (20.4)
Asia Pacific	495/4,268 (11.6)	713/7,246 (9.8)	214/2,288 (9.4)	95/889 (10.7)
Duration of type 2 diabetes (years)				
Mean (SD)	11.4 (7.2)	13.0 (8.2)	14.8 (8.9)	17.4 (9.4)
Median (Q1, Q3)	10.0 (6.0, 15.0)	12.0 (7.0, 18.0)	14.0 (8.0, 20.0)	16.0 (11.0, 22.0)
<5	717/4,249 (16.9)	1,001/7,231 (13.8)	225/2,275 (9.9)	57/883 (6.5)
≥5 to <15	2,333/4,249 (54.9)	3,571/7,231 (49.4)	1,020/2,275 (44.8)	312/883 (35.3)
≥15	1,199/4,249 (28.2)	2,659/7,231 (36.8)	1,030/2,275 (45.3)	514/883 (58.2)
BMI (kg/m^2)	32.8 (6.6)	32.6 (6.3)	32.8 (6.4)	32.8 (6.7)
Prior CV event	2,799/4,268 (65.6)	5,364/7,246 (74.0)	1,864/2,288 (81.5)	763/889 (85.8)
Coronary artery disease	1,969/4,268 (46.1)	3,825/7,246 (52.8)	1,365/2,288 (59.7)	607/889 (68.3)
Cerebrovascular disease	617/4,267 (14.5)	1,202/7,246 (16.6)	464/2,288 (20.3)	218/888 (24.5)
Peripheral arterial disease	685/4,267 (16.1)	1,404/7,246 (19.4)	499/2,288 (21.8)	206/889 (23.2)
Prior congestive heart failure				
Yes	558/4,268 (13.1)	1,113/7,246 (15.4)	477/2,288 (20.8)	232/888 (26.1)
No	3,710/4,268 (86.9)	6,133/7,246 (84.6)	1,811/2,288 (79.2)	656/888 (73.9)
Cigarette smoking status				
Current	691/4,266 (16.2)	786/7,245 (10.8)	188/2,287 (8.2)	50/886 (5.6)
Former	1,554/4,266 (36.4)	2,904/7,245 (40.1)	909/2,287 (39.7)	396/886 (44.7)
Never	2,021/4,266 (47.4)	3,555/7,245 (49.1)	1,190/2,287 (52.0)	440/886 (49.7)
HbA_{1c}				
%	8.2 (1.0)	8.1 (1.0)	8.1 (1.0)	8.1 (1.0)
mmol/mol	65.6 (10.6)	65.0 (10.4)	65.0 (10.5)	64.9 (10.4)
<8% (<63.93 mmol/mol)	2,019/4,243 (47.6)	3,557/7,208 (49.3)	1,122/2,281 (49.2)	442/886 (49.9)
≥8% (≥63.93 mmol/mol)	2,224/4,243 (52.4)	3,651/7,208 (50.7)	1,159/2,281 (50.8)	444/886 (50.1)
eGFR (mL/min/1.73 m^2)	107.1 (18.5)	74.4 (8.6)	53.2 (4.2)	38.8 (4.0)
Albuminuria	558/3,120 (17.9)	1,122/5,277 (21.3)	445/1,680 (26.5)	221/650 (34.0)
Microalbuminuria	478/3,120 (15.3)	931/5,277 (17.6)	321/1,680 (19.1)	135/650 (20.8)
Macroalbuminuria	80/3,120 (2.6)	191/5,277 (3.6)	124/1,680 (7.4)	86/650 (13.2)

Unless otherwise indicated, data are the mean (SD) or number with the characteristic/Number in the column subgroup with nonmissing data (proportion), as appropriate for continuous and categorical variables.

5 (eGFR <15 mL/min/1.73 m^2). Subgroups for CKD stages 4 (n = 14) and 5 (n = 0) were too small to allow robust analyses and have been excluded from this report. Although few of the individuals categorized as having CKD stage 1 or stage 2 had concomitant albuminuria, as classically defined (12,13), we use CKD staging nomenclature throughout for descriptive simplicity.

