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Estimated glomerular filtration rate slope and risk of primary and secondary major adverse cardiovascular events and heart failure hospitalization in people with type 2 diabetes: An analysis of the EXSCEL trial

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Abstract

Aim: The decline in estimated glomerular filtration rate (eGFR), a significant predictor of cardiovascular disease (CVD), occurs heterogeneously in people with diabetes because of various risk factors. We investigated the role of eGFR decline in predicting CVD events in people with type 2 diabetes in both primary and secondary CVD prevention settings.

Materials and Methods: Bayesian joint modelling of repeated measures of eGFR and time to CVD event was applied to the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trial to examine the association between the eGFR slope and the incidence of major adverse CV event/hospitalization for heart failure (MACE/hHF) (non-fatal myocardial infarction, non-fatal stroke, CV death, or hospitalization for heart failure). The analysis was adjusted for age, sex, smoking, systolic blood pressure, baseline eGFR, antihypertensive and lipid-lowering medication, diabetes duration, atrial fibrillation, high-density cholesterol, total cholesterol, HbA1c and treatment allocation (once-weekly exenatide or placebo).

Results: Data from 11 101 trial participants with ($n = 7942$) and without ($n = 3159$) previous history of CVD were analysed. The mean ± SD eGFR slope per year in participants without and with previous CVD was −0.68 ± 1.67 and −1.03 ± 2.13 mL/min/1.73 m^2, respectively. The 5-year MACE/hHF incidences were 7.5% (95% CI 6.2, 8.8) and 20% (95% CI 19, 22), respectively. The 1-SD decrease in the eGFR slope was associated with increased MACE/hHF risks of 48% (HR 1.48, 95% CI 1.12, 1.98, $p = 0.007$) and 33% (HR 1.33, 95% CI 1.18,1.51, $p < 0.001$) in participants without and with previous CVD, respectively.

Conclusions: eGFR trajectories over time significantly predict incident MACE/hHF events in people with type 2 diabetes with and without existing CVD, with a higher hazard ratio for MACE/hHF in the latter group.

KEYWORDS

cardiovascular disease, estimated glomerular filtration rate, heart failure hospitalization, major adverse cardiovascular events, type 2 diabetes

1 | INTRODUCTION

Diabetes is a well-recognized risk factor for the development and progression of chronic kidney disease (CKD), cardiovascular disease (CVD) and associated complications.[1] The estimated glomerular filtration rate (eGFR) is an established marker for assessing and monitoring kidney function.[2] Evidence suggests that eGFR deteriorates twice as rapidly in people with compared with those without, diabetes.[3] However, kidney function declines heterogeneously in people with diabetes because of various factors such as hyperfiltration in early diabetes, comorbidities, hyperglycaemia, pharmacological interventions and other clinical risk factors.[3,4]

Besides being a kidney function marker, eGFR has consistently been shown as an independent risk factor for various CV events, including myocardial infarction, stroke, heart failure and CV mortality in people with CKD, diabetes, high CVD risk, and the general population.[4–12] Even a modest decrease in eGFR has been shown to significantly increase CVD risk in recent studies.[13,14] Given these data, eGFR has been included in CVD risk scores as a marker to improve their predictive performance.[15–17]

The eGFR is a dynamic marker and its decline over time (slope) has been shown to predict adverse clinical outcomes better than its absolute value in various patient populations.[18–21] A commonly used approach to assess the association between eGFR slope and the incidence of CVD is to estimate, through a linear mixed effect model (LMEM), the slope in eGFR for each individual using data up to a given index follow-up time. The estimated eGFR slope is then used as the main covariate in a Cox proportional hazard model to estimate its association with CVD using the remaining data and the specified index follow-up time as the time origin.[22,23] This approach, despite its popularity, has some serious drawbacks. First, it uses the estimated eGFR slope, which is measured with error, as the main covariate in the Cox proportional hazard (CoxPH) model. This might lead to an underestimation of the true association. The extent of this underestimation may be significant when the precision of the eGFR slope estimate is compromised, such as in cases with a limited number of repeat measurements per individual.[24] Secondly, this method is particularly sensitive to the choice of the index follow-up time. The longer the index follow-up time, the higher the precision in estimating the eGFR slope; however, this usually leaves researchers with a shorter follow-up time for incident CVD, limiting the power of the analysis.

In recent years, a newly developed class of survival models called 'Joint Models for Longitudinal and Time-to-Event Data' has gained attention in biomedical research because these models incorporate repeated measurements of risk factors to predict the risk of subsequent outcomes.[25] Several studies have applied such joint models to assess the longitudinal impact of various risk factors, such as glycated haemoglobin, fasting blood glucose, anthropometric indices, lipids and blood pressure, on CVD risk.[26–32] These models address the above-described drawbacks of the standard methods by accounting for measurement errors in the longitudinal data[25] and by allowing the investigation of the association between eGFR slope and CVD risk without splitting the data.

In this paper, we investigated the role of the eGFR slope in the prediction of CVD events in people with type 2 diabetes in both primary and secondary CVD prevention settings. We used the joint model as the primary method to assess the association of the eGFR slope with the incidence of CVD. We also utilized the standard approach using the index follow-up time to perform a sensitivity analysis.

