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Rate of Kidney Function Decline is Associated With Kidney and Heart Failure in Individuals With Type 1 Diabetes

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Introduction: Diabetes is the most common cause of chronic kidney disease (CKD). Urinary albumin excretion rate (AER) and estimated glomerular filtration rate (eGFR) are commonly used to monitor the onset and progression of diabetic kidney disease (DKD). We studied if the preceding rate of kidney function decline, that is, the eGFR slope, is independently associated with incident clinical cardiorenal events.

Methods: This study included longitudinal data for 2498 Finnish individuals with type 1 diabetes (T1D). The eGFR slope was calculated from 5 years preceding the study visit. Data on kidney failure, coronary heart disease (CHD), stroke, 3-point major adverse cardiovascular events (MACE), heart failure, and death were obtained from national registries. The associations between the eGFR slope and incident events were assessed with multivariable competing risk models during the average follow-up of 9.2 years.

Results: The eGFR slopes were associated ($P \leq 0.001$) with all outcomes when adjusted for age, sex, and HbA1c. However, eGFR slope remained associated only with the composite outcome of kidney failure or death when the albuminuria group and eGFR at the study visit were included in the model ($P = 0.041$). In addition, eGFR slope was independently associated with kidney failure in individuals without CKD (eGFR $>$ 60 ml/min per 1.73 m^2; $P = 0.044$), and with heart failure in those with CKD ($P = 0.033$). However, eGFR slope did not markedly improve the model C-index.

Conclusion: The eGFR slope was independently associated with kidney failure in those without CKD, and with heart failure in those with CKD. However, it is unlikely to have major relevance for clinical practice when the current eGFR and albuminuria status are known.

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Diabetes is the most common cause of CKD, accounting for 31% of the CKD-associated disability-adjusted life-years.[1] Individuals with T1D develop the disease early in life, and are at particularly high risk: 1 in 4 individuals with T1D is reported to develop kidney failure after 40 years of diabetes duration in the United States.[2] Even though the incidence of kidney failure has significantly decreased in people with T1D over the past decades, the 40-year cumulative risk remains over 10% in more recent studies despite improvements in the treatment of elevated blood glucose and hypertension.[3] In particular, the progression rate from severe albuminuria to kidney failure remains high at 35%,[4] emphasizing the need for early intervention to prevent DKD. In addition, the risk of both cardiovascular disease (CVD) and all-cause mortality increases steeply with the severity of DKD.[5,6] Although the risk of CVD has markedly decreased over time, the standardized incidence ratio remains 9-fold for CHD and 3-fold for stroke in individuals diagnosed with T1D in the 1990s compared with the general population.[7] Although there is no cure for

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DKD, improved glycemic control[8–10] and antihypertensive treatment with renin-angiotensin system inhibitors can slow down the progression of the disease.[11–13] Therefore, effective identification and early intervention with standard of care is essential for the prevention of both kidney failure and CVD events.

Prediction of kidney failure remains a challenge, even among those with severe albuminuria.[14] Kidney function can be assessed with eGFR based on serum creatinine or cystatin C measurements. For people without CKD, kidney function declines gradually with age from normal values (≥90 ml/min per 1.73 m^2) by approximately 1 ml/min per 1.73 m^2 per year.[15,16] However, the rate of the eGFR decline, that is, the eGFR slope, varies greatly among individuals. In a study from the Joslin Diabetes Center, 25% of participants who developed kidney failure had an eGFR slope of −15 ml/min per 1.73 m^2 per year or steeper, resulting in kidney failure within 2 to 5 years, when starting from an eGFR of 100 ml/min per 1.73 m^2. Previous studies have shown that clinical risk factors such as higher HbA1c, urine albumin-to-creatinine ratio (ACR), and eGFR are associated with rapid eGFR decline.[17]

It has been suggested that once kidney function starts to decline, the rate of eGFR decline is linear.[18] Therefore, the following questions arise: whether knowing the rate of eGFR decline in the past would improve the prediction of kidney failure and other clinical end points, and whether this information would provide additional prognostic information to the clinical measurements available at the time of a visit to a clinic. Studies in the general population and in individuals with CKD indicate that a steep decline of eGFR is associated with CVD events[19,20] and/or death,[19–23] in some studies even independent of the baseline kidney parameters.[23] Rapid kidney function decline has been associated with MACE among individuals with type 2 diabetes.[24] Furthermore, in 8879 participants with type 2 diabetes, a decrease in eGFR of < −1.63 ml/min per 1.73 m^2 per year was associated with the future risk of kidney and cardiovascular events and all-cause mortality even after adjustment for the baseline eGFR.[25] On the contrary, in a study of 1441 participants with a relatively well-preserved kidney function and a short duration of T1D from the Diabetes Control and Complications Trial and the subsequent Epidemiology of Diabetes Interventions and Complications study, an early rapid eGFR loss (≥3% per year) was not associated with the risk of CKD, mortality, or MACE after adjusting for the baseline eGFR.[26] Given these contradictory results, the aim of the present study was to evaluate whether the preceding eGFR slope would provide additional value beyond the kidney parameters measured at the study visit in predicting the risk of kidney and CVD end points as well as death, in a large cohort of Finnish individuals with T1D with a wide range of eGFR, age, and duration of diabetes.

METHODS

Data Collection

The original study population included 5505 individuals with T1D from the Finnish Diabetic Nephropathy (FinnDiane) Study, which is an ongoing nationwide multicenter study launched in 1997. The recruitment and clinical characterization of the participants has been described earlier.[27] In brief, adult individuals with T1D are recruited from >80 hospitals and health centers throughout Finland. Data on diabetic complications, history of cardiovascular event(s), and prescribed medications are registered during a standard visit to the attending physician using standardized questionnaires, and blood and urine samples are collected during this FinnDiane "A-visit." Participants are invited to a second, FinnDiane "B-visit" following a similar study protocol approximately 5 to 7 years after the FinnDiane A-visit. ACR was measured from a 24-hour or overnight urine collection at the time of the study visits. Serum creatinine values were measured and used to calculate eGFR with the CKD-Epidemiology Collaboration (CKD-EPI) formula.[28]

In addition, we considered 3084 additional individuals with T1D from the Finnish Institute for Health and Welfare (THL) diabetes studies with phenotypic data obtained from the medical files and national registries. For 584 of these participants, we had data on ACR, eGFR, and HbA1c from blood, serum, and urine collected at THL during 1995 to 2004; the sample collection date was considered as the study baseline visit. For the remaining participants without sample collection, the latest date from medical files available (median 2014, range 1991–2016) was considered as the baseline date for this study.

The study protocols were approved by the Helsinki and Uusimaa Hospital District Ethics Committee, and the study was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from each participant.