The impact of EQW on the two renal composite outcomes was estimated with interval-censored time-to-event models to account for clustering of eGFR collection dates around study visits. Unadjusted models and models adjusted for prespecified variables including age, sex, ethnicity, race, region, diabetes duration, history of CV event, diabetes therapy at baseline (including insulin use), baseline HbA_{1c}, eGFR, and BMI are presented. Unadjusted and adjusted Cox regression models were used to estimate the impact of treatment on all other end points with continuous dates of events. Only unadjusted models are presented unless adjustment resulted in notably different changes.

RESULTS

Baseline characteristics by CKD stage for the 14,691 participants included in the intention-to-treat analysis were well balanced between treatment groups (data not shown) and broadly demonstrate

Table 2—Microvascular outcomes by randomized treatment group

	EQW	Placebo	HR (95% CI)	*P* value
New macroalbuminuria	158/7,132 (2.2)	180/7,137 (2.5)	0.87 (0.70–1.07)	0.19
Adjusted HR*			0.84 (0.67–1.04)	0.11
Renal composite 1	246/6,459 (3.8)	273/6,466 (4.2)	0.88 (0.74–1.05)	0.16
Adjusted HR*			0.87 (0.73–1.04)	0.13
40% decline in eGFR	239	266		
Renal replacement	7	7		
Renal death	0	0		
Renal composite 2	366/6,259 (5.8)	407/6,230 (6.5)	0.88 (0.76–1.01)	0.07
Adjusted HR*			0.85 (0.74–0.98)	0.03
40% decline in eGFR	216	228		
Renal replacement	7	6		
Renal death	0	0		
New macroalbuminuria	143	173		
Postbaseline retinopathy				
First event	214/7,356 (2.9)	237/7,396 (3.2)	0.89 (0.74–1.07)	0.22
Adjusted HR*			0.89 (0.74–1.08)	0.24
All events	244	275		
By HbA_{1c} change (unadjusted)				0.853
Tertile 1	38/1,247 (3.1)	82/2,783 (3.0)	1.08 (0.74–1.59)	
Tertile 2	47/1,903 (2.5)	49/1,966 (2.5)	0.99 (0.67–1.48)	
Tertile 3	78/2,909 (2.7)	36/1,264 (2.9)	0.92 (0.62–1.37)	
By HbA_{1c} decrease >2%				0.614
Yes	25/814 (3.1)	7/260 (2.7)	1.15 (0.50–2.66)	
No	138/5,245 (2.6)	160/5,753 (2.8)	0.93 (0.74–1.17)	
History of retinopathy at baseline (unadjusted)				0.483**
Yes	59/1,270 (4.6)	71/1,246 (5.7)	0.79 (0.56–1.11)	
No	155/6,085 (2.5)	166/6,150 (2.7)	0.93 (0.75–1.16)	

Data are the number with the event/total population (%) unless otherwise indicated. *Analyses were adjusted for age, sex, ethnicity, race, region, duration of diabetes, history of CV event, insulin use, baseline HbA_{1c} and eGFR, and BMI. **P value for interaction by HbA_{1c} tertile.

advancing age, increasing duration of diabetes, and increasing burden of comorbidities with advancing CKD (Table 1). To inform the retinopathy subgroup analysis, participants were divided into tertiles according to the degree of HbA_{1c} change achieved during the first 6 months of study enrollment: 13.5% of the EQW group and 4.4% of the placebo group achieved an HbA_{1c} reduction >2% (Supplementary Table 1).

