ORIGINAL RESEARCH

Association Between Renal Function and Troponin T Over Time in Stable Chronic Kidney Disease Patients

Nicholas C. Chesnaye, PhD; Karolina Szummer, MD, PhD; Peter Bárány, MD, PhD; Olof Heimbürger, MD, PhD; Hasan Magin, MD; Tora Almquist, MD, PhD; Fredrik Uhlin, PhD; Friedo W. Dekker, PhD; Christoph Wanner, MD, PhD; Kitty J Jager, MD, PhD; Marie Evans, MD, PhD; the EQUAL Study Investigators*

***Background*—**People with reduced glomerular filtration rate (GFR) often have elevated cardiac troponin T (cTnT) levels. It remains unclear how cTnT levels develop over time in those with chronic kidney disease (CKD). The aim of this study was to prospectively study the association between cTnT and GFR over time in older advanced-stage CKD patients not on dialysis.

***Methods and Results*—**The EQUAL (European Quality Study) study is an observational prospective cohort study in stage 4 to 5 CKD patients aged ≥65 years not on dialysis (incident estimated GFR, <20 mL/min/1.73 m²). The EQUAL cohort used for the purpose of this study includes 171 patients followed in Sweden between April 2012 and December 2018. We used linear mixed models, adjusted for important groups of confounders, to investigate the effect of both measured GFR and estimated GFR on high-sensitivity cTnT (hs-cTnT) trajectory over 4 years. Almost all patients had at least 1 hs-cTnT measurement elevated above the 99th percentile of the general reference population (≤14 ng/L). On average, hs-cTnT increased by 16%/year (95% CI, 13–19; $P<0.0001$). Each 15 mL/min/1.73 m^2 lower mean estimated GFR was associated with a 23% (95% CI, 14–31; $P<0.0001$) higher baseline hs-cTnT and 9% (95% CI, 5–13%; $P<0.0001$) steeper increase in hs-cTnT. The effect of estimated GFR on hs-cTnT trajectory was somewhat lower than a previous myocardial infarction (15%), but higher than presence of diabetes mellitus (4%) and male sex (5%).

***Conclusions*—**In CKD patients, hs-cTnT increases over time as renal function decreases. Lower CKD stage (each 15 mL/min/1.73 m^2 lower) is independently associated with a steeper hs-cTnT increase over time in the same range as other established cardiovascular risk factors. **(*J Am Heart Assoc*. 2019;8:e013091. DOI: 10.1161/JAHA.119.013091.)**

Key Words: cardiorenal syndrome • renal disease • renal function • troponin T

Cardiac troponins are proteins in the cardiomyocyte which are released into the bloodstream and used as a biomarker for diagnosing an acute coronary event. However, a substantial proportion of the patients presenting with chest pain have elevated high-sensitivity cardiac troponin (hs-cTn) levels without having an acute myocardial infarction (AMI).[1] Among those with a permanently elevated hs-cTn above the reference are patients with advanced chronic kidney disease (CKD). Given that elevated hs-cTn without signs of AMI is associated with worse prognosis, measurement of high-sensitivity cardiac troponin T (hs-cTnT) is acknowledged by the US Food and Drug Administration to be used for risk stratification of dialysis patients.[2]

However, clearance and degradation of cardiac troponins are not yet fully understood.[2] There are 2 possible mechanisms for the increased hs-cTn levels observed in CKD

From the Departments of Clinical Science, Intervention and Technology (P.B., O.H., H.M., M.E.) and Medicine (K.S.), Karolinska Institutet, Stockholm, Sweden; Department of Medical Informatics, Academic Medical Center, University of Amsterdam, Amsterdam Public Health Research Institute, Amsterdam, The Netherlands (N.C.C., K.J.); Department of Cardiology Huddinge, Karolinska University Hospital, Stockholm, Sweden (K.S.); Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands (F.W.D.); Division of Nephrology, University Hospital of Wurzburg, Wurzburg, Germany (C.W.); Division of Nephrology, Department of Clinical Sciences, Karolinska Institutet, Danderyd Hospital, Stockholm, Sweden (T.A.); Departments of Nephrology (F.U.) and Medical and Health Sciences (F.U.), Linköping University, Linköping, Sweden; Centre of Biomedical Engineering, Department of Health Technologies, School of Informatics, Tallinn University of Technology, Tallinn, Estonia (F.U.).