2 | MATERIALS AND METHODS

2.1 | Data source

We used the 'Exenatide Study of Cardiovascular Event Lowering' (EXSCEL) data in this study. The EXSCEL was a multinational placebo-controlled, double-blind, parallel-group, pragmatic randomized clinical

trial that investigated the treatment effects of subcutaneous once-weekly exenatide (EQW) in addition to usual care, compared with usual care, on major adverse CV events (MACE) in people with type 2 diabetes. The trial enrolled 14 752 individuals, of whom 7356 were randomized to EQW and 7396 to placebo. Approximately 70% (10 782) of study participants had established CVD. EXSCEL was conducted from January 2010 to April 2017 in 35 countries, and participants were followed for a median time of 3.2 years. No significant difference was observed in the risk of composite MACE between the EQW and the control group in the trial. The methodology, baseline characteristics and primary results of the trial have been published.[33–35]

2.2 | Outcomes and predictors

The primary composite outcome investigated in this study was MACE/hospitalization for heart failure (hHF), defined as non-fatal myocardial infarction, non-fatal stroke, CV death, or hospitalization for heart failure. The primary endpoint was the duration of time from the date of randomization until the occurrence of the first MACE/hHF event. Participants who were lost to follow-up, discontinued the study without any record of MACE/hHF, or did not develop MACE/hHF at the end of the study were right-censored.

The primary predictor was the eGFR slope, derived from repeated eGFR measurements. The median (Q1, Q3) number of eGFR measurements used was 5 (3, 7). The details of eGFR slope estimation and its incorporation into the survival model are described in Section 2.3. The association between eGFR slope and MACE/hHF was adjusted for baseline demographic, clinical and laboratory measurements, including age, sex, smoking, ethnicity, systolic blood pressure, baseline eGFR, antihypertensive and lipid-lowering medication use, duration of diabetes, history of atrial fibrillation, and randomization to either EQW or placebo. Laboratory measurements included glycated haemoglobin, total cholesterol and high-density cholesterol. The history of CVD was used as a stratification variable to account for differences in the baseline hazard of MACE/hHF between patients with and without a history of CVD.

2.3 | Statistical analysis

We summarized baseline characteristics using mean ± SD or median and first (Q1) and third (Q3) quartiles for continuous measures and frequency tables for categorical variables. We compared categorical variables using the chi-squared or Fisher's exact tests, and continuous variables using the unpaired *t*-test or its non-parametric equivalent Wilcoxon rank sum test if the normality assumption was violated.

2.3.1 | Primary analysis: joint model using the estimated glomerular filtration rate slope as a covariate

The association between eGFR slope and the incidence of MACE/hHF was investigated by jointly modelling repeated measurements of eGFR since randomization and time-to-MACE/hHF using a Bayesian joint model of longitudinal and time-to-event data.[25] Repeated eGFR measurements were first modelled using an LMEM and then incorporated into a survival model where the hazard function at any follow-up time t_{fup} was expressed as a function of eGFR slope at that time t_{fup}, in addition to baseline covariates. The eGFR slope at the follow-up time t_{fup} was derived directly from the LMEM component, taking measurement errors into account.[25] For illustration purposes, the eGFR slopes were extracted from the joint model and grouped into tertiles. Cumulative incidence curves of MACE/hHF were then estimated using the Kaplan–Meier method and compared according to eGFR slope tertiles using the log-rank test.

2.3.2 | Sensitivity analysis: Cox proportional hazard model using the index follow-up time

For the sensitivity analysis, we used the standard split-data approach described in the introduction. For a given index follow-up time t_{index} (e.g. $t_{index} = 2$ years), the dataset was divided into two parts, i.e. the eGFR slope estimation and the MACE/hHF prediction. The first part included all repeated eGFR measurements collected between randomization and the index follow-up time t_{index}. This dataset was used to estimate and extract the eGFR slope for each participant by fitting the LMEM with a random intercept and random slope with no assumption on the covariance matrix (i.e. unstructured) and without any adjustment. The remaining data were used to estimate the association between the eGFR slope and the incidence of MACE/hHF using the CoxPH. At this stage, time-to-MACE/hHF was defined as the duration of time from the index follow-up time t_{index} (time origin for CoxPH model) to the occurrence of MACE/hHF. The eGFR slope extracted in the first stage was used as the main predictor in the CoxPH model adjusting for covariates measured at the index follow-up time t_{index}, or just before this time, whichever was available. In this sensitivity analysis, we used different index follow-up times to investigate the impact of the choice of duration used for the eGFR slope estimation and MACE/hHF prediction.

2.4 | Ethical considerations

The EXSCEL trial was approved by local ethics committees and institutional review boards of each participating centre. All study participants provided written consent to take part in the trial. Permission to analyse the data was obtained from the EXSCEL Publications Committee. The study was registered on clinicaltrials.gov (NCT01144338, registration date 14 June 2010).

3 | RESULTS

The data of 11 101 patients with ($N = 7942$) and without ($N = 3159$) a history of CVD were analysed in this study. The median (Q1, Q3)

number of study visits was 5 (3, 7) in the overall study cohort, 5 (3, 6) in those with a history of CVD, and 5 (3, 8) in those without a history of CVD. At baseline, the mean age of the patients was 63 ± 9 years (64 ± 9 years in those with a history of CVD and 59 ± 10 in those without a history of CVD), 63% were males (68% in those with a history of CVD and 50% in those without a history of CVD), and 12% were smokers (12% in those with a history of CVD and 11% in those without a history of CVD). Baseline eGFR was 78 ± 22 mL/min/1.73 m^2 (76 ± 22 in those with a history of CVD and 83 ± 23 in those without a history of CVD). During follow-up, MACE/hHF occurred in 1092 subjects (936 with and 156 without a history of CVD) (Table 1).

TABLE 1 Characteristics of EXSCEL participants, overall, and by CVD status at baseline.

Variable	All ($N = 11\,101$)	Without CVD ($N = 3159$)	With CVD ($N = 7942$)	*P*-value
Number of visits, median (Q1, Q3)	5 (3, 7)	5 (3, 8)	5 (3, 6)	<0.001
eGFR, mL/min/1.73 m^2; mean ± SD	78 ± 22	83 ± 23	76 ± 22	<0.001
Age, years; mean ± SD	63 ± 9	59 ± 10	64 ± 9	<0.001
Sex, *n* (%)				
Female	4144 (37%)	1587 (50%)	2557 (32%)	<0.001
Male	6957 (63%)	1572 (50%)	5385 (68%)	
Ethnicity, *n* (%)				
African American	605 (5.4%)	184 (5.8%)	421 (5.3%)	<0.001
Asian	1123 (10.0%)	271 (8.6%)	852 (11.0%)	
Hispanic	709 (6.4%)	239 (7.6%)	470 (5.9%)	
Indian American or Alaska Native	17 (0.2%)	2 (<0.1%)	15 (0.2%)	
Native Hawaiian or other Pacific Islander	28 (0.3%)	8 (0.3%)	20 (0.3%)	
White	8619 (78%)	2455 (78%)	6164 (78%)	
Ethnicity (used in modelling)				
White/Hispanic	9328 (84%)	2694 (85%)	6634 (84%)	0.023
Others	1773 (16%)	465 (15%)	1308 (16%)	
Smoking status, *n* (%)				
No	9823 (88%)	2802 (89%)	7021 (88%)	0.700
Yes	1278 (12%)	357 (11%)	921 (12%)	
Congestive heart failure, *n* (%)	1704 (15%)	242 (8%)	1462 (18%)	<0.001
Body mass index, kg/m^2; mean ± SD	33 ± 6	34 ± 7	32 ± 6	<0.001
Systolic blood pressure, mmHg; mean ± SD	135 ± 16	134 ± 15	135 ± 16	0.029
Diastolic blood pressure, mmHg; mean ± SD	78 ± 10	80 ± 10	77 ± 10	<0.001
HbA1c, %; mean ± SD	8.05 ± 1.00	8.12 ± 1.00	8.01 ± 1.00	<0.001
Total cholesterol, mg/dL; mean ± SD	171 ± 45	182 ± 44	167 ± 45	<0.001
Total cholesterol, mmol/L; mean ± SD	4.39 ± 1.15	4.66 ± 1.14	4.28 ± 1.14	<0.001
LDL-C, mg/dL; mean ± SD	96 ± 39	105 ± 39	93 ± 39	<0.001
LDL-C, mmol/L; mean ± SD	2.47 ± 1.01	2.69 ± 1.00	2.38 ± 1.00	<0.001
HDL-C, mg/dL; mean ± SD	44 ± 11	45 ± 12	43 ± 11	<0.001
HDL-C, mmol/L; mean ± SD	1.12 ± 0.29	1.16 ± 0.30	1.10 ± 0.29	<0.001
Non-HDL, mg/dL; mean ± SD	128 ± 43	136 ± 43	124 ± 43	<0.001
Non-HDL, mmol/L; mean ± SD	3.27 ± 1.11	3.50 ± 1.10	3.18 ± 1.10	<0.001
Triglycerides, mg/dL; mean ± SD	188 ± 121	191 ± 120	187 ± 122	0.200
Triglycerides, mmol/L; mean ± SD	2.11 ± 1.36	2.14 ± 1.35	2.10 ± 1.37	0.200
Composite MACE/hHF event, *n* (%)	1092 (9.8%)	156 (4.9%)	936 (12.0%)	<0.001

Note: Continuous variables were compared using the two-sample *t*-test or Wilcoxon rank-sum test. Categorical variables were compared using the Pearson's chi-squared test.

Abbreviations: CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MACE/hHF, major adverse cardiovascular event/hospitalization for heart failure.

3.1 | Estimated glomerular filtration rate slope

Figure S1 shows the changes in the mean and median eGFR over study visits. In participants with and without a history of CVD, the eGFR decreased progressively, indicating a decline in kidney function over time. The distribution of eGFR slopes in participants with and without a history of CVD is shown in Figure S2. The mean eGFR slope was −0.68 ± 1.67 mL/min/1.73 m^2 per year in patients without CVD and −1.03 ± 2.13 mL/min/1.73 m^2 per year in those with CVD. The mean ± SD eGFR slope declined from −2.36 ± 1.15 in the first tertile to 0.98 ± 1.18 in the third tertile in patients without history of CVD, and from −3.15 ± 1.35 to 1.13 ± 1.59 in patients with previous history of CVD (Table S1).

3.2 | Crude incidence of major adverse cardiovascular events/hospitalization for heart failure

Overall, the median (interquartile range) follow-up was 3.3 (2.2, 4.3) years, and the 5-year incidence of MACE/hHF was 16% (95% CI 15, 17). In participants without CVD, the median follow-up was 3.9 (2.5, 4.8) years, and the 5-year incidence of MACE/hHF was 7.5% (95% CI 6.2, 8.8). In patients with CVD, the median follow-up was 3.0 (2.2, 4.1) years, and the 5-year incidence of MACE/hHF was 20% (95% CI 19%, 22%) (Figure S3).

3.3 | Crude incidence of major adverse cardiovascular events/hospitalization for heart failure by estimated glomerular filtration rate slope tertiles

Figure 1 shows the cumulative incidence curves of MACE/hHF for participants with and without a history of CVD according to eGFR slope tertiles. The cumulative incidence of MACE/hHF was significantly different with respect to eGFR slope tertiles in patients with ($p < 0.001$) and without a history of CVD ($p < 0.001$), meaning the steeper the eGFR decline, the higher the incidence of MACE/hHF. Moreover, the difference in the cumulative incidence was greater between patients in the first tertile compared with those in the second and third tertiles in participants without history of CVD, while it was greater in those in the first and second tertiles compared with those in the third tertile in participants with history of CVD. (This is just a descriptive note without any underlying statistical test.) In participants without a history of CVD, the 5-year risk of MACE/hHF was 17% (95% CI 14%, 20%) for the first tertile, 2.6% (95% CI 0.8%, 4.4%) for the second tertile, and 1.3% (95% CI 0.3%, 2.3%) for the third tertile.

In participants with a history of CVD, the 5-year risk of developing MACE/hHF was 39% (95% CI 36%, 41%) for the first tertile, 13% (95% CI 10%, 16%) for the second tertile, and 7.1% (95% CI 5%, 9%) for the third tertile.

3.4 | Association between estimated glomerular filtration rate slope and major adverse cardiovascular events/hospitalization for heart failure

3.4.1 | Primary analysis using joint models

The results of the joint model stratified by CVD history are presented in Table 2. The table provides the fit for the two components of the joint model: the linear mixed effect component showing how eGFR is evolving over time adjusting for risk factors at baseline, and the Cox-proportional hazard component showing the association between eGFR slope and the hazard for MACE/hHF adjusting for risk factors at baseline.

The joint model results show that 1 SD decrease in eGFR slope is associated with 48% (HR 1.48; 95% CI 1.12, 1.98; $p = 0.007$) increased risk of MACE/hHF in participants without a history of CVD and 33% (HR 1.33; 95% CI 1.18, 1.51; $p < 0.001$) increased risk of MACE/hHF in participants with a history of CVD. The randomization to either EQW or placebo had no impact on the reported associations. Table 3 provides hazard ratios for the association between the eGFR slope and each component of MACE/hHF, namely, MACE and heart failure.

3.4.2 | Sensitivity analyses using different follow-up index times

The results of sensitivity analyses in both patients with and without history of CVD are presented in Table S2 for index follow-up times of 2 and 3 years. In participants without a history of CVD, the decline in eGFR slope by 1 SD was associated with a 23% (HR 1.23; 95% CI 1.00, 1.52; $p = 0.054$) and a 23% (HR 1.23, 95% CI 0.94, 1.63; $p = 0.136$) increased risk of MACE/hHF at 2-year and 3-year index follow-up time, respectively. In participants with a history of CVD, the decrease in eGFR slope by 1 SD was associated with a 10% (HR 1.10; 95% CI 0.99, 1.22; $p = 0.066$) and an 18% (HR 1.18; 95% CI 1.02, 1.38; $p = 0.031$) increased risk of MACE/hHF at 2-year and 3-year index follow-up times.

Figure 2 shows the association between the eGFR slope and the risk of MACE/hHF at various index follow-up times, indicating that the magnitude of the association and its statistical significance depend upon the index follow-up time chosen for fitting the survival model. Table S3 provides the details on the number of participants, the number of repeat measures of eGFR, and the median follow-up years used in the primary (joint modelling) and sensitivity analyses.

4 | DISCUSSION

Our post-hoc analysis of the EXSCEL data confirms that eGFR slope is a significant predictor of MACE/hHF risk in people with type 2 diabetes with and without established CV disease. In addition, the joint

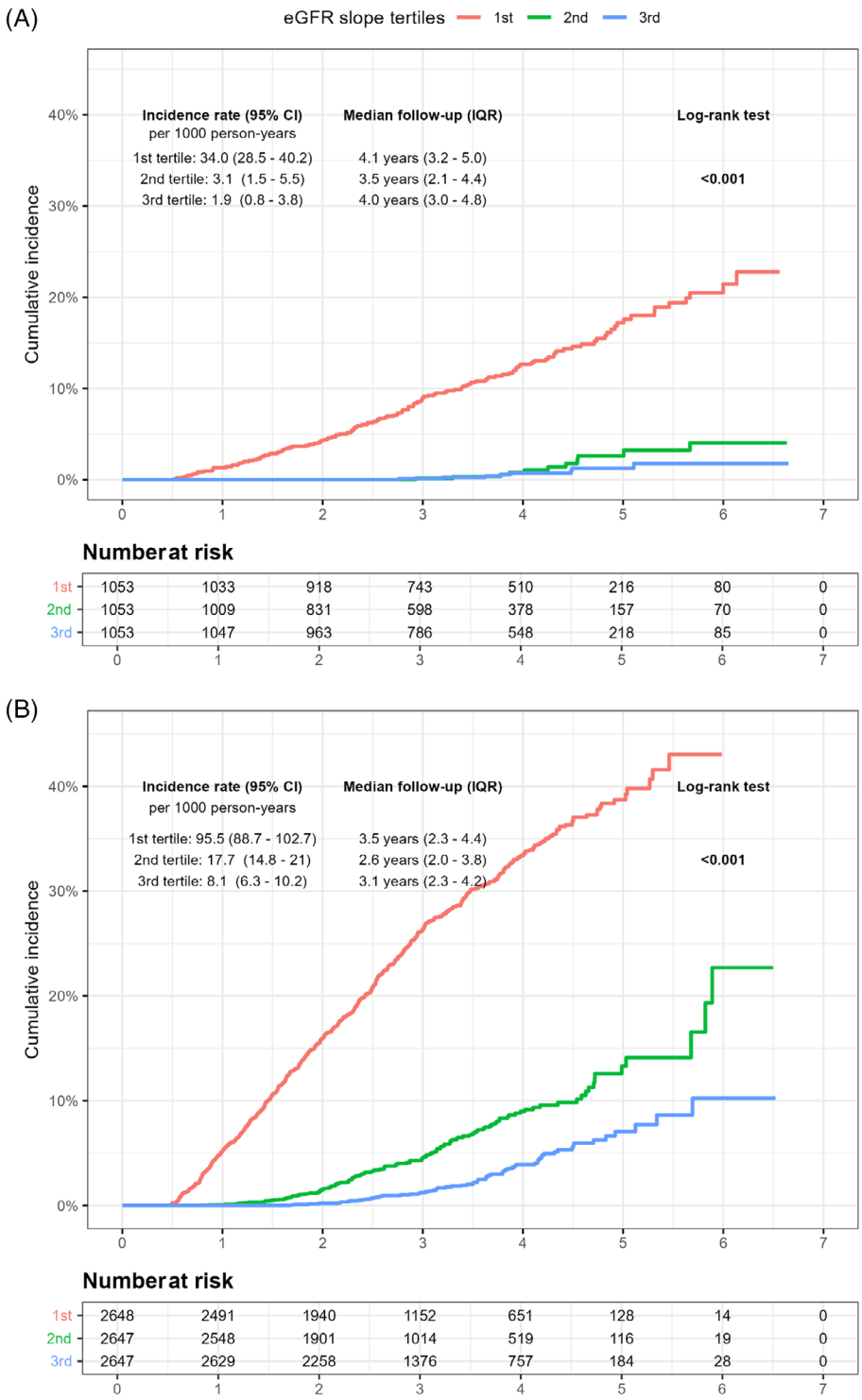

FIGURE 1 (A) Cumulative incidence of composite major adverse cardiovascular event/hospitalization for heart failure by the eGFR slope tertiles in participants without cardiovascular disease. Tertiles of the eGFR slope are: first tertile = (−9.04; −1.19), second tertile = (−1.19; −0.19), third tertile = (−0.19; 8.47). (B) Cumulative incidence of composite major adverse cardiovascular event/hospitalization for heart failure by eGFR slope tertiles in participants with cardiovascular disease. Tertiles of the eGFR slope are: first tertile = (−11.80, −1.76); second tertile = (−1.76, −0.43); third tertile = (−0.43, 11.00). CI, confidence interval; eGFR, estimated glomerular filtration rate; IQR, interquartile range.

longitudinal risk factor and outcome modelling approach was shown to be an effective statistical approach to overcome the limitations inherent in the eGFR slope estimation using a two-step approach for assessing CVD risk.

Our data confirm and extend previous analyses concerning the relationship of eGFR slope to CVD risk in various patient populations. For instance, the multicentre real-world cohort data analysis of patients from Japan reported an 80% higher risk of CVD events in people with a declining eGFR slope compared with those with a normal slope.[36] A recent study from Iran showed that the risk of CVD was two-fold higher in people with a decline in eGFR slope of −1.05 to −0.74 mL/min/1.73 m^2 per year compared with those with a slope of −0.51 to 0.16 mL/min/1.73 m^2 per year.[23] In a French population with diabetes, a rapid decline in eGFR was noted in people with CVD compared with those without CVD and the adjusted risk of MACE was 4.11 times higher in people with a rapid decline in eGFR.[37] An

TABLE 2 Joint model for major adverse cardiovascular event/hospitalization for heart failure.

	CoxPH component		Mixed-effect component	
Variable	**HR (95% CI)**	***p*-Value**	**HR (95% CI)**	***p*-Value**
Participants without history of CVD				
eGFR at baseline (1 SD decrease)	0.91 (0.72, 1.14)	0.445	NA	NA
eGFR slope (1-SD increase)	1.48 (1.12, 1.98)	0.007	NA	NA
Follow-up time	NA	NA	−0.68 (−0.86, −0.51)	<0.001
Age (1-SD increase)	1.42 (1.14, 1.77)	0.002	−7.83 (−8.54, −7.10)	<0.001
Sex (female vs. male)	0.62 (0.44, 0.87)	0.005	−2.44 (−3.76, −1.09)	<0.001
Smoking (yes vs. no)	0.80 (0.42, 1.38)	0.460	2.57 (0.55, 4.60)	0.012
Ethnicity (White/Hispanic vs. Others)	0.99 (0.60, 1.65)	0.942	−1.35 (−3.24, 0.50)	0.149
Antihypertensive treatment (yes vs. no)	1.54 (0.90, 2.72)	0.114	−3.95 (−5.73, −2.20)	<0.001
Lipid-lowering treatment (yes vs. no)	1.09 (0.77, 1.58)	0.645	0.07 (−1.32, 1.50)	0.925
Diabetes duration (1-SD increase)	1.07 (0.91, 1.26)	0.397	−0.89 (−1.55, −0.22)	0.009
Atrial fibrillation (yes vs. no)	2.17 (1.22, 3.70)	0.011	−4.62 (−7.73, −1.37)	0.004
Randomization to EQW (yes vs. no)	1.02 (0.74, 1.39)	0.912	−0.35 (−1.63, 0.96)	0.588
Systolic blood pressure (1-SD increase)	1.21 (1.03, 1.42)	0.019	−0.46 (−1.12, 0.19)	0.172
HDL-C (1-SD increase)	0.93 (0.78, 1.10)	0.371	2.04 (1.33, 2.76)	<0.001
Total cholesterol (1-SD increase)	1.22 (1.03, 1.44)	0.024	−0.87 (−1.56, −0.15)	0.015
HbA1c (1-SD increase)	1.11 (0.94, 1.32)	0.213	−0.11 (−0.73, 0.53)	0.752
Participants with history of CVD				
eGFR at baseline (1 SD decrease)	0.73 (0.65, 0.82)	<0.001	NA	NA
eGFR slope (1-SD increase)	1.33 (1.18, 1.51)	<0.001	NA	NA
Follow-up time	NA	NA	−1.03 (−1.18, −0.88)	<0.001
Age (1-SD increase)	1.23 (1.13, 1.35)	<0.001	−6.48 (−6.94, −6.04)	<0.001
Sex (female vs. male)	0.71 (0.61, 0.83)	<0.001	−4.46 (−5.41, −3.49)	<0.001
Smoking (yes vs. no)	1.37 (1.11, 1.66)	0.002	2.51 (1.20, 3.83)	<0.001
Ethnicity (White/Hispanic vs. Others)	1.08 (0.89, 1.32)	0.422	−1.59 (−2.73, −0.46)	0.006
Antihypertensive treatment (yes vs. no)	1.90 (1.23, 3.06)	0.001	−5.15 (−7.01, −3.26)	<0.001
Lipid-lowering treatment (yes vs. no)	1.04 (0.85, 1.28)	0.703	−2.03 (−3.23, −0.87)	0.001
Diabetes duration (1-SD increase)	1.09 (1.02, 1.16)	0.009	−2.28 (−2.71, −1.85)	<0.001
Atrial fibrillation (yes vs. no)	1.48 (1.20, 1.81)	<0.001	−3.54 (−5.13, −1.93)	<0.001
Randomization to EQW (yes vs. no)	0.96 (0.84, 1.09)	0.526	0.15 (−0.69, 0.95)	0.722
Systolic blood pressure (1-SD increase)	0.99 (0.93, 1.05)	0.656	0.05 (−0.37, 0.47)	0.819
HDL-C (1-SD increase)	0.91 (0.85, 0.98)	0.011	2.03 (1.58, 2.47)	<0.001
Total cholesterol (1-SD increase)	1.10 (1.02, 1.18)	0.013	−1.11 (−1.57, −0.64)	<0.001
HbA1c (1-SD increase)	1.10 (1.03, 1.18)	0.004	−0.09 (−0.50, 0.33)	0.686

Notes: HR for continuous variables are expressed in terms of 1 SD change.
Abbreviations: CI, confidence interval; CoxPH, Cox proportional hazards model; CVD, cardiovascular disease; EQW, once-weekly exenatide; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; NA, not applicable.

TABLE 3 HRs for 1-SD decrease in estimated glomerular filtration rate slope for MACE, hHF and MACE/hHF in participants with and without history of CVD using the joint modelling approach.

	MACE/hHF		MACE		hHF	
	HR (95% CI)	***p*-Value**	**HR (95% CI)**	***p*-Value**	**HR (95% CI)**	***p*-Value**
Patients without history of CVD	1.48 (1.12, 1.98)	0.007	1.37 (1.05, 1.78)	0.022	3.79 (1.79, 9.26)	<0.001
Patients with history of CVD	1.33 (1.18, 1.51)	<0.001	1.25 (1.09, 1.44)	<0.001	2.28 (1.78, 2.98)	<0.001

Note: 1 SD is 1.73 (2.04) for patients without (with) history of CVD.
Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MACE/hHF, major adverse cardiovascular event/hospitalization for heart failure.

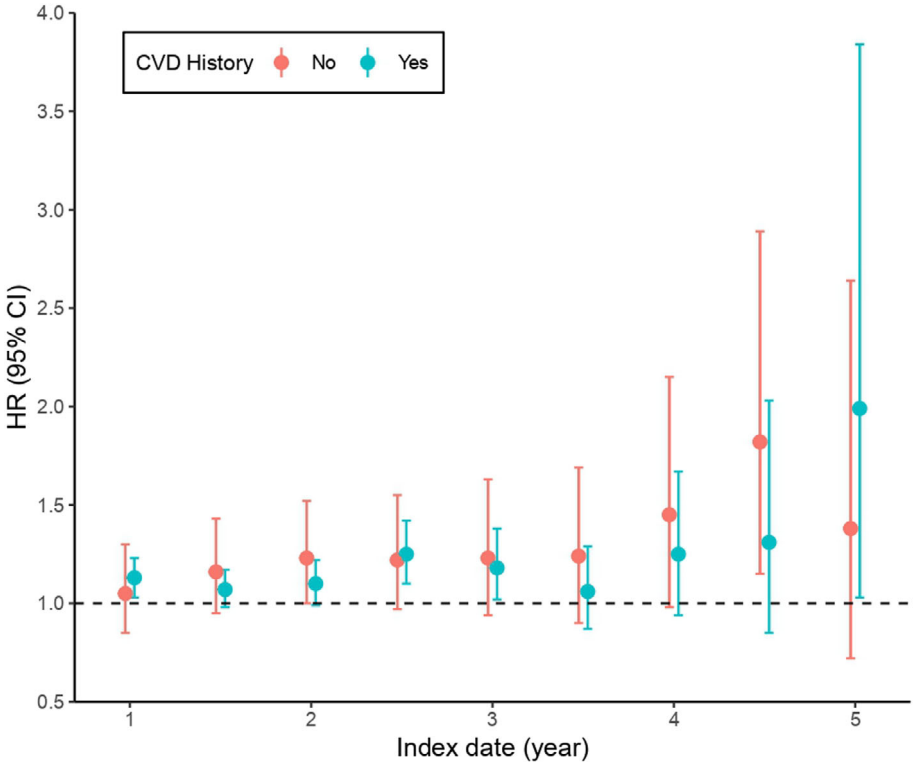

FIGURE 2 HRs of major adverse cardiovascular event/hospitalization for 1-SD decrease in the estimated glomerular filtration rate slope according to different index follow-up times. CI, confidence interval; cardiovascular disease; HRs, hazard ratios.

analysis of the ADVANCE-ON study showed that an annual eGFR slope of <−1.63 mL/min/1.73 m^2 was associated with a 26% increased risk of subsequent major CVD events in people with type 2 diabetes compared with a more stable eGFR slope of −1.63 to 0.33 mL/min/1.73 m^2.[38] A retrospective analysis of the Hong Kong health registry among people with CKD and type 2 diabetes reported that the highest eGFR decline was associated with a 36%–197% elevated risk of both microvascular and macrovascular complications compared with a lesser eGFR decline.[39] Among people with moderate-to-severe CKD, an eGFR slope of 1-SD below average was associated with a 19% higher risk of CVD.[22] Similarly, a large cohort analysis of US veterans with stage III CKD found that both low-intercept and fast-negative and high-intercept and fast-negative eGFR trajectories were associated with CVD among other clinical outcomes.[40]

The EXSCEL dataset was large enough to allow us to stratify people with type 2 diabetes according to the presence or absence of CVD at baseline. While we showed a significant association of eGFR trajectories with MACE/hHF in both cohorts, the association was numerically stronger in those without CVD with a hazard ratio of 1.48 compared with the hazard ratio of 1.33 per 1 SD of eGFR decline in people with pre-existing CVD. This is in line with data showing a more pronounced association of the number of uncontrolled established CV risk factors with CV events in people without a cardio-reno disease compared with those with the condition.[41] Moreover, the association of eGFR decline appears to be stronger with hHF compared with MACE events in participants with and without existing CVD. This is in line with previously published data from the SURDIAGENE cohort, which showed eGFR decline, estimated using the joint modelling approach, to be a significant predictor for hHF in people with type 2 diabetes.[42]

The literature delineates several mechanisms by which a decline in kidney function contributes to the development and progression of CVD. Kidney function impairment results in the accumulation of waste products and toxins, which may trigger chronic inflammation, oxidative stress and endothelial dysfunction, leading to the development and progression of CVD.[43,44] Besides, deterioration in kidney function compromises blood pressure regulation, which leads to hypertension, a major CVD risk factor.[45] Moreover, compromised kidney function can imbalance calcium and phosphate homeostasis, which can increase the risk of vascular calcification and CVD.[46] Increasing the production of angiotensin II and aldosterone hormones via activation of the renin–angiotensin–aldosterone system in response to kidney function decline is another mechanism that can contribute to CVD.[47] However, in our dataset, where the mean eGFR was >70 mL/min/1.73 m^2, the latter pathophysiological pathways are thought to play the most prominent role, as uraemic toxicity does not occur at this stage of mildly impaired renal function.

Most previous analyses used a two-step statistical approach to estimate the association between the eGFR slope and the CVD risk—eGFR slope estimation followed by CVD event prediction. Figure 2 shows that the magnitude and precision of the association significantly depend on the selection of t_{index}, which defines the end of the eGFR slope estimation period and the beginning of the CVD follow-up period. In addition, the sensitivity analysis shows that the magnitude of the association between eGFR slope and MACE/hHF, derived from using index follow-up times (i.e. the traditional approach), is lower and sometimes non-significant compared with the one

estimated from the joint model in both patients with and without CVD. This confirms the assumption that the use of the index follow-up time tends to underestimate the true association.

A few studies have also assessed the association of eGFR slope with CVD events using joint models. In this perspective, a recent review has strongly recommended using joint models in the field of nephrology for analysing the longitudinal trajectories of biomarkers such as troponin and eGFR and investigating their role in predicting adverse outcomes, including CVD.[48] In addition, a large cohort analysis ($N = 24\,777$) of patients with stages III–IV CKD has reported a stronger association of eGFR slope with the risk of CVD for the joint model [HR 1.06 (95% CI 1.03, 1.10) for 2 mL/min/1.73 m^2 decline per year] compared with the Cox model [HR 1.05 (95% CI 1.04, 1.06) for 5 mL/min/1.73 m^2 decrease in eGFR].[49] However, our analysis of the EXSCEL trial data extends these findings to people with good kidney function, as the mean eGFR was 78 ± 22 mL/min/1.73 m^2.

The main strength of our analysis is the large sample size with many repeated eGFR measurements, which allowed us to precisely estimate the eGFR slope and its association with subsequent MACE/hHF for patients with and without previous CVD. As we used joint modelling to assess the association of eGFR slope with MACE/hHF, which is robust in making use of the full data and taking into consideration measurement errors of eGFR slope and, therefore, would probably estimate the true association compared with the traditional two-step approach. Furthermore, the EXSCEL trial adjudicated all CVD events, indicating that the measurement of CVD events is highly reliable. Last, we accounted for well-known risk factors for both eGFR and CVD in our analysis.

The EXSCEL clinical trial enrolled patients who met certain inclusion criteria. Therefore, our findings may not be transferrable to other populations. In addition, the urinary albumin–creatinine ratio was only available in a subset of the EXSCEL participants, which did not allow us to analyse this parameter simultaneously with eGFR.

Our analysis shows the eGFR slope to be a significant predictor of future MACE/hHF events in people with type 2 diabetes, with a somewhat stronger predictive power in those without pre-existing CVD. In addition, the flexibility and superior prediction offered by the joint model can help clinicians to monitor the eGFR slope and the effectiveness of therapies, and perform personalized dynamic risk predictions.

AUTHOR CONTRIBUTIONS

AO and HS conceived the study. AO and AS performed the statistical analysis. HS, AO and FA drafted the manuscript. All authors provided intellectual inputs into the manuscript and revised the manuscript.

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CONFLICT OF INTEREST STATEMENT

RRH reports personal fees from Anji Pharmaceuticals, AstraZeneca and Novartis. HS received investigator-initiated study funding (paid to the Medical University of Graz) from Boehringer Ingelheim, Eli Lilly, MSD, Novo Nordisk and Sanofi-Aventis, and is on the advisory board and/or has received speaker honoraria from Amgen, Amarin, Astra Zeneca, Bayer, Boehringer-Ingelheim, Daiichi Sankyo, Eli Lilly, Kapsch, MSD, Novo Nordisk and Sanofi-Aventis. JB has received grant support from Bayer, Boehringer-Ingelheim, Carmot, Corcept, Dexcom, Eli Lilly, Insulet, MannKind, Novo Nordisk and vTv Therapeutics; consulting contracts from Alkahest, Altimmune, Anji, Aqua Medical Inc, AstraZeneca, Boehringer-Ingelheim, CeQur, Corcept Therapeutics, Dasman Diabetes Center (Kuwait), Eli Lilly, embecta, Fortress Biotech, GentiBio, Glyscend, Insulet, Mediflix, Medscape, Mellitus Health, Metsera, Moderna, Novo Nordisk, Pendulum Therapeutics, Praetego, ReachMD, Stability Health, Tandem, Terns Inc. and Vertex; expert witness engagement by Medtronic MiniMed; and stock options from Glyscend, Mellitus Health, Pendulum Therapeutics, Praetego and Stability Health. The other authors have no conflicts of interest to declare.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15817.

DATA AVAILABILITY STATEMENT

Requests for access to EXSCEL study data should be submitted via https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/.

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