Microvascular Outcomes by Treatment Group

Mean change in eGFR from baseline was similar with EQW treatment and placebo during follow-up in 13,844 patients (LSMD 0.21 mL/min/1.73 m^2 [95% CI −0.27 to 0.70]; $P = 0.39$). Among 14,269 participants without macroalbuminuria at baseline, incident macroalbuminuria occurred in 2.2% of patients in the EQW group and 2.5% of those in the placebo group (HR 0.87 [95% CI 0.70–1.07]; $P = 0.19$) (Table 2). The hazard of experiencing the renal composite 1 end point, driven by eGFR decline events, was numerically but not statistically significantly reduced with EQW (Table 2). The hazard of experiencing the renal composite 2 end point, driven by eGFR decline and macroalbuminuria events, was significantly reduced with EQW in adjusted, but not unadjusted, models (Table 2). The impact of treatment was similar across all CKD stages, without evidence for interaction (Supplementary Table 2).

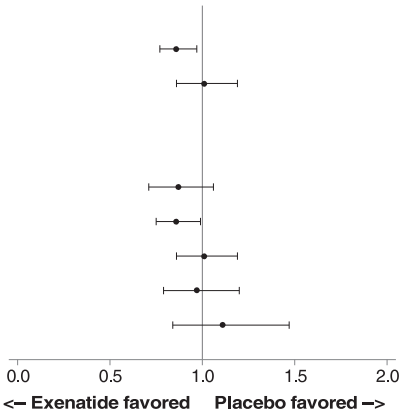
EQW treatment did not increase the risk for retinopathy events among the overall population (HR 0.89 [95% CI 0.74–1.07]; $P = 0.22$) (Table 2). In particular, no significant impact of EQW was identified in subgroups defined by tertiles of initial HbA_{1c} change from baseline to 6 months, in those whose HbA_{1c} decreased by >2% from baseline to 6 months, or in those with a history of retinopathy.

CV Safety Outcomes by Baseline Renal Status

CV safety outcomes were calculated for those with a baseline eGFR ≥60 mL/min/1.73 m^2 ($n = 11,514$) or <60 mL/min/1.73 m^2 ($n = 3,177$) and for those with CKD stages 1, 2, 3a, and 3b (Fig. 1 and Supplementary Tables 2 and 3). In patients with eGFR <60 mL/min/1.73 m^2 (CKD stage 3a or 3b), EQW had a neutral impact on CV outcomes. In univariate analyses unadjusted for multiplicity, risk was significantly reduced for MACE (HR 0.86 [95% CI 0.77–0.97]), all-cause mortality (HR 0.78 [95% CI 0.67–0.91]), CV-related death (HR 0.77 [95% CI 0.64–0.93]), and fatal or nonfatal stroke (HR 0.74 [95% CI 0.58–0.93]) in those with baseline eGFR ≥60 mL/min/1.73 m^2 and treated with EQW. P values for interaction were significant only for fatal or nonfatal stroke (P for interaction = 0.035) and CV-related death (P for interaction = 0.031) (Fig. 1 and Supplementary Table 3). In analyses by CKD stage, risk reductions were nominally significant for MACE, fatal or nonfatal stroke, CV-related death, and all-cause mortality for CKD stage 2 and CKD stage 1; however, none of the P values for interaction for all event types by CKD stage were statistically significant, except for hospitalization for heart failure ($P = 0.014$), but risk was not significantly reduced in individual CKD stage subgroups (Supplementary Table 2).

A

MACE-3	P value for Homogeneity	Exenatide n / N (%)	Placebo n / N (%)	Hazard Ratio	95% CI
eGFR group (mL/min/1.73m²)	0.132				
eGFR ≥60		549 / 5769 (9.5%)	620 / 5745 (10.8%)	0.86	0.77–0.97
eGFR <60		280 / 1557 (18.0%)	282 / 1620 (17.4%)	1.01	0.86–1.19
eGFR renal function categories (mL/min/1.73m²)	0.366				
Stage 1: 90+		181 / 2127 (8.5%)	208 / 2141 (9.7%)	0.87	0.71–1.06
Stage 2: 60–89		368 / 3642 (10.1%)	412 / 3604 (11.4%)	0.86	0.75–0.99
Stage 3: 30–59		280 / 1557 (18.0%)	282 / 1620 (17.4%)	1.01	0.86–1.19
Stage 3a: 45–59		181 / 1140 (15.9%)	182 / 1148 (15.9%)	0.97	0.79–1.20
Stage 3b: 30–44		99 / 417 (23.7%)	100 / 472 (21.2%)	1.11	0.84–1.47



B

ALL-CAUSE MORTALITY	P value for Homogeneity	Exenatide n / N (%)	Placebo n / N (%)	Hazard Ratio	95% CI
eGFR group (mL/min/1.73m²)	0.050				
eGFR ≥60		302 / 5769 (5.2%)	382 / 5745 (6.6%)	0.78	0.67–0.91
eGFR <60		195 / 1557 (12.5%)	200 / 1620 (12.3%)	1.00	0.82–1.22
eGFR renal function categories (mL/min/1.73m²)	0.206				
Stage 1: 90+		88 / 2127 (4.1%)	121 / 2141 (5.7%)	0.73	0.55–0.96
Stage 2: 60–89		214 / 3642 (5.9%)	261 / 3604 (7.2%)	0.80	0.67–0.96
Stage 3: 30–59		195 / 1557 (12.5%)	200 / 1620 (12.3%)	1.00	0.82–1.22
Stage 3a: 45–59		126 / 1140 (11.1%)	123 / 1148 (10.7%)	1.01	0.79–1.30
Stage 3b: 30–44		69 / 417 (16.5%)	77 / 472 (16.3%)	1.01	0.73–1.40

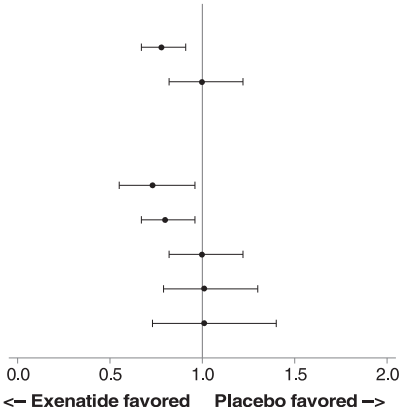


Figure 1—CV safety outcomes by baseline renal function: MACE (*A*) and all-cause mortality (*B*). MACE-3, three-item MACE composite.

CONCLUSIONS

Among patients with or without previous CV events who were receiving usual care for their type 2 diabetes, the addition of EQW was not associated with clinically meaningful change in eGFR and did not affect renal composite outcomes in unadjusted analyses. In analyses adjusted for demographic characteristics and disease severity, EQW was associated with a significant 15% reduction of relative risk in renal composite 2, driven mainly by a lower incidence of macroalbuminuria in the EQW group. EQW had no impact on the incidence of retinopathy overall or in any subgroup, and the CV safety of EQW was confirmed across a wide range of renal function.

Guarding against nephropathy in type 2 diabetes is a major tenant of therapy to prevent microvascular complications. SGLT-2 inhibitors—shown in several large outcomes trials (BI 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients [EMPA-REG OUTCOME] [14], Canagliflozin Cardiovascular Assessment Study [CANVAS] [15], Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation [CREDENCE] [16], Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 [DECLARE-TIMI 58] [17]) to reduce the incidence of nephropathy by both reducing proteinuria and delaying decline in glomerular filtration—are considered second-line therapy (after metformin) for patients with diabetes and increased risk for progression of CKD (18). GLP-1 RAs, which affect the progression of proteinuria but have little effect on glomerular filtration (19), follow in the treatment algorithm for those who do not tolerate SGLT-2 inhibitors or in whom they are contraindicated. Both liraglutide (8,20) and semaglutide (21) have reduced the risk for nephropathy in CV outcomes trials, whereas EQW and albiglutide demonstrated renal safety (22). Although the analyses shown here demonstrate a reduction in a renal composite comprising a 40% eGFR decline, incident macroalbuminuria, renal replacement, or renal death, these results were adjusted for covariates and were not adjusted for multiplicity. Limitations to interpretation are introduced by the pragmatic data collection policy in EXSCEL. Data on eGFR were collected only as available from routine outpatient clinical surveillance, resulting in missing data; 93% of EXSCEL participants had both baseline and follow-up eGFR values recorded. Similarly, incomplete data exist regarding baseline albuminuria status, an important predictive variable for both CV and renal outcomes (23). Categorical data for baseline albuminuria status

(micro-, macro-, or normoalbuminuria) were not collected for 27% of EXSCEL participants, and quantitative measures of albuminuria were not routinely collected.

Results from other CV outcomes trials have raised concerns about the impact of GLP-1 RAs on retinopathy. Both semaglutide, in the Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) (HR 1.76 [95% CI 1.11–2.78]) (21), and liraglutide, in the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial (HR 1.15 [95% CI 0.87–1.52]) (20), showed higher rates of retinopathy in groups treated with a GLP-1 RA than in those receiving the placebo. In both trials, the risk of retinopathy was highest in those with a history of retinopathy; this high risk may have been related to rapid HbA_{1c} lowering early after randomization rather than to an independent adverse effect of the GLP-1 RA (24). Indeed, there are reasons to believe that GLP-1 RA therapies may be beneficial for patients with diabetic retinopathy. The GLP-1 receptor is expressed in the retina, and animal studies have suggested that GLP-1 RAs decrease apoptosis of retinal nerve cells and provide protection against damage to the blood-retinal barrier (25–28). It is encouraging that the Harmony Outcomes trial, evaluating albiglutide, did not demonstrate evidence of increased risk of retinopathy (22), and EXSCEL showed no statistically increased risk, regardless of the initial HbA_{1c} change. However, there are limitations in ascertaining retinopathy events for all of these studies. Because none of the studies were designed or powered to investigate retinal outcomes, event numbers are small, and the results of fundoscopic exams and retinal images were not collected during follow-up. For EXSCEL, collection of retinopathy events was pragmatic, prospectively ascertained from a yes/no question; retinal imaging or other fundoscopic exam results were not collected.

GLP-1 RAs are effective treatments for type 2 diabetes, lowering glucose with minimal risk for hypoglycemia and often with accompanying weight loss (29). Agents in this class have consistently demonstrated CV safety (30), and some have shown CV benefit (20–22,31). Our analysis demonstrates a consistent CV safety profile for EQW over the spectrum of renal function studied (patients with eGFR <30 mL/min/1.73 m^2 at baseline were excluded), without clear evidence of benefit. The suggestion of a greater impact on CV outcomes in patients with eGFR ≥ 60 mL/min/1.73 m^2 is consistent with subgroup analyses performed in both SUSTAIN-6 with semaglutide and the Harmony Outcomes trial with albiglutide (but not in LEADER with liraglutide); however, these analyses were not adjusted for multiplicity (18–20). These findings support revised treatment guidelines advocating a broader use of GLP-1 RAs as the first injectable therapy for most patients (18).

With the increasing prominence of GLP-1 RAs in the treatment of type 2 diabetes, leveraging available long-term outcomes data to characterize the safety profile of drugs within the class can guide medication selection for individual patients. For EQW, the consistency of the CV and renal safety profiles across the range of renal function studied provides reassurance as the drug becomes used more widely, for example, in patients with established atherosclerotic CV disease or before the development of CV disease or CKD in patients who require glucose lowering but have a compelling need to minimize hypoglycemia or weight gain.

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designed the study, interpreted data, and reviewed and edited the manuscript. J.C.C., S.G.G., N.J., Y.L., R.D.L., A.P.M., T.T., and A.F.H. reviewed and edited the manuscript. M.A.B. and R.R.H. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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