Phenotype Definitions and Study Inclusion Criteria

The participant inclusion and exclusion criteria are presented in Figure 1. All participants were diagnosed with T1D by their attending physician. Furthermore, we included only participants with the age at diabetes onset <40 years and insulin treatment initiated within 1 calendar year from the diagnosis of diabetes (or unknown for the THL participants, if no suspicion

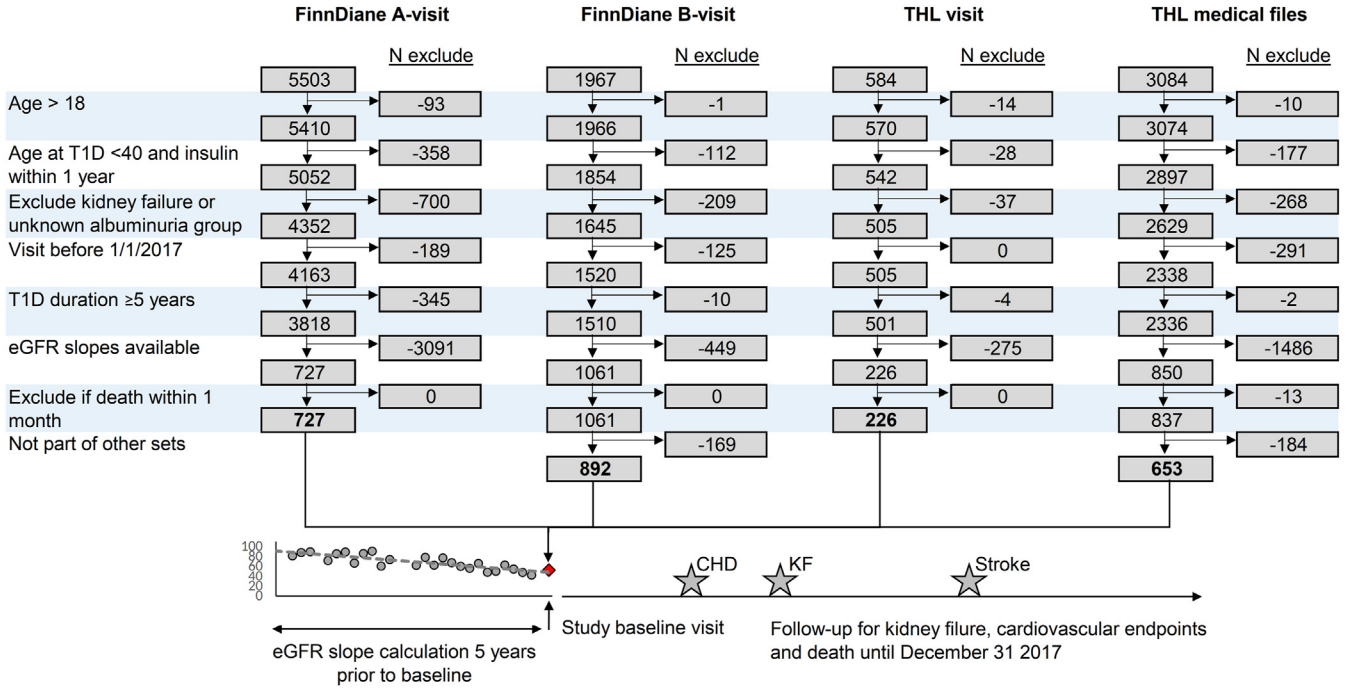

Figure 1. Participant inclusion flowchart for the 4 data sets. KF, kidney failure. T1D, type 1 diabetes; THL, the Finnish Institute for Health and Welfare.

of other type of diabetes). We excluded participants with age <18 years at the study visit, or diabetes duration of <5 years. The participants were classified as having normal AER, moderate albuminuria or severe albuminuria based on AER or ACR values from 2 out of 3 consecutive overnight, 24-hour, or spot urine collections as described earlier.[29] Kidney failure was defined as requiring dialysis or kidney transplant. Participants with kidney failure, unknown albuminuria class, or eGFR <10 ml/min per 1.73 m^2 at the study baseline were excluded. Study visits until December 31, 2016, were included.

Serum (or plasma) creatinine values were collected from the medical files for all participants, and values were extracted within 5 years before the study visits. The serum creatinine measurement method changed from the Jaffe to the isotope dilution mass spectrometry method in 2002 in the entire country. Therefore, the values before 2002 were calibrated to isotope dilution mass spectrometry measurements with the following formula, Serum creatinine (isotope dilution mass spectrometry) = (0.953 × Serum Creatinine [Jaffe]) − 7.261.

eGFR was calculated with the CKD-EPI formula,[28] assuming European origin. For the slope calculation, we required at least 3 eGFR measurements over a 3-year period within the 5-year window before the baseline. In addition, we required the last eGFR measurement included in the slope calculation to be within half a year from the baseline visit. As sensitivity analysis, we tested requiring up to 24 eGFR measurements. The slope was estimated by fitting a slope with linear regression. The baseline eGFR value was included in the slope estimation, and the median number of eGFR measurements used for slope estimation was 7 (interquartile range 5–11). A small number (16/2514 = 0.6%) of implausible slopes (potentially data errors or acute kidney events affecting the slope) were excluded after visual inspection.

If the inclusion criteria were not fulfilled, or slopes were not available at the FinnDiane A-visit, we selected the FinnDiane B-visit as the study baseline, when available. Similarly, we prioritized the THL study visit over the study dates based on latest medical files. We excluded 13 medical file records for which the latest record was from the date of death (n = 7) or within 1 month from the death (n = 6). Altogether 2498 individuals were selected: 727 individuals from the FinnDiane A-visit, 892 individuals from FinnDiane B-visit, 226 individuals from the THL visit, and 653 individuals from the THL medical files (Figure 1).

Definition of Kidney Failure, Cardiovascular End Points, and Death

The end points included kidney failure, all-cause mortality, CHD including myocardial infarction or coronary revascularization, heart failure, ischemic or hemorrhagic stroke, and 3-point MACE that was defined as composite of the first occurrence of nonfatal acute CHD event or stroke, or cardiovascular death. In addition, we included a composite event of kidney failure or any death. These data were retrieved from the Finnish Care Register for Health Care and the

Finnish Cause of Death Register using the International Classification of Diseases codes and Nordic Classification of Surgical Procedure codes until December 31, 2017 (Supplementary Table S1). The coding of such diagnoses in these registers has been previously evaluated and found valid.[30,31]

Statistical Analysis

Group differences between the eGFR slopes and baseline characteristics were analyzed with Kruskal-Wallis rank sum test for continuous variables and with χ^2 test for categorical variables. Due to the large number of deaths during the follow-up, the associations between the preceding eGFR slope and the incident clinical end points were estimated with the Fine and Gray competing risk model[32] to fit the proportional subdistribution hazards using death as the competing risk. Prevalent cases were excluded from the corresponding analyses. Cox proportional hazards regression was utilized to test association with death or the composite of kidney failure or death, and, as a sensitivity analysis, to estimate the cause-specific hazards for other outcomes. In addition to univariable tests, we performed several multivariable competing risk and Cox survival models as follows: (i) model 2: including investigator classified sex, baseline age, and HbA1c; (ii) model 3: model 2 variables and the albuminuria group (i.e., normal AER/ moderate/ severe albuminuria); and (iii) model 4: model 3 variables and the baseline eGFR value. Furthermore, we fitted models (model 3b and model 4b) where albuminuria group was replaced by continuous ACR ($\log_2$-transformed) as sensitivity analyses. Individuals with missing covariate values were excluded from the corresponding analysis. Analyses were repeated for different strata based on the albuminuria or CKD group, and with the albuminuria or CKD group as an interaction term. The proportional hazards assumption was tested for the global model and the eGFR slope separately, and the Schoenfeld residuals were plotted for eGFR slope. For each outcome and strata, we compared model 4 with and without eGFR slope by calculating the concordance of the models (Harrel's C-index), and with likelihood-ratio test and continuous net reclassification index with 1000 bootstrap samples based on the Cox models.

Statistical analysis was performed with R (https://www.r-project.org/) version 4.2.0/4.2.1/4.3.0, using the "survival" package (v.3.2-13/v.3.4-0/v.3.5-5)[33] for Cox regression, tidycmprsk (v.0.1.2/v.0.2.0) for the competing risk analysis.

RESULTS

The mean age of the participants at study baseline was 42.7 years (SD 12.0), with a diabetes duration of 27.4 years (SD 11.2) at the index visit. A total of 296 (11.8%) participants had CKD, defined as eGFR <60 ml/min per 1.73 m^2, whereas the mean eGFR was 93.6 ml/min per 1.73 m^2 at baseline (median 100 ml/min per 1.73 m^2, interquartile range 80.5–113; Supplementary Table S2). At baseline, 151 participants (6.0%) had experienced a CHD event, 92 (3.7%) had experienced stroke, and 175 (7.0%) had experienced a combined 3-point MACE.

eGFR Slopes are Steepest Among Those With the Lowest Baseline eGFR

The mean annual eGFR slope, calculated from values within 5 years before the baseline, was −1.32 ml/min per 1.73 m^2 per year (SD 3.45) ranging from −36.0 to +14.9 ml/min per 1.73 m^2 per year. The slope quintiles were associated with sex, diabetes duration, HbA1c, and systolic blood pressure ($P < 0.05$; Supplementary Table S3). The eGFR slope was the steepest among people with the lowest eGFR at baseline. It was −7.37 ml/min per 1.73 m^2 per year (SD 5.26) among those with eGFR <15 ml/min per 1.73 m^2, whereas among those with eGFR ≥90 ml/min per 1.73 m^2 it was −0.332 ml/min per 1.73 m^2 per year (SD 2.54) (Figure 2a). Similarly, the preceding eGFR slope was the steepest among people with severe albuminuria (Figure 2b).

eGFR Slopes are Associated With Incident Clinical Outcomes

The eGFR slopes were steeper among people who developed kidney failure (−5.49 ml/min per 1.73 m^2 per year (SD 4.89), $n = 191$), on average 5.3 years after the baseline, compared with those who did not (−0.972 ml/min per 1.73 m^2 per year (SD 3.06), $n = 2307$, $P = 3.1\times10^{-46}$) within an average follow-up time of 9.0 years. Similarly, the eGFR slope was steeper among people who developed a CVD event during the follow-up ($P < 0.001$ for each; Table 1). During the average 9.2 years of follow-up, 325 (13.0 %) of the participants died.

In univariable competing risk survival models, the eGFR slope was significantly associated with the clinical end points (Figure 3a, Supplementary Figure S1). The hazard ratio (HR) for kidney failure was 0.59 (95% confidence interval [CI] 0.50–0.70; $P < 0.001$) per 1 SD increment in the eGFR slope (i.e., per 3.45 ml/min per 1.73 m^2 per year; Table 2). As expected, the strongest predictors of kidney failure included baseline eGFR, ACR, albuminuria group, and the eGFR slope (C-index 0.95, 0.94, 0.89, and 0.83, respectively; Figure 3b). The eGFR slope was a significant ($P < 0.001$) but a relatively weak predictor of CVD events and death, with C-index ranging from 0.60 to 0.64 (Supplementary Table S4).

The eGFR slope remained associated with each outcome in multivariable competing risk survival models including sex, and baseline age and HbA1c as

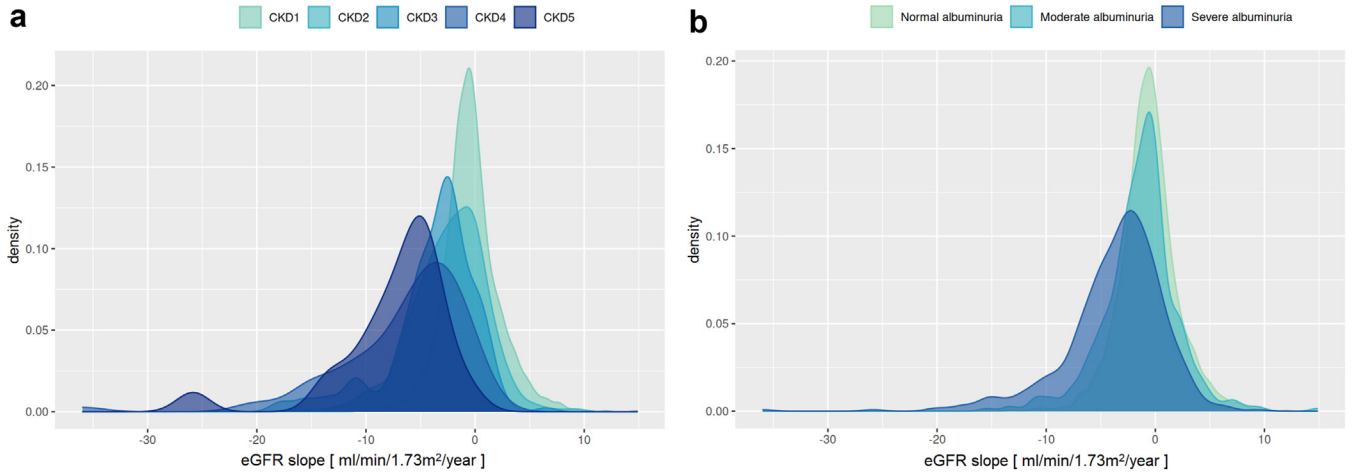

Figure 2. Distribution of the eGFR slopes within the 5 years preceding the study baseline. (a) stratified by the CKD classes 1–5. CKD1: eGFR ≥ 90 ml/min per 1.73 m^2; CKD2: 60 ml/min per 1.73 m^2 ≥ eGFR > 90 ml/min per 1.73 m^2; CKD3: 30 ml/min per 1.73 m^2 ≥ eGFR > 60 ml/min per 1.73 m^2; CKD4: 15 ml/min per 1.73 m^2 ≥ eGFR > 30 ml/min per 1.73 m^2; CKD5: eGFR <15 ml/min per 1.73 m^2. (b) Stratified by albuminuria status. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

covariates (model 2). However, to answer the question about whether it is clinically useful to know the preceding eGFR slope in addition to the clinical measurements available at patient visit, we further adjusted the models for the baseline albuminuria group (model 3; normal AER/moderate albuminuria/severe albuminuria) and eGFR (model 4). The eGFR slope remained a significant predictor ($P < 0.05$) of heart failure, kidney failure, and death in model 3, and of the composite outcome of kidney failure or death in model 4 adjusted for the baseline eGFR (Cox regression HR 0.91, 95% CI 0.83–1.00, $P = 0.041$; Table 2, Figure 3a). In the same model, higher age, male sex, higher baseline HbA1c, moderate and severe albuminuria, and lower baseline eGFR were significantly associated with incident kidney failure or death ($P < 0.05$ for each; Supplementary Figure S2). Adding the eGFR slope to the clinical model did not improve the model's C-index (0.87 for both), but the likelihood-ratio test indicated nominal improvement ($P = 0.044$; Supplementary Table S5). As a sensitivity analysis, the association disappeared in the model 4b that adjusted for $\log_2$(ACR) instead of the albuminuria group. However, the exact ACR values were available for fewer people and the number events dropped from 404 to 303, potentially explaining the loss of association (Supplementary Figure S2).

As a further sensitivity analysis, the subdistribution hazards obtained from the Fine and Gray competing risk analysis were similar to the cause-specific hazards obtained with Cox proportional hazards regression, with a tendency for larger effect size estimates for the Cox models as reported earlier.[34] The eGFR slope was additionally a significant predictor of kidney failure in the fully adjusted Cox regression model 4 (HR = 0.86, 95% CI 0.77–0.96, $P = 0.010$; Supplementary Table S4). Some of the covariates violated the proportional hazards assumption ($P < 0.05$; Supplementary Table S5); however, visual inspection of the scaled Schoenfeld residual plots indicated no major departure from a horizontal line for the eGFR slope (Supplementary Figure S3). Requirement of an increasing number of available eGFR measurements within the preceding 5-year period strongly reduced the number of controls for kidney failure; however, eGFR slope remained associated with kidney failure or death in model 4 (Supplementary Figure S4).

eGFR Slope is Independently Associated With Incident Kidney and Heart Failure in Stratified Analyses

To assess if the eGFR slope could be informative in specific patient groups, we stratified the competing risk survival models by the baseline albuminuria group and eGFR. The eGFR slopes were associated (model 4, $P < 0.05$) with kidney failure in individuals without CKD (eGFR ≥60 ml/min per 1.73 m^2; HR = 0.69, 95% CI 0.48–0.99, $P = 0.04$; Supplementary Figure S5). The likelihood-ratio test suggested that adding the eGFR slope improved model 4 ($P = 0.013$); however, the C-index did not improve markedly (0.92 vs. 0.93). eGFR slope had only limited value in predicting kidney failure among the participants with established CKD at baseline (eGFR <60 ml/min per 1.73 m^2; univariate C-index 0.66, Figure 4b, $P = 0.90$ in model 4). However, the CKD × eGFR slope interaction term was not significant for kidney failure (Supplementary Table S6). For the composite outcome of kidney failure or death, eGFR was a significant predictor in the multivariable models in those with severe albuminuria or CKD ($P = 0.019$ and $P = 0.017$, respectively; Figure 4a; Supplementary Table S5). The

Table 1. eGFR slope and other clinical characteristics stratified by the incident clinical outcomes

	Kidney failure		CHD		Stroke		3P−MACE		Heart failure		Death		
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	All
Parameter	**(n = 191)**	**(n = 2307)**	**(n = 266)**	**(n = 2081)**	**(n = 120)**	**(n = 2286)**	**(n = 235)**	**(n = 2088)**	**(n = 171)**	**(n = 2282)**	**(n = 325)**	**(n = 2173)**	**N = 2498**
eGFR slope (ml/min per 1.73 m^2 per year)	−5.49 (4.89)	−0.97 (3.06)[a]	−2.15 (3.88)	−1.15 (3.39)[a]	−2.67 (4.10)	−1.20 (3.41)[a]	−2.11 (4.03)	−1.14 (3.40)[a]	−3.04 (4.36)	−1.15 (3.32)[a]	−2.95 (4.67)	−1.07 (3.16)[a]	−1.32 (3.45)
Baseline eGFR (ml/min per 1.73 m^2)	41.2 (26.1)	98.0 (22.1)[a]	72.4 (29.6)	98.2 (24.2)[a]	71.8 (30.5)	95.9 (25.4)[a]	73.1 (31.0)	98.3 (23.5)[a]	63.3 (30.6)	96.7 (24.6)[a]	64.8 (29.8)	98.0 (23.7)[a]	93.6 (27.0)
ACR (mg/mmol)	115 [33.8, 246]	0.73 [0.30, 2.76]	5.25 [0.99, 59.7]	0.70 [0.30, 2.83]	11.2 [1.18, 85.3]	0.76 [0.30, 3.44]	7.22 [1.06, 85.9]	0.70 [0.30, 2.67]	18.2 [1.74, 106]	0.75 [0.30, 3.25]	16.3 [1.57, 89.3]	0.70 [0.30, 2.72]	0.86 [0.32, 4.84]
ACR missing, n (%)	52 (27.2)	584 (25.3)	49 (18.4)	547 (26.3)	28 (23.3)	584 (25.5)	57 (24.3)	532 (25.5)	36 (21.1)	584 (25.6)	81 (24.9)	555 (25.5)	636 (25.5)
Male sex, n (%)	111 (58.1)	1100 (47.7)[b]	135 (50.8)	988 (47.5)[b]	73 (60.8)	1092 (47.8)[b]	130 (55.3)	987 (47.3)[b]	82 (48.0)	1100 (48.2)	188 (57.8)	1023 (47.1)[a]	1211 (48.5)
Age (years)	44.1 (9.93)	42.6 (12.2)[b]	50.0 (9.98)	40.9 (11.5)[a]	47.5 (10.6)	42.1 (12.0)[a]	48.1 (10.3)	41.2 (11.7)[a]	50.7 (10.8)	41.9 (11.8)[a]	50.7 (10.7)	41.5 (11.8)[a]	42.7 (12.0)
Duration (years)	31.1 (9.06)	27.1 (11.3)[a]	34.9 (10.0)	25.6 (10.4)[a]	31.6 (10.0)	26.8 (11.0)[a]	33.0 (10.3)	25.9 (10.6)[a]	35.8 (10.6)	26.6 (10.9)[a]	34.4 (10.8)	26.4 (10.9)[a]	27.4 (11.2)
HbA1c (%)	9.03 (1.59)	8.27 (1.29)[a]	8.79 (1.64)	8.26 (1.28)[a]	8.79 (1.39)	8.30 (1.32)[a]	8.78 (1.57)	8.27 (1.29)[a]	8.99 (1.58)	8.27 (1.30)[a]	8.83 (1.53)	8.25 (1.29)[a]	8.32 (1.33)
HbA1c (mmol/mol)	75.2 (17.4)	66.9 (14.2)[a]	72.6 (17.9)	66.8 (14.0)[a]	72.6 (15.2)	67.2 (14.5)[a]	72.5 (17.2)	66.8 (14.1)[a]	74.8 (17.2)	66.9 (14.2)[a]	73.0 (16.7)	66.7 (14.1)[a]	67.5 (14.6)
HbA1c missing, n (%)	8 (4.2)	40 (1.7)	11 (4.1)	33 (1.6)	3 (2.5)	44 (1.9)	11 (4.7)	33 (1.6)	3 (1.8)	40 (1.8)	10 (3.1)	38 (1.7)	48 (1.9)
SBP (mm Hg)	146 (22.0)	136 (17.9)[a]	146 (19.8)	135 (17.6)[a]	149 (21.8)	136 (17.8)[a]	147 (20.8)	135 (17.3)[a]	148 (21.3)	136 (17.8)[a]	145 (21.4)	136 (17.6)[a]	137 (18.4)
SBP missing, n (%)	35 (18.3)	329 (14.3)	43 (16.2)	292 (14.0)	20 (16.7)	331 (14.5)	35 (14.9)	298 (14.3)	25 (14.6)	329 (14.4)	65 (20.0)	299 (13.8)	364 (14.6)
BMI (kg/m^2)	25.4 (4.11)	26.1 (4.13)	26.1 (3.59)	26.0 (4.17)	26.0 (4.65)	26.0 (4.12)	26.1 (4.16)	26.0 (4.11)	26.6 (4.31)	26.0 (4.11)	25.9 (3.89)	26.0 (4.16)	26.0 (4.13)
BMI missing, n (%)	50 (26.2)	453 (19.6)	68 (25.6)	403 (19.4)	28 (23.3)	454 (19.9)	54 (23.0)	409 (19.6)	32 (18.7)	455 (19.9)	96 (29.5)	407 (18.7)	503 (20.1)
Albuminuria													
Normal AER n (%)	6 (3.1)	1601 (69.4)[a]	99 (37.2)	1449 (69.6)[a]	34 (28.3)	1547 (67.7)[a]	79 (33.6)	1472 (70.5)[a]	43 (25.1)	1552 (68.0)[a]	79 (24.3)	1528 (70.3)[a]	1607 (64.3)
Moderate alb, n (%)	5 (2.6)	398 (17.3)	50 (18.8)	316 (15.2)	24 (20.0)	352 (15.4)	42 (17.9)	315 (15.1)	29 (17.0)	367 (16.1)	58 (17.8)	345 (15.9)	403 (16.1)
Severe alb, n (%)	180 (94.2)	308 (13.4)	117 (44.0)	316 (15.2)	62 (51.7)	387 (16.9)	114 (48.5)	301 (14.4)	99 (57.9)	363 (15.9)	188 (57.8)	300 (13.8)	488 (19.5)
N eGFR measurements	19.0 [10.0, 28.0]	6.00 [5.00, 10.0]	9.00 [6.00, 15.0]	6.00 [5.00, 10.0]	11.0 [6.75, 17.5]	7.00 [5.00, 10.0]	10.0 [6.00, 16.5]	6.00 [5.00, 9.00]	12.0 [8.00, 19.0]	7.00 [5.00, 10.0]	12.0 [8.00, 23.0]	6.00 [5.00, 10.0]	7.00 [5.00, 11.0]
Baseline visit	2001 [1999, 2005]	2007 [2004, 2014][a]	2004 [2000, 2005]	2007 [2004, 2014][a]	2003 [2000, 2005]	2007 [2004, 2013][a]	2003 [2000, 2005]	2007 [2004, 2014][a]	2003 [1999, 2006]	2007 [2004, 2014][a]	2003 [1999, 2006]	2007 [2004, 2014][a]	2007 [2003, 2013]

ACR, urinary albumin-to-creatinine ratio; AER, albumin excretion rate; alb, albuminuria; BMI, body mass index; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; 3P-MACE, 3-point major adverse cardiovascular events; SBP, systolic blood pressure.

[a] P-value < 0.001.

[b] P-value < 0.05.

Prevalent events are not shown. Values are given as mean (SD) or median [interquartile range] for continuous variables, and as N (%) for counts.

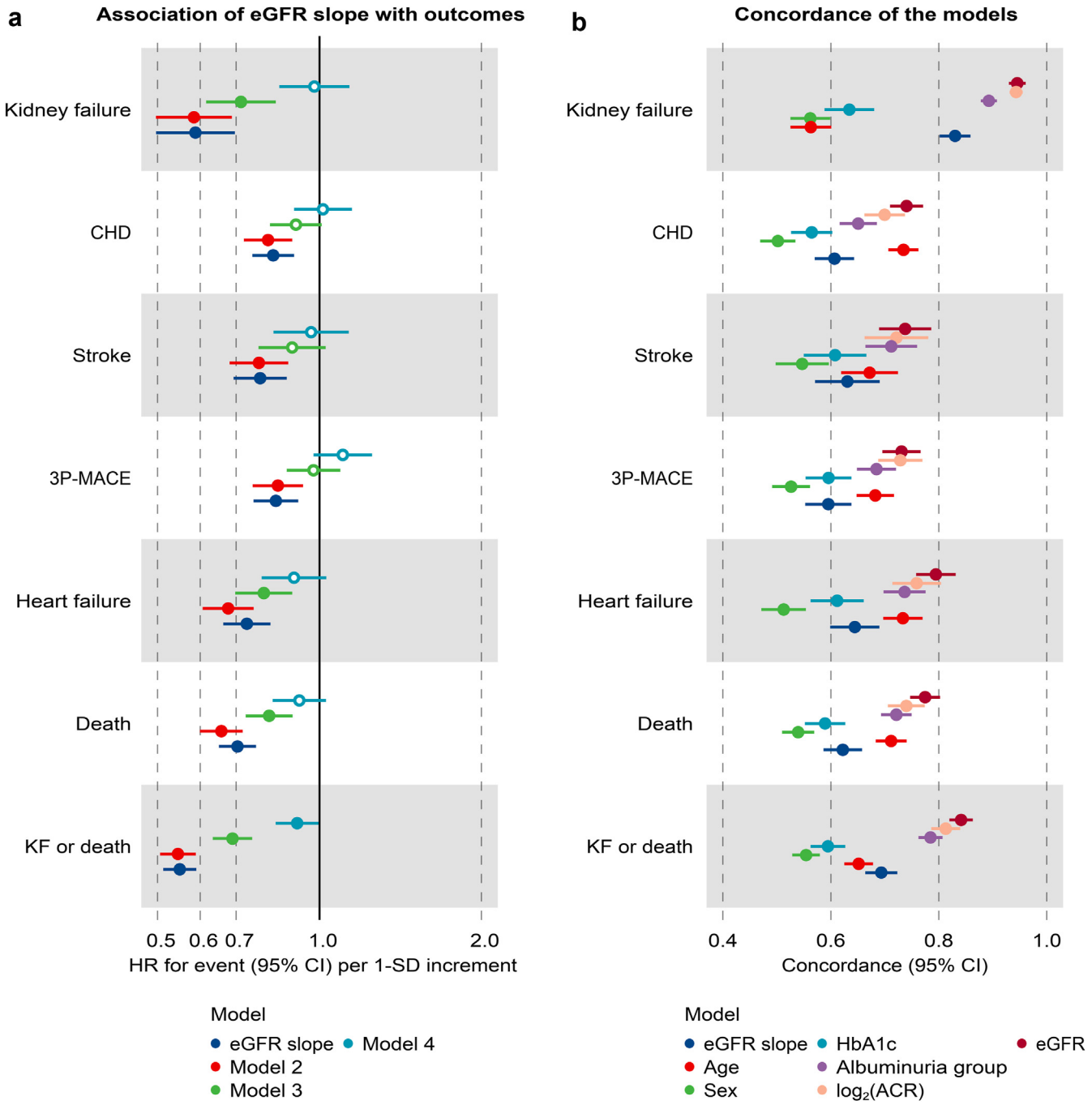

Figure 3. Association between the eGFR slope and clinical outcomes. (a) Hazard ratio for the association of eGFR slope with clinical outcomes in the full cohort with different multivariable models. Model 2: eGFR slope, sex, baseline age and HbA1c; Model 3: the previous model plus baseline albuminuria group; Model 4: the previous model plus baseline eGFR. Closed circles indicate significant ($P < 0.05$) values. (b) Model concordance C-index for the univariable models in the full cohort. Horizontal bars indicate 95% confidence intervals. ACR, albumin-to-creatinine ratio; CI, confidence interval; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; KF, kidney failure; MACE, major adverse cardiovascular event.

interaction term between the CKD status and the eGFR slope was significant, such that the risk was more pronounced in those with CKD ($P = 0.0018$; Supplementary Table S6). Adding eGFR slope to the fully adjusted multivariable Cox models improved the model in these strata (likelihood-ratio test $P < 0.05$; Supplementary Table S5); however, eGFR slope did not markedly change the model C-indexes (Figure 4c).

Furthermore, the eGFR slope was significantly associated with heart failure in individuals with CKD (model 4, HR = 0.86, 95% CI 0.75–0.99, $P = 0.033$, 77 events; Supplementary Figure S6). In addition, CKD × eGFR slope interaction term was significant ($P = 0.048$) in the full cohort supporting the association of eGFR slope with heart failure in individuals with CKD but not in individuals without CKD. The association also remained

Table 2. Association between estimated glomerular filtration rate slope and clinical outcomes in survival models (Fine and Gray competing risk models with death as competing risk; or Cox proportional hazards regression if death included as outcome)

	Model 1			Model 2			Model 3		Model 4	
Outcome	*N*	HR (95% CI)	*P*-value	*N*	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Kidney failure	191/2498	0.59 (0.50, 0.70)	<0.001	183/2450	0.58 (0.50, 0.69)	<0.001	0.71 (0.62, 0.83)	<0.001	0.98 (0.84, 1.14)	0.80
CHD	266/2347	0.82 (0.75, 0.90)	<0.001	255/2303	0.8 (0.72, 0.89)	<0.001	0.9 (0.81, 1.01)	0.074	1.01 (0.90, 1.15)	0.80
Stroke	120/2406	0.78 (0.69, 0.87)	<0.001	117/2359	0.77 (0.68, 0.87)	<0.001	0.89 (0.77, 1.03)	0.11	0.96 (0.82, 1.13)	0.70
3P-MACE	235/2323	0.83 (0.75, 0.91)	<0.001	224/2279	0.84 (0.75, 0.93)	0.001	0.97 (0.87, 1.09)	0.7	1.1 (0.97, 1.25)	0.12
Heart failure	171/2453	0.73 (0.66, 0.81)	<0.001	168/2410	0.68 (0.61, 0.75)	<0.001	0.79 (0.70, 0.89)	<0.001	0.9 (0.78, 1.03)	0.12
Death	325/2498	0.70 (0.65, 0.76)	4.3×10^{-18}	315/2450	0.66 (0.60, 0.72)	2.5×10^{-19}	0.81 (0.73, 0.89)	2.6×10^{-05}	0.92 (0.82, 1.03)	0.14
Kidney failure or death	419/2498	0.55 (0.51, 0.59)	2.3×10^{-61}	404/2450	0.55 (0.51, 0.59)	2.8×10^{-54}	0.69 (0.63, 0.75)	4.6×10^{-18}	0.91 (0.83, 1.00)	0.041

CI, confidence interval; CHD, coronary heart disease; HR, hazard ratio; 3P-MACE, 3-point major adverse cardiovascular events; *N*, number of events/total number of individuals. Model 1: estimated glomerular filtration rate slope. Model 2: estimated glomerular filtration rate slope + baseline age, sex, HbA1c. Model 3: Model 2 + baseline albuminuria group. Model 4: model 3 + baseline estimated glomerular filtration rate. For Models 3 and 4 the numbers were identical to model 2 for each outcome, thus not shown. For kidney failure, CHD, stroke, 3P-MACE or heart failure, survival analysis was performed with Fine and Gray competing risk models with death as competing risk; for death and the combined outcome of kidney failure or death, Cox proportional hazards regression was used.

significant when adjusting for the continuous $\log_2$(ACR) (model 4b, HR = 0.86, 95% CI 0.73–1.00, $P = 0.046$; Supplementary Figure S6), or when evaluated with Cox regression (HR = 0.81, 95% CI 0.67–0.97, $P = 0.023$). Likelihood-ratio test suggested improvement of the model performance when eGFR slope was added to model 4 ($P = 0.029$), even though it did not improve the C-index markedly, which changed from 0.72 to 0.73 (Figure 4c), suggesting that knowing the preceding eGFR slope had very little predictive advantage beyond the eGFR and albuminuria status measured at the study visit.

DISCUSSION

Despite the improvements in the treatment of diabetes over the past decades, DKD and kidney failure remain a significant concern in diabetes.[4] Nevertheless, the early identification of individuals at high risk for DKD is still challenging.[17] With the notion that the rate of kidney function decline, that is, the eGFR slope is relatively constant over the development of the disease,[18] there has been enthusiasm both in biomarker studies searching for biomarkers for rapid kidney function decline,[35–37] and evaluating the potential of the preceding eGFR slope for the prediction of future kidney and CVD events.[19,26] In this large prospective study of 2498 individuals with T1D with varying baseline diabetes duration and eGFR, we showed that the preceding eGFR slope was strongly associated with incident kidney failure, CVD outcomes, and death among individuals with T1D. However, when the baseline albuminuria status and eGFR were considered, the preceding eGFR slope remained a significant predictor only for the composite outcome of kidney failure or death, with limited improvement in the model performance. These findings suggest that knowing the preceding eGFR slope adds little value to the clinical assessment, especially when data on the albuminuria status and eGFR are available at the clinic visit.

In the stratified analysis, the preceding eGFR slope remained a significant predictor of kidney failure among people without renal impairment (eGFR ≥ 60 ml/min per 1.73 m^2) even after adjusting the model for the baseline albuminuria group and eGFR. This is in contrast to the previous reports in individuals with T1D from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study, where the slope did not predict kidney or other clinical outcomes after adjusting for the baseline covariates.[26] The Diabetes Control and Complications Trial study participants were primarily normoalbuminuric and had relatively short diabetes duration (mean 12 years) at the time of the eGFR slope evaluation. The authors suggested that the changes in eGFR during the early years of diabetes may reflect resolution of hyperfiltration rather than the CKD trajectory, explaining their lack of association with future clinical outcomes.[26] In our current study, even the participants with eGFR ≥ 90 ml/min per 1.73 m^2 had a long duration of diabetes (mean 24.1 years) and median eGFR of 109 ml/min per 1.73 m^2 (interquartile range 100–118), suggesting that they are past the potential hyperfiltration phase. The nominal increase in the C-index from 0.92 to 0.93 in the fully adjusted model upon addition of the eGFR slope suggests, similar to the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study[26], that considering the preceding eGFR slope is unlikely to have any major clinical impact in addition to the clinical measurements available at the study visit. It should be noted that the C-index of 0.92 in the fully adjusted model is excellent and difficult to improve with any additional variables.

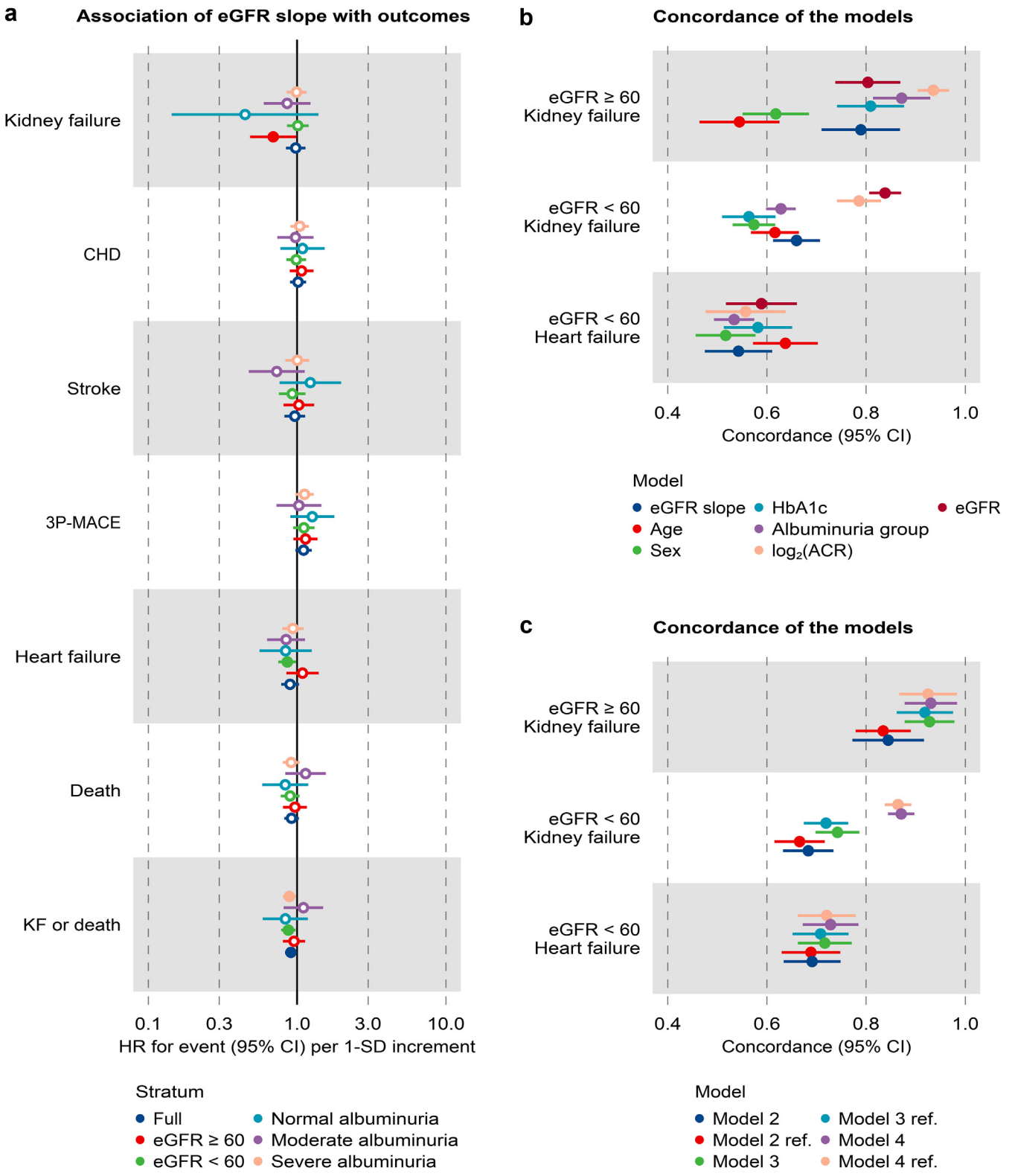

Figure 4. Association between the eGFR slope and clinical outcomes in different strata. (a): The association of the eGFR slope with clinical outcomes stratified by the baseline kidney function and albuminuria status. Model adjusted for sex, baseline age and HbA1c, albuminuria group, and eGFR at the study visit (model 4). (b) C-index of concordance for the univariable models in the eGFR ≥ 60 and eGFR < 60 strata for kidney failure or heart failure. (c): C-index of concordance for the multivariable models in the eGFR ≥ 60 and eGFR < 60 strata for kidney failure or heart failure. Closed circles indicate significant ($P < 0.05$) values, horizontal bars indicate 95% confidence intervals. CI, confidence interval; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; KF, kidney failure; MACE, major adverse cardiovascular event.

Among the participants with CKD at baseline, the eGFR slope was associated with incident heart failure and the composite outcome of kidney failure or death in the fully adjusted model; and, adding the eGFR slope to the model did not improve the model's C-index. The interaction analysis suggested that the CKD class significantly modified the effect of eGFR slope on heart failure and the composite outcome of kidney failure or death, such that the risk imposed by the steeper eGFR slope was more important among individuals with prevalent CKD. Although no previous reports exist for individuals with T1D and preexisting CKD, previous studies from the general population suggest that a steep decline of eGFR is associated with CVD events[19,20] and/or death[19–23] even after adjusting for the study visit eGFR.[23] However, even in the general population, the current eGFR was more strongly associated with the 5-year kidney failure risk than the preceding eGFR slope.[38]

Our study is one of the largest of its kind performed in individuals with T1D to date. The strengths of this study include the long diabetes duration (median 26.4 years), large number of kidney and CVD events, as well as a wide distribution of baseline eGFR values (median 100 ml/min per 1.73 m^2, range 10.2–175 ml/min per 1.73 m^2) and various stages of albuminuria, making the results generalizable for the large T1D population. Furthermore, this allowed us to perform stratified analyses to answer the study questions in detail. Nonetheless, all stratified analyses suggested that there is only a limited advantage of considering the preceding rate of the kidney function decline when the current albuminuria status and eGFR are known.

The study has limitations. The eGFR values were calculated based on serum (or plasma) creatinine measurements, rather than cystatin C, which more accurately captures changes in kidney function.[39] Although the serum creatinine-based eGFR measurements and slopes are more commonly available in the clinical practice, the use of the cystatin C–based eGFR slope might improve the clinical prediction accuracy. Given the observational nature of our study, our data had missing values, and the number of the eGFR measurements available for the slope definition varied among individuals, reflecting the real-life frequency of patient visits. Consequently, the participants with a higher eGFR at baseline had fewer measurements of eGFR available for the calculation of slope; that is, the values were missing not-in-random. However, in our sensitivity analysis, requiring a larger number of eGFR measurements did not markedly influence the results. In addition, despite many participants having normal AER at baseline ($n = 1607$), we only observed among them, 6 cases of incident kidney failure during the median of 9.5 (interquartile range 3.4 –12.5) year follow-up time, leading to low statistical power. Consequently, interaction analysis did not suggest significant differences between the albuminuria groups in the association of eGFR slope with kidney failure. Finally, despite the wide clinical spectrum of participants with T1D, we do not know whether our results would generalize to individuals with type 2 diabetes as well.

To conclude, our results indicate that among individuals with T1D, the preceding eGFR slope is an independent risk factor for the composite outcome of kidney failure or death. In addition, it independently predicts kidney failure in individuals without CKD, and heart failure in individuals with CKD. However, adding the preceding eGFR slope to the multivariable model did not substantially improve the model's prediction performance. Thus, knowledge of the preceding eGFR slope is unlikely to have any major relevance in the clinical practice when the current eGFR and albuminuria status are known.

APPENDIX

List of FinnDiane Study Members

The list of FinnDiane physicians and nurses participating in the collection of the FinnDiane study subjects is provided in the Supplementary Table S7.

DISCLOSURE

P-HG has received lecture honoraria from Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, EloWater, Genzyme, Medscape, MSD, Mundipharma, Novartis, Novo Nordisk, Peer Voice, Sanofi, and Sciarc; is an advisory board member for AbbVie, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Medscape, MSD, Mundipharma, Novartis, Novo Nordisk, and Sanofi; and has received investigator-initiated grants from Eli Lilly and Roche. JT owns stocks in Orion Pharma and Aktivolabs. All the other authors declared no competing interests.

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Data Availability

The datasets used in the current study are not publicly available because of restrictions due to the study consent and local regulations.

AUTHOR CONTRIBUTIONS

NS contributed to the study design and interpretation of the results and wrote the manuscript. EV performed the statistical analysis and produced the figures, contributed to the study design, the interpretation of the results and writing of the manuscript. VH contributed to the acquisition of data and study design, and critically revised the manuscript. JT contributed to the acquisition of the data and interpretation of the results, and critically revised the manuscript. P-HG designed the study, contributed to the interpretation of the results, and critically reviewed the manuscript. All authors gave their final approval of this version of the manuscript. P-HG is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Competing risk cumulative incidence plots.

Figure S2. The preceding eGFR slope is associated with the composite outcome of kidney failure or death.

Figure S3. The scaled Schoenfeld residuals for the eGFR slope in the fully adjusted model (model 4) for each outcome for the full cohort.

Figure S4. eGFR slope association with clinical outcomes when an increasing number of eGFR measurements is required within the preceding 5-year period as a sensitivity analysis.

Figure S5. The preceding eGFR slope is associated with kidney failure among individuals with eGFR $\geq$ 60 ml/min per 1.73 m^2 at the study visit.

Figure S6. The preceding eGFR slope is associated with heart failure among individuals with CKD (eGFR $<$60 ml/min per 1.73 m^2) at the study visit.

Table S1. International Classification of Diseases (ICD)-codes (ICD-8: 1969-1986, ICD-9: 1987-1995, ICD-10: since 1996) and procedure codes used for ascertaining coronary heart disease, stroke and heart failure.

Table S2. Clinical characteristics of the participants, stratified by the recruitment method.

Table S3. Baseline characteristics and incident events by eGFR slope quintiles.

Table S4. Survival analysis for eGFR slope and clinical outcomes using Fine and Gray competing risk analysis (primary analysis) and Cox proportional hazards regression (sensitivity analysis and calculation of C-index).

Table S5. eGFR slope association with clinical end points in the fully adjusted (model 4) competing risk analysis (hazard ratio and p-value).

Table S6. Estimates for the interaction of eGFR slope with eGFR group (eGFR$\geq$60/eGFR$<$60) or albuminuria group (normal AER/moderate albuminuria/severe albuminuria) when the interaction term is added to model 4 for the full cohort.

Table S7. FinnDiane physicians and nurses participating in the collection of the FinnDiane study subjects.

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