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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).

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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<sup>2</sup> (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 <sup>2</sup> ; 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 <sup>2</sup> ; 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  $-0.68 \pm 1.67$  mL/min/1.73 m<sup>2</sup> per year in patients without CVD and  $-1.03 \pm 2.13$  mL/min/1.73 m<sup>2</sup> per year in those with CVD. The mean  $\pm$  SD eGFR slope declined from  $-2.36 \pm 1.15$  in the first tertile to  $0.98 \pm 1.18$  in the third tertile in patients without history of CVD, and from  $-3.15 \pm 1.35$  to  $1.13 \pm 1.59$  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.

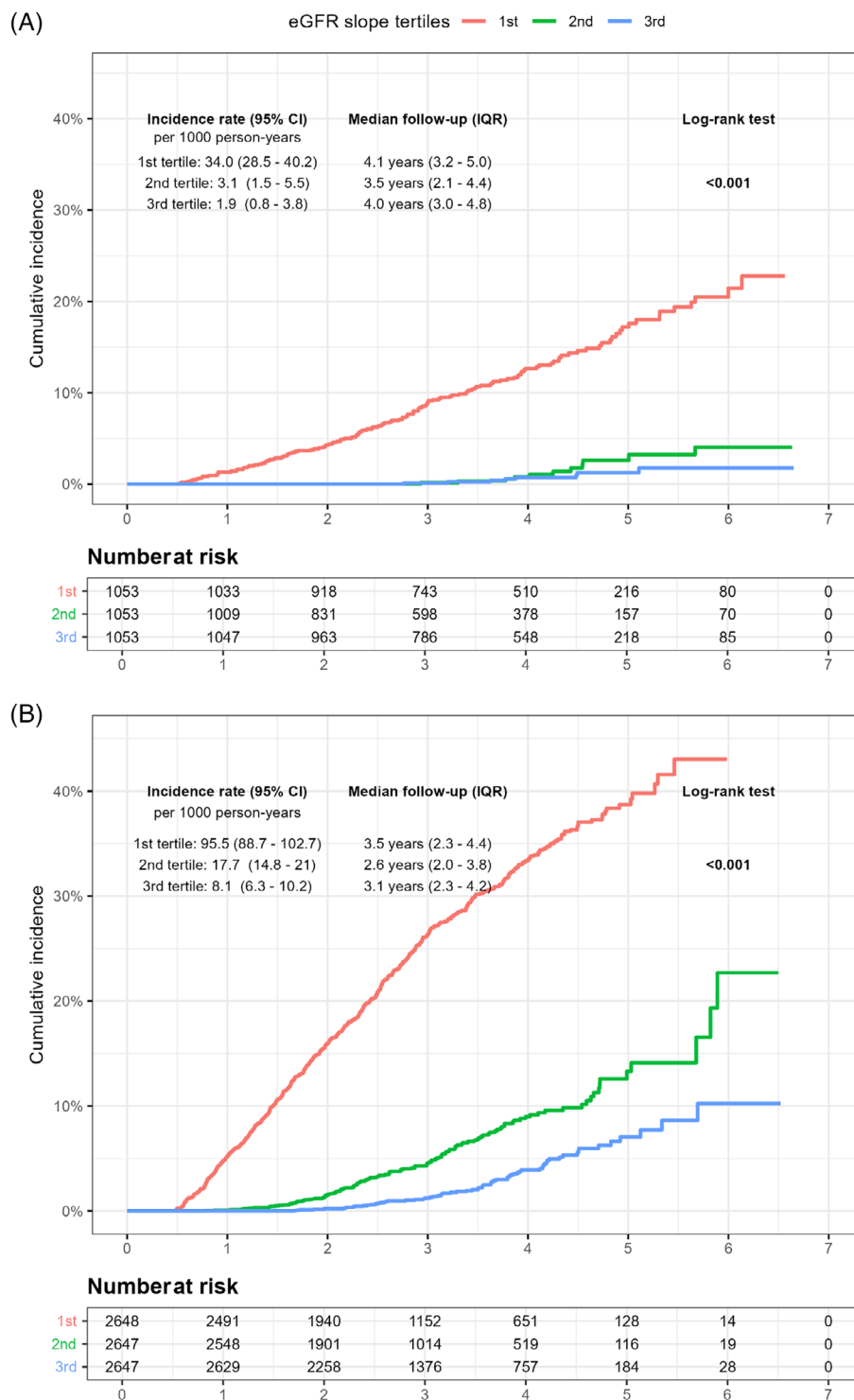
#### 3.4.2 | Sensitivity analyses using different follow-up index times

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 EXSCCEL 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.

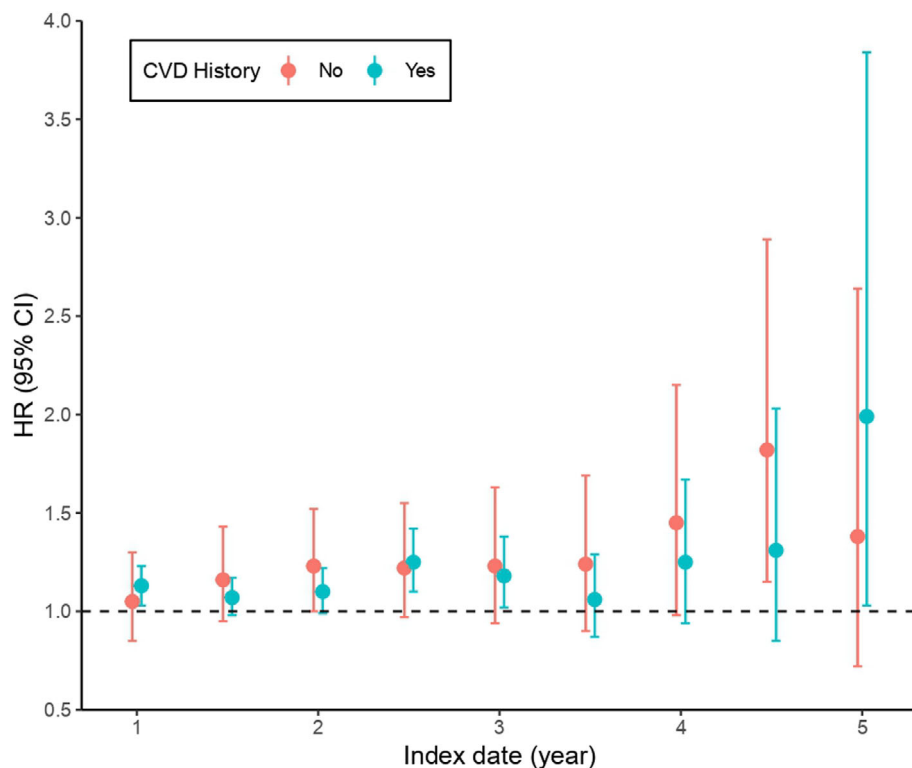
longitudinal risk factor and outcome modelling approach was shown to be an effective statistical approach to overcome the limitations inherent in the eGFR slope estimation using a two-step approach for assessing CVD risk.

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.<sup>36</sup> 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<sup>2</sup> per year compared with those with a slope of −0.51 to 0.16 mL/min/1.73 m<sup>2</sup> per year.<sup>23</sup> 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.<sup>37</sup> An







**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<sup>2</sup> 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<sup>2</sup>.<sup>38</sup> 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.<sup>39</sup> Among people with moderate-to-severe CKD, an eGFR slope of 1-SD below average was associated with a 19% higher risk of CVD.<sup>22</sup> 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.<sup>40</sup>

The EXSCCEL 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.<sup>41</sup> 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.<sup>42</sup>

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.<sup>43,44</sup> Besides, deterioration in kidney function compromises blood pressure regulation, which leads to hypertension, a major CVD risk factor.<sup>45</sup> Moreover, compromised kidney function can imbalance calcium and phosphate homeostasis, which can increase the risk of vascular calcification and CVD.<sup>46</sup> 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.<sup>47</sup> However, in our dataset, where the mean eGFR was  $>70$  mL/min/1.73 m<sup>2</sup>, 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  $t_{\text{index}}$ , 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.<sup>48</sup> 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<sup>2</sup> decline per year] compared with the Cox model [HR 1.05 (95% CI 1.04, 1.06) for 5 mL/min/1.73 m<sup>2</sup> decrease in eGFR].<sup>49</sup> However, our analysis of the EXSCEL trial data extends these findings to people with good kidney function, as the mean eGFR was  $78 \pm 22$  mL/min/1.73 m<sup>2</sup>.

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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EXSCEL 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. HS and AO had full access to the analysis dataset and are the guarantors of this work. RRH is an Emeritus National Institutes of Health Research Senior Investigator.

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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, Altimune, 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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## SUPPORTING INFORMATION

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