Accompanying Data S1, Table S1, and Figures S1 and S2 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013091

*A complete list of the EQUAL Study Investigators can be found in the Appendix at the end of the article.

Correspondence to: Marie Evans, MD, M99 Renal Department, Karolinska University Hospital Huddinge, S-14186 Stockholm, Sweden. E-mail: marie.evans@ki.se

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Clinical Perspective

What Is New?

- In our prospective, longitudinal study of chronic kidney disease patients not on dialysis with an incident estimated glomerular filtration rate <20 mL/min/1.73 m^2, we demonstrate that lower estimated glomerular filtration rate is independently associated with a steeper high-sensitivity cardiac troponin T increase over time, with the effect size in the same range as other established risk factors, such as cardiovascular disease, diabetes mellitus, and male sex, and with effect modification by previous myocardial infarction and diabetes mellitus.

What Are the Clinical Implications?

- Knowledge of the course and which factors modify the trajectory of cardiac troponins with progression of chronic kidney disease will help clinicians in the difficult task to interpret high-sensitivity cardiac troponin T levels in these patients.
- In spite of the independent association between lower estimated glomerular filtration rate and increased high-sensitivity cardiac troponin T, increasing high-sensitivity cardiac troponin T over time could reflect the subclinical development of heart disease resulting from the chronic kidney disease state.

patients. First, CKD is associated with cardiovascular morbidity; the raised values could represent continuous myocardial damage caused by long-term exposure to uremic toxins and/or comorbidities. Thus, an elevated hs-cTn is more difficult to interpret in patients with CKD, especially in the setting of a suspected acute coronary event.[3] Second, recent studies have demonstrated that hs-cTnT levels could be affected by reduced renal clearance per se, especially at levels just above the 99th percentile concentration of the reference population.[4,5] This has led to the proposal of estimated (eGFR) glomerular filtration rate (GFR)-corrected hs-cTn measurements.[4,6] Although large studies have evaluated the cross-sectional association between eGFR and hs-cTn, there is a lack of prospective, longitudinal studies in stable CKD patients where the interaction between change in hs-cTn and eGFR can be studied over time.

The aim of this study was to prospectively study the association between hs-cTnT and GFR in CKD stage 4 and 5 patients (not on dialysis). Furthermore, we aimed to study the attributable effect of eGFR on the development of myocardial strain over time measured by hs-cTn. For this purpose, we measured GFR, eGFR, and hs-cTnT along with other relevant clinical data over a 4-year follow-up period in patients aged >65 years with stage 4 to 5 CKD.

Methods

Study Design and Population

The EQUAL (European Quality Study) study is an ongoing observational, multicenter, prospective cohort study including stage 4 to 5 CKD patients not on dialysis receiving routine medical care in Germany, Italy, the Netherlands, Poland, Sweden, and the United Kingdom. Patients aged ≥65 years were included with an incident eGFR<20 mL/min/1.73 m^2 calculated by the Modification of Diet in Renal Disease equation. Patients were excluded if the drop in eGFR resulted from an acute event or if they had previously received dialysis or a kidney transplant. Approval was obtained from the medical ethical committees in each country, and informed consent was obtained from all patients. A full description of the study has been published elsewhere.[7] The EQUAL cohort used for the purpose of this study includes 171 patients recruited at 5 nephrology clinics in Sweden, where hs-cTnT was collected as an extension to the study protocol. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Data Collection

Clinical data were collected between April 2012 to December 2018 through an online case report form on patient demographics, primary renal disease, laboratory data, and cardiovascular risk factors (smoking status, body mass index, hemoglobin, blood pressure, cholesterol, and diabetes mellitus). Data on the following preexisting cardiovascular comorbid conditions, confirmed by investigation, were also collected (definitions provided in Data S1): cerebrovascular disease, peripheral vascular disease, myocardial infarction, angina pectoris, congestive heart failure, left ventricular hypertrophy, hypertension, and cardiac arrhythmias. Study visits were scheduled at 6-month intervals, and patients were followed until dialysis initiation, kidney transplantation, death, refusal for further participation, loss to follow-up, or end of follow-up. eGFR was calculated from serum creatinine level standardized to isotope dilution mass spectrometry using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation.[8] GFR was also measured using iohexol clearance at baseline. In addition, GFR was measured during follow-up after routine 24-hour urine collection by taking the average of creatinine clearance and urea clearance, normalized to body surface area following the Dubois and Dubois formula. Albumin-creatinine ratio was also determined following routine 24-hour urine collection. High-sensitivity troponin T was analyzed at 3 different laboratories using instruments from Roche Diagnostics (Cobas e601/602, e411, or Modular E; Roche Diagnostics, Basel, Switzerland). The limit of detection was 5 ng/L, with an upper limit of 10 000 ng/L, and the

coefficient of variation was between 4% and 7%. Primary kidney disease was classified using the codes of the European Renal Association–European Dialysis and Transplantation Association and grouped as glomerulonephritis, diabetes mellitus, tubulointerstitial disease, hypertension, and miscellaneous kidney diseases.

Statistical Analysis

Patient characteristics were reported by hs-cTnT tertiles as mean values with SDs for normally distributed continuous variables, as medians with interquartile ranges for skewed continuous variables, and as proportions for categorical variables. Differences between hs-cTnT tertiles were tested using the Kruskal–Wallis test for continuous variables and the chi-square test for categorical variables. Linear mixed models were used to model the hs-cTnT trajectory. A random intercept was included to capture the variation in hs-cTnT baseline value between patients and a random slope for time to capture variability in the patient hs-cTn T trajectory. Because of the nonlinear patient trajectories of hs-cTnT, the latter was included as a cubic B-spline with 3 equally spaced knots positioned between the minimum and maximum of follow-up. Using this model, we investigated the univariable effect of patient characteristics on mean hs-cTnT. Subsequently, we modeled the mean linear trajectory of hs-cTnT over time by including time as a fixed effect. In subsequent models, we investigate the effect of eGFR on hs-cTnT trajectory (given by the eGFR×time interaction coefficient) and hs-cTnT at baseline (given by the eGFR coefficient), adjusted for various groups of a priori–defined confounders. Because of the large amount of missing measured GFR (mGFR) measurements, we studied the association between mGFR and hs-cTnT only as a sensitivity analysis.

We estimated the attributable effect of eGFR on hs-cTn T by calculating the R^2 for various mixed-effects models as described by Nakagawa and Schielzeth[9] and Johnson.[10] The R^2 is categorized into 2 types; the marginal R^2, which represents the variance explained by fixed effects, and the conditional R^2, which describes the variance explained by the entire model. For the purposes of this study, here we report the former.

Q-Q plots were used to check whether the residuals were normally distributed, and hs-cTnT was log-transformed to fulfil this assumption. Consequently, regression coefficients were exponentiated and interpreted as the mean percent change in hs-cTn T for each unit increase in determinant. Missing values are reported in Table S1. All analyses were performed with SAS (version 9.4; SAS Institute Inc., Cary, NC) and R software (version 3.4.1; R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient Characteristics

Table 1 describes the baseline characteristics of 171 patients by hs-cTnT tertile. On average, patients were 75 years old at inclusion, two-thirds were men, and the measured GFR based on iohexol clearance (mGFR) at baseline was 19.6 mL/min/1.73 m^2. During the study period, 106 patients reached CKD stage 5, and 48 patients initiated dialysis (25 on hemodialysis and 23 on peritoneal dialysis). Median hs-cTnT level at baseline was 35 ng/L (interquartile range, 24–54). Almost all patients (170) had at least 1 hs-cTnT measurement elevated above the 99th percentile of the general reference population (≤14 ng/L). The 99th percentile reference value, using all available measurements, was estimated at 132, 264, and 486 for CKD stage 4, CKD stage 5 not on dialysis, and for patients who initiated dialysis during the study period, respectively. Patients of male sex, with preexisting diabetes mellitus, heart failure, and atrial fibrillation, had higher levels of hs-cTnT at baseline.

Patient Characteristics and Mean hs-cTnT

We included 821 measurements during the predialysis period in 171 patients, with a median of 3 measurements per patient, and a median follow-up time of 24.4 months. Individual hs-cTnT measurements and modelled trajectories are illustrated in Figure 1, together with the population average hs-cTnT trajectory. In the unadjusted analysis, reduced renal function was associated with increased levels of hs-cTnT (Table 2). Overall, patients with a 5 mL/min/1.73 m^2 lower mean eGFR had 13% higher levels of mean hs-cTnT. Furthermore, patients with preexisting chronic heart failure had a 34% higher level of hs-cTnT compared with those without, as did patients with a history of hypertension (34%), myocardial infarct (33%), angina pectoris (31%), atrial fibrillation (26%), of male sex (24%), diabetes mellitus (24%), and patients with lower hemoglobin (4% per 10 g/L). Interestingly, an inverse relationship was noted for systolic blood pressure, body mass index, and cholesterol. An increase by 10 mm Hg mean systolic blood pressure was associated with a 2% decrease in mean hs-cTnT, as was body mass index (12% per 10 kg/m^2) and cholesterol (6% per mmol/L). When analyzing these variables with splines to deal with slight nonlinearity in the relationship with hs-cTnT, these associations persisted. Mean hs-cTnT was similar across all 5 nephology clinics (not presented).

The Effect of eGFR on hs-cTnT Trajectory

On average, hs-cTnT increased by 16% (95% CI, 13–19; $P<0.0001$) every year. Patients with reduced renal function

Table 1. Baseline Patient Characteristics by Troponin T Tertiles

Troponin Tertile (N=171)	All (N=171)	hs-cTnT Range 10 to 27 (N=55)	hs-cTnT Range 28 to 45 (N=58)	hs-cTnT Range 46 to 379 (N=58)	*P* Value
Demographics					
Age, y, mean (SD)	75.4 (6.5)	74.9 (6.4)	75.7 (6.5)	75.6 (6.6)	0.66
Male, %	67	53	74	72	0.03
PRD, %					0.10
Glomerular disease	13	13	10	16	
Tubulo-interstitial disease	6	11	7	2	
Diabetes mellitus	22	9	31	26	
Hypertension	42	45	41	40	
Miscellaneous	16	22	10	17	
Cardiovascular risk factors					
BMI, kg/m^2 mean (SD)	27.6 (5.6)	27.8 (6.2)	27.5 (4.3)	27.6 (6.3)	0.91
BP diastolic, mm Hg, mean (SD)	76.5 (11.6)	76 (10.7)	80.3 (11.3)	73 (11.8)	0.01
BP systolic, mm Hg, mean (SD)	145.8 (21.8)	142.3 (21.6)	153.3 (20.5)	141.4 (21.7)	0.01
Total cholesterol, mmol/L, mean (SD)	4.6 (1.2)	4.8 (1.2)	4.6 (1.3)	4.5 (1.3)	0.29
Diabetes mellitus, %	37	20	45	47	0.005
Troponin, ng/L, median (IQR)	35 (24–54)	21 (18–24)	34 (30–40)	65.5 (54–91)	NA
Hb, g/L, mean (SD)	118.5 (16.9)	119.7 (15.0)	119.8 (18.0)	116.1 (17.3)	0.28
Current smoking, %	8	5	9	9	0.67
Renal function					
eGFR, mL/min/1.73 m^2, median (IQR)	17.3 (13.4–21.6)	18.2 (15.7–22.4)	17.3 (12.3–21.6)	16.1 (12.4–20.2)	0.07
mGFR iohexol, mL/min/1.73 m^2, median (IQR)	19.5 (14–24)	20 (16–24)	21 (13–24)	18 (12–23)	0.37
mGFR 24-h urine, mL/min/1.73 m^2, median (IQR)	15.4 (11.2–19.6)	17.7 (13.9–22.1)	16.8 (12.1–21.1)	12.6 (8.9–16.8)	0.001
ACR, median (IQR)	46.1 (12.5–169.1)	32.0 (5.1–128.3)	60.3 (23.5–163.3)	47.5 (10.3–281.4)	0.15
Preexisting CVD comorbidity					
Cerebrovascular, %	16	9	16	22	0.15
Myocardial infarct, %	14	5	19	17	0.08
Angina, %	15	7	17	21	0.12
Peripheral arterial disease, %	13	7	16	17	0.26
Atrial fibrillation, %	16	7	17	24	0.05
Heart failure, %	18	5	14	33	0.001
Left ventricular hypertrophy, %	15	9	19	17	0.30
Hypertension, %	92	87	91	97	0.20

ACR indicates albumin creatinine ratio; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate (CKDEPI); Hb, hemoglobin; hs-cTnT, high-sensitivity cardiac troponin T; IQR, interquartile range; mGFR, measured glomerular filtration rate; NA, not applicable; PRD, primary renal disease.

had higher baseline hs-cTnT values and steeper increases in hs-cTnT (slope) over time (Figure 2). Specifically, each 5 mL/min/1.73 m^2 lower mean eGFR was associated with an 8.2% (95% CI, 4.8–11.5; $P<0.0001$) higher baseline hs-cTnT and 3.0% (95% CI, 1.6–4.5; $P<0.0001$) steeper increase in hs-cTnT (Table 3). Correspondingly, each 15 mL/min/1.73 m^2 lower mean eGFR was associated with a 23% (95% CI, 14–31; $P<0.0001$) higher baseline hs-cTnT and 9% (95% CI, 5–13; $P<0.0001$) steeper increase in hs-cTnT. The effect of eGFR on hs-cTnT baseline and hs-cTnT change over time remained largely unchanged after adjustment for patient demographics, cardiovascular risk factors, and preexisting cardiovascular comorbidities (Table 3). The marginal R^2 for eGFR was 14%, meaning that eGFR explained 14% of the variation in patient hs-cTnT values.

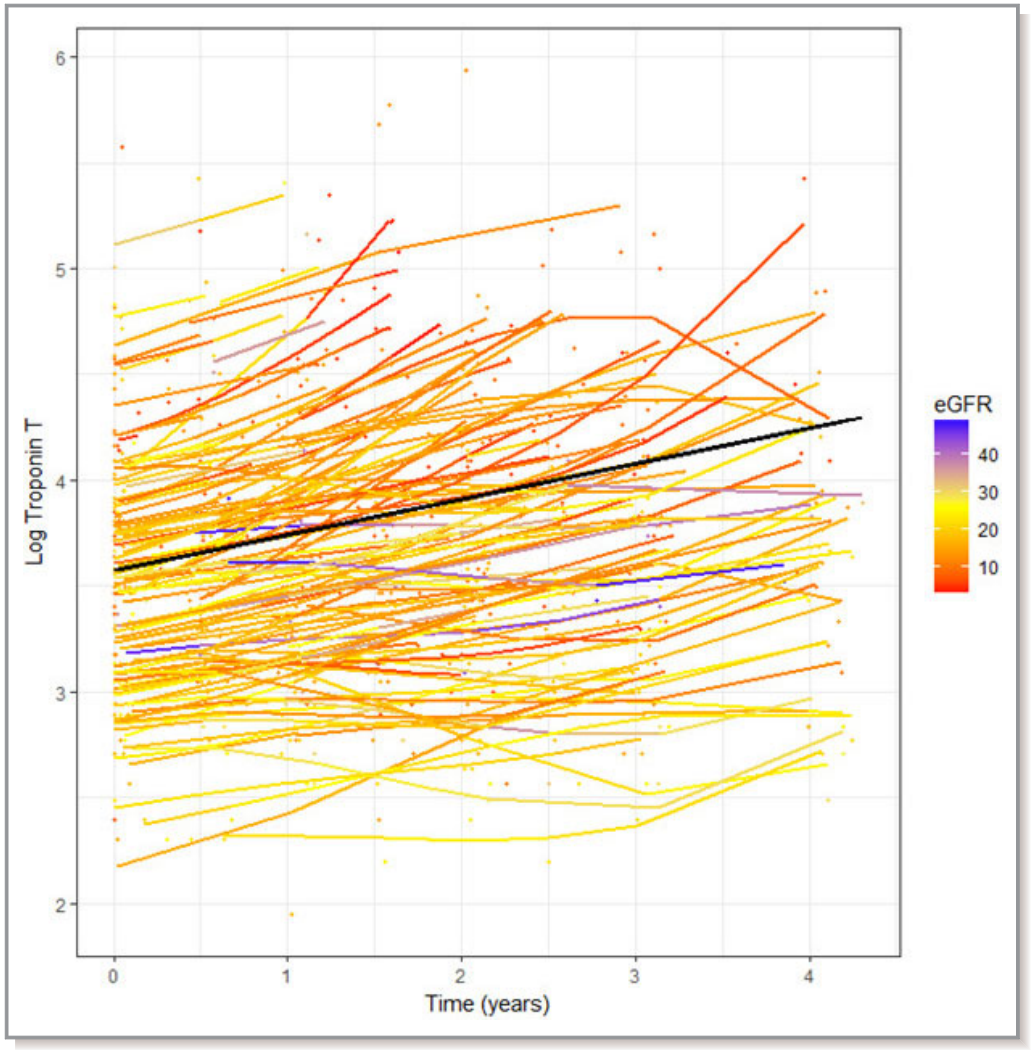

Figure 1. