Prediction and validation of exenatide risk marker effects on progression of renal disease: Insights from EXSCEL

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Abstract
Aim: To assess whether the previously developed multivariable risk prediction framework (PRE score) could predict the renal effects observed in the EXSCEL cardiovascular outcomes trial using short-term changes in cardio-renal risk markers.

Materials and Methods: Changes from baseline to 6 months in HbA1c, systolic blood pressure (SBP), body mass index (BMI), haemoglobin, total cholesterol, and new micro- or macroalbuminuria were evaluated. The renal outcomes were defined as a composite of a sustained 30% or 40% decline in estimated glomerular filtration rate (eGFR) or end-stage renal disease (ESRD). Relationships between risk markers and long-term renal outcomes were determined in patients with type 2 diabetes from the ALTITUDE study using multivariable Cox regression analysis, and then applied to short-term changes in risk markers observed in EXSCEL to predict the exenatide-induced impact on renal outcomes.

Results: Compared with placebo, mean HbA1c, BMI, SBP and total cholesterol were lower at 6 months with exenatide, as was the incidence of new microalbuminuria. The PRE score predicted a relative risk reduction for the 30% eGFR decline + ESRD endpoint of 11.3% (HR 0.89; 95% CI 0.83–0.94), compared with 12.7% (HR 0.87; 0.77–0.99) observed risk reduction. For the 40% eGFR decline + ESRD endpoint, the predicted and observed risk reductions were 11.0% (HR 0.89; 0.82–0.97) and 13.7% (HR 0.86, 0.72–1.04), respectively.

Conclusions: Integrating short-term risk marker changes into a multivariable risk score predicted the magnitude of renal risk reduction observed in EXSCEL.
1 | INTRODUCTION

Recent cardiovascular outcome trials in patients with type 2 diabetes (T2D) have characterized the cardiovascular safety of glucagon-like peptide-1 receptor agonists (GLP-1RAs) with some trials also showing cardiovascular protective effects. The Exenatide Study of Cardiovascular Event Lowering (EXSCEL, NCT01144338) assessed the cardiovascular safety of the GLP-1RA exenatide in a broad range of patients with T2D, with or without atherosclerotic cardiovascular disease (ASCVD), and confirmed that exenatide did not increase cardiovascular risk. Secondary analyses of some of the cardiovascular safety trials with GLP-1RAs have suggested that this drug class may also delay the progression of diabetic kidney disease (DKD); multiple GLP-1RA trials in T2D have shown a robust effect on new persistent macroalbuminuria. Additionally, there is some evidence of slowing eGFR decline, either as a percentage reduction in eGFR or improvement in eGFR slope in some populations. This benefit probably results in part from improvement in glycemic control but may also be mediated by other effects such as reductions in blood pressure, body weight, albuminuria, and inhibition of proinflammatory mediators, although the size of contribution from each factor is not well understood.

Recognizing the potential contributions of these different processes to GLP-1RA-mediated slowing of renal disease progression, we hypothesized that a multivariate risk score may be able to predict GLP-1RA-mediated renal effects better than a single risk marker. We have previously developed and validated such a multi-variable risk prediction framework (PRE score) to predict longer term drug impact on renal and/or cardiovascular outcomes. The PRE score has not been applied to a GLP-1RA and it is not known whether it can predict renal outcomes for this class of glucose-lowering agents.

We performed a post hoc analysis of EXSCEL to determine the short-term effects of exenatide on multiple cardio-renal risk markers, and examined whether the PRE score could accurately predict the longer term impact of a GLP-1RA, exenatide, on the observed renal disease progression in EXSCEL.

2 | MATERIALS AND METHODS

2.1 | Patient population

EXSCEL included patients with T2D, of whom 73% had prior ASCVD. Participants were assigned to receive subcutaneous injections of once-weekly exenatide (EQW) at a dose of 2 mg or matching placebo, and were followed for a median of 3.2 years. The EXSCEL design and primary results have been previously published.

Key inclusion criteria included an HbA1c of 6.5% to 10%, aged ≥18 years, one or fewer severe hypoglycaemia episodes in the past year, and an estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m².

The PRE score was used to predict the effect of exenatide on renal outcomes in the EXSCEL trial. The PRE score is a flexible framework that can be customized to any population, drug, and set of risk markers of interest by fitting the beta coefficients in the underlying Cox model to the appropriate set of risk markers in a relevant population. For this analysis, the relationships between risk markers and renal outcomes were established at baseline in a background population derived from the ALTITUDE trial, a study in patients with T2D at high cardiovascular and renal risk. A subgroup of patients with urine albumin:creatinine ratio (UACR) <400 mg/g and eGFR >55 mL/min/1.73m² was included in the analysis to calculate risk marker-outcome relationships in a population that is representative of patients included in the EXSCEL trial. The baseline characteristics of the ALTITUDE population are presented in Table S1.

2.2 | Cardio-renal risk markers

Variables measured in the EXSCEL intention-to-treat population, and which have previously been identified as risk markers for progression of renal disease, included: HbA1c, systolic blood pressure (SBP), UACR, body mass index (BMI), haemoglobin (Hb) and total cholesterol (TC). Because of a lack of consistently collected continuous data for UACR in EXSCEL, categorical information on new micro- or macroalbuminuria was used to reflect short-term UACR changes. Data on UACR levels in the ALTITUDE population used were similarly categorized into normo-, micro- or macroalbuminuria.
2.4 | Statistical analysis

The observed drug-induced reduction in risk of the composite renal outcome was calculated using a Cox proportional hazards model with exenatide treatment as explanatory variable. Relative risk reductions were calculated by \( (1 - \text{hazard ratio}) \times 100\% \).

A Cox proportional hazards model was used to estimate the coefficients associated with each risk marker for the first recorded renal event in the background population derived from the ALTITUDE placebo arm among subjects with all required covariates measured at baseline. These coefficients were then applied to the baseline and 6-month cardio-renal risk factor measurements using the Modification of Diet in Renal Disease (MDRD) formula. A sustained 30% eGFR decline was used as a component of the composite outcome because it reflects a large decline in eGFR in patients with preserved renal function such as those included in EXSCEL, and has been proposed as an alternative renal endpoint for drugs without acute eGFR effects such as GLP-1RAs. We also assessed the effect of exenatide on the composite of 40% eGFR decline or ESRD because in certain settings this may be a more robust endpoint than a 30% eGFR decline. In the ALTITUDE subpopulation, the composite renal outcome with 30% eGFR decline and the outcome with 40% eGFR decline occurred in 292 (17.4%) and 153 (9.1%) patients during a median follow-up of 2.8 years, respectively.

3 | RESULTS

A total of 14,752 patients were randomly assigned to receive placebo (N = 7396) or EQW (N = 7356) and were included in the EXSCEL intention-to-treat population. Demographic and clinical characteristics of these patients were well-balanced between the treatment groups (Table 1). EXSCEL participants were generally characterized by a low risk of complications attributable to renal disease. At baseline, 25% of participants had an eGFR of >90 mL/min/1.73m², 50% had an eGFR between 60 and 90 mL/min/1.73m², and 24% had an eGFR between 30 and 59 mL/min/1.73m². The prevalence of micro- and macroalbuminuria was 12.7% and 3.3%, respectively. The β-coefficients of the PRE score fit to the ALTITUDE subpopulation with UACR <400 mg/g and eGFR >55 mL/min/1.73m² are shown in Table S2.

3.1 | Effects of exenatide on cardio-renal risk markers

A total of 3395 participants in the placebo group and 3523 in the exenatide group had ≤1 risk marker missing at baseline or 6 months, and were included in these analyses after imputation of missing values. Their baseline characteristics were similar to those of the total population (Table S3).

Changes in cardio-renal risk markers from baseline to 6 months after treatment with EQW or placebo are shown in Figure 1. Compared with placebo, greater reductions were seen with EQW in HbA1c (−0.79%, 95% CI −0.84 to −0.74, P < 0.001), BMI (−0.50 kg/m², 95% CI −0.57 to −0.43, P < 0.001), SBP (−1.7 mmHg, 95% CI −2.5 to −0.9, P < 0.001) and TC (−0.19 to −0.09, P < 0.001). During the first 6 months of placebo treatment, 136 (4.0%) participants with normoalbuminuria at baseline progressed to microalbuminuria or macroalbuminuria versus 106 (3.0%) in the EQW
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predicted the effect of EQW on the composite renal endpoint in (Figure 2A). The PRE score with coefficients fit in ALTITUDE UACR is presented as median [IQR]. Categorical variables are presented as

<table>
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<th>Placebo (n = 7396)</th>
<th>Exenatide (n = 7356)</th>
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<td>61.8 (9.4)</td>
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<td>8.1 (1.0)</td>
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<tr>
<td>Diastolic BP (mmHg)</td>
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<td>78.2 (10.3)</td>
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<td>22.9 [11.6, 34.1]</td>
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<tr>
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<td>6151 (83.6)</td>
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<td>UACR 30–300 mg/g</td>
<td>892 (12.1)</td>
<td>981 (13.3)</td>
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<tr>
<td>UACR &gt;300 mg/g</td>
<td>259 (3.5)</td>
<td>224 (3.0)</td>
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<td>3732 (50.9)</td>
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<td>eGFR 30–59 mL/min/1.73m²</td>
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<td>1712 (23.3)</td>
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<td>18 (0.2)</td>
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| Abbreviations: BP, blood pressure; eGFR, estimated glomerular filtration rate; UACR, urine protein:urine creatinine ratio. Numeric variables are presented as mean (SD) if normally distributed. UACR is presented as median [IQR]. Categorical variables are presented as frequency (%). *Calculated with the Modification of Diet in Renal Disease study equation (MDRD).

In the overall EXSCEL population, the composite renal outcome of ≥ 30% eGFR decline or ESRD occurred in 546 (7.4%) participants in the placebo group compared with 489 (6.7%) in the EQW group (HR 0.87, 95% CI 0.73 to 0.99, P = 0.03; Figure 3A). A ≥ 30% eGFR decline occurred in 533 (8.3%) participants in the placebo group versus 482 (7.5%) in the EQW group (HR 0.88, 95% CI 0.78 to 1.00, P = 0.10). The composite renal outcome of ≥ 40% eGFR decline or ESRD occurred in 241 (3.3%) participants in the placebo group and 213 (2.9%) in the EQW group during a median follow-up of 2.6 years (Figure 3B), a relative risk reduction with EQW of 14% (HR 0.86, 95% CI 0.73 to 1.04; P = 0.12). ESRD was an infrequent event during the trial, occurring in 39 (0.5%) participants in the placebo group and 25 (0.3%) participants in the EQW group, with an ESRD HR of 0.65 (95% CI 0.39 to 1.08; P = 0.10).

Among the population used for the PRE score analysis with ≥ 1 cardio-renal risk factor missing (N = 6918), the observed relative risk reduction of 11.6% for the composite outcome of ≥ 30% eGFR decline and ESRD was consistent with that of the overall population (HR 0.88; 95% CI 0.74 to 1.05, P = 0.26). Although the confidence intervals were wider, reflecting the smaller number of patients. Similarly, the observed relative risk reduction of 14.2% for the composite outcome of ≥ 40% eGFR decline and ESRD did not differ from that in the overall population (hazard ratio 0.86; 95% CI 0.66 to 1.12, P = 0.26).

The predicted risk change for the composite renal endpoint of ≥ 30% eGFR decline or ESRD based on the observed placebo corrected change in HbA1c alone was −9.9% (95% CI −14.7 to −4.9) with EQW (Figure 2A). The PRE score with coefficients fit in ALTITUDE predicted the effect of EQW on the composite renal endpoint in EXSCEL to be −11.3% (95% CI −16.7 to −5.9). The predicted risk change for the composite endpoint of ≥ 40% eGFR decline or ESRD in EXSCEL was −11.0% (95% CI −18.5 to −3.2) (Figure 2B). For both endpoints, HbA1c provided the largest contribution to the observed risk reduction, followed by SBP and Hb.

3.3 | Impact of EQW on renal outcomes

arm (P for difference 0.03). Progression to microalbuminuria occurred in 97 (2.9%) of the participants on placebo versus 69 (2.0%) patients on EQW (P for difference 0.02). Progression to macroalbuminuria occurred in 39 (1.1%) and 37 (1.0%) of participants in the placebo and EQW groups, respectively (P for difference 0.79).

3.2 | Predicted longer term effect of EQW on renal outcomes

The predicted risk change for the composite renal endpoint of ≥ 30% eGFR decline or ESRD based on the observed placebo corrected change in HbA1c alone was −9.9% (95% CI −14.7 to −4.9) with EQW (Figure 2A). The PRE score with coefficients fit in ALTITUDE predicted the effect of EQW on the composite renal endpoint in EXSCEL to be −11.3% (95% CI −16.7 to −5.9). The predicted risk change for the composite endpoint of ≥ 40% eGFR decline or ESRD in EXSCEL was −11.0% (95% CI −18.5 to −3.2) (Figure 2B). For both endpoints, HbA1c provided the largest contribution to the observed risk reduction, followed by SBP and Hb.

In this post hoc analysis of the EXSCEL trial, we showed that EQW 2 mg reduced multiple cardio-renal risk markers after 6 months treatment in a broad population of patients with T2D. Integrating these short-term changes in multiple risk markers resulted in a predicted renal risk reduction of 11% when using the PRE score calibrated to ALTITUDE, which was of a similar magnitude to the relative risk reduction observed in the trial. These results support further clinical trials to prospectively assess the renal efficacy of EQW.

Prior studies have suggested that GLP-1RAs may slow renal disease progression in patients with T2D. A prespecified analysis from the ELIXA trial reported that patients treated with the short-acting GLP-1RA lixisenatide showed a smaller increase in albuminuria from baseline to 108 weeks compared with placebo-treated patients (24% vs. 34%; P = 0.004).18 No effect was observed on eGFR decline in that study. In the LEADER and SUSTAIN-6 trials, liraglutide and semaglutide reduced the composite renal outcome of new onset of

4 | DISCUSSION

In this post hoc analysis of the EXSCEL trial, we showed that EQW 2 mg reduced multiple cardio-renal risk markers after 6 months treatment in a broad population of patients with T2D. Integrating these short-term changes in multiple risk markers resulted in a predicted renal risk reduction of 11% when using the PRE score calibrated to ALTITUDE, which was of a similar magnitude to the relative risk reduction observed in the trial. These results support further clinical trials to prospectively assess the renal efficacy of EQW.

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persistent macroalbuminuria, persistent doubling of serum creatinine level and ESRD by 22% and 36%, respectively. These favourable effects were predominantly driven by reductions in the risk for macroalbuminuria. The benefit on a clinically meaningful endpoint of doubling of serum creatinine or ESRD in these trials was less clear, although slowing of eGFR decline in subjects with moderate-to-severe CKD was observed in LEADER and AWARD-7 as well as a reduction of 40% eGFR decline or ESRD with the higher dose of dulaglutide (1.5 mg) in AWARD-7, driven by events in participants with macroalbuminuria at baseline. In the REWIND trial, dulaglutide reduced the risk of a composite endpoint of new onset macroalbuminuria, sustained 30% eGFR decline or ESRD with the clearest and statistically significant effect for the development of macroalbuminuria. Although the risks for the 30% eGFR decline and ESRD components were numerically reduced, they did not reach statistical significance in REWIND. A sensitivity analysis of sustained 40% and 50% eGFR declines in REWIND did show a nominally significant improvement with dulaglutide in the median 5.4 year follow-up in REWIND. In this analysis, we showed for the first time that treatment with exenatide nominally significantly lowered the risk of a composite endpoint—30% eGFR decline or ESRD—that did not include the surrogate albuminuria. Replacing the 30% eGFR decline by a more robust yet less frequent endpoint of 40% eGFR decline yielded similar estimates of the treatment effect size, although it did not reach statistical significance. As reported elsewhere, a renal composite endpoint of sustained 40% eGFR drop, ESRD, and new macroalbuminuria was statistically improved in EXSCEL by exenatide, although only in the adjusted analysis. Given the low frequency of renal outcomes in this population with preserved eGFR and low UACR at baseline, we did not analyse outcomes or the predictive ability of the PRE score as a function of baseline eGFR. Dedicated renal outcome trials with GLP-1RAs are needed to more definitively assess the renoprotective potential of these compounds; the FLOW renal outcomes trial for semaglutide is currently ongoing (NCT03819153). While the results here suggest a large contribution of HbA1c to the improvement in renal outcomes in EXSCEL, treatment with EQW and other GLP-1RAs has multiple additional effects that are also associated with improved renal outcomes. Although the mechanisms underlying the effects of incretin-based therapies are not completely understood, there is growing evidence that several nonglycaemic mechanisms mediate the renoprotective effects of incretin-based therapies, possibly to a larger extent than observed here in at least some populations. Firstly, GLP-1RAs have been suggested to enhance sodium excretion by inhibition of the sodium-hydrogen exchange 3 transporter without altering intraglomerular pressure. Enhanced sodium excretion may result in blood pressure and body weight reductions. Secondly, GLP1-RAs appear to exert direct effects on the renal vascular endothelium, which may be involved in their albuminuria-lowering effect and stabilization of renal function decline. Further research will be needed to fully elucidate the contributions of these different risk factors to GLP-1RA effects on renal function decline in different populations.
The longer term effects of EQW on renal outcomes were accurately predicted by the PRE score algorithm. The PRE score has previously been used to predict the long-term renal effects of renin angiotensin aldosterone system (RAAS) inhibitors, endothelin receptor antagonists and sodium-glucose co-transporter-2 inhibitors. Differences in the measurement and registration between prior trials and the EXSCEL trial (eg, pragmatically collected data on transition in albuminuria stage in EXSCEL without confirmation via UACR vs. percentage change in UACR in other trials), as well as the large proportion of patients with low levels of albuminuria in EXSCEL, may explain this. However, the results here do suggest that a reasonable prediction of drug effect on renal risk may be plausible even if only categorical information on UACR is collected, highlighting the ability to tailor the PRE score construct to risk factors of interest that were collected in a particular population.

### Table 1

<table>
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<th>Placebo</th>
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<th>Favours Exenatide</th>
<th>Favours Placebo</th>
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<tr>
<td>HbA1c (%)</td>
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<td>Haemoglobin (mg/L)</td>
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<td>-11.3 (-16.7,-5.9)</td>
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<td>-11.3 (-16.7,-5.9)</td>
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**Figure 2** Predicted risk change for the composite renal outcome of ≥30% estimated glomerular filtration rate (eGFR) decline or end-stage renal disease (ESRD) (A) and for the composite renal outcome of ≥40% eGFR decline or ESRD (B) in the EXSCEL population based on changes in single risk markers and the integrated effects of all risk markers. Circles indicate point estimates of the percentage mean change in relative risks with end-stage renal disease compared with placebo, with their 95% confidence intervals. BMI, body mass index; SBP, systolic blood pressure

*Because of a lack of continuous data for albuminuria in the EXSCEL trial, categorical information on new micro- or macroalbuminuria was used to reflect short-term changes in albuminuria.
Surrogate endpoints based on a single risk marker may not capture the overall drug effect. Indeed, multiple examples exist where drug effects on single surrogates insufficiently predict the drug effect on long-term clinical outcomes.\textsuperscript{13,37-39} Apparently, additional drug effects on single surrogates insufficiently predict the drug effect on the overall drug effect.\textsuperscript{14} Integrating multiple effects of a drug assists in better long-term drug efficacy prediction, yet few tools or applications of such tools exist to date. The PRE score is intended as a flexible framework for predicting drug effects based on short-term changes in clinical chemistry variables that have been measured in trials, as opposed to using a fixed set of biomarkers as many individual risk prediction scores do. As such, the PRE score can be applied during early clinical trials and provide information as to whether (or in which patients) the drug is probable to be effective and may inform power and sample size calculations. In this analysis, we used 6-month risk markers from EXSCEL to predict long-term outcomes in the same trial after fitting the coefficients to a background population in ALTITUDE, as opposed to the intended future use of predicting outcomes based on earlier data prior to initiation of the outcomes trial. This is because, as the first attempt to apply the PRE score construct to the GLP-1RA class, we were interested in whether, given the true risk marker changes, the PRE score could predict outcomes. This validity for the GLP-1RA class must be established before the PRE score is used to prospectively inform the design of an outcomes trial (ie, using phase 2 trial data to predict the effect of a drug on long-term outcomes in a phase 3 trial). Note that the purpose of the PRE score is not to predict individual renal risk, but rather to predict long-term drug efficacy. An intentional choice to include only modifiable risk factors in the score captures many drug-induced changes in risk factors. Risk factors not alterable by drug exposure (eg, age or demographics) do not contribute to drug efficacy estimation and therefore are not included.

An important feature of the PRE score is that the beta coefficients can be fit to an independent dataset, collected from a trial designed to study a different drug, where baseline risk marker levels and long-term outcomes data are collected. Here, we fit the beta coefficients to a subpopulation from ALTITUDE, then made predictions in EXSCEL. A new background dataset is not needed for every drug desired to be studied. However, we selected a background dataset that includes a similar population to the population of interest, and in which the relevant risk factors known or thought to be modified by the drug of interest are measured, to appropriately predict the drug-induced risk change for our target population.

This analysis has limitations. The analyses were exploratory and post hoc in nature and therefore the results should be interpreted as hypothesis generating. The majority of participants in the EXSCEL trial had only mild to moderate chronic kidney disease, and therefore the number of ESRD events during the trial was low. Thus, further study would be required to evaluate the validity of the PRE score in predicting EQW effects on renal outcomes in more advanced kidney disease. Determining whether EQW genuinely slows progression of renal function decline would require a dedicated hard outcome trial in a population at risk of renal disease progression to capture a sufficient number of clinically meaningful ESRD events. Furthermore, despite the use of multiple imputation in participants missing ≤1 of the required risk marker data at baseline and/or month 6, a small proportion of participants in the EXSCEL trial had complete risk marker data available. As a result, our predictions are based on a subset of patients in the EXSCEL trial with most risk marker data available, possibly inducing bias. Additionally, to keep the PRE score easy to apply and focused on modifiable risk factors, it does not account for changes in risk factors not included in the score (eg, changes in medication use), demographics, or complex interactions between risk factors. To allow the PRE score to be used when only short-term risk marker changes

**FIGURE 3** Rates of the composite renal outcome of ≥30% estimated glomerular filtration rate (eGFR) decline or end-stage renal disease (ESRD) (A) and ≥40% eGFR decline or ESRD (B) in the once-weekly exenatide (EQW) and placebo groups among the total EXSCEL population.
are available, the PRE score estimates drug-induced risk reduction based on 6-month changes in risk markers; changes occurring on a longer timescale may be under-represented in the PRE score. Finally, the high premature discontinuation rate in the EXSCEL trial may have influenced the observed effect of EQW on renal outcomes, as well as the observed changes in risk markers upon which the PRE score is built.

In conclusion, among patients with T2D at cardiovascular risk, EQW compared with placebo decreased multiple cardio-renal risk markers and reduced the risk for progression of renal disease. Integration of the short-term risk marker changes resulted in a predicted risk reduction of similar magnitude to the actual observed risk reduction for renal outcomes.

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CONFLICT OF INTEREST

L.E.C., R.C.P. and D.W.B. are employees of AstraZeneca. N.M.A.I. reports no conflicts of interest. A.F.H. reports receiving research funding from AstraZeneca, GlaxoSmithKline, Merck and Novartis; and consulting fees from AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Merck, Novartis and Pfizer. G.B. is on the steering committees of CREDENCE, CALM-2 and FIDELIO, and is principal investigator of FIDELIO: he is a consultant for Bayer, Relypsa, Janssen, Merck and Vascular Dynamics. R.C.P. is a stockholder of Novartis. D.W.B. is a stockholder of Bristol-Myers Squibb. M.A.B. reports receiving research support from Merck and AstraZeneca; participating in advisory boards for Boehringer Ingelheim and NovoNordisk; receiving honoraria, personal fees and other support from Merck, Novo Nordisk, AstraZeneca and Sanofi; and receiving nonfinancial research support from Bayer and Merck Serono. R.R.H. reports receiving grants from AstraZeneca and personal fees from Bayer, Boehringer Ingelheim and Merck, personal fees from Novartis, Amgen and Servier, and other support from Elcelyx, GlaxoSmithKline, Janssen and Takeda outside the submitted work. H.J.L.H. serves as a consultant for AbbVie, Astellas, AstraZeneca, Boehringer Ingelheim, Fresenius, Gilead, Janssen, Merck, Mundipharma, Mitsubishi Tanabe and Retrophin.

AUTHOR CONTRIBUTIONS

N.M.A.I., L.E.C., R.C.P., D.W.B., and H.J.L.H. designed the analysis. N.M.A.I. and L.E.C. performed the analysis and wrote the first draft of the manuscript. A.F.H., G.B., M.A.B., and R.R.H. were involved in the conduct of EXSCEL, and contributed to the design and interpretation of this analysis. All authors reviewed and approved the final manuscript. N.M.A.I. and L.E.C. contributed equally to this study.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of this article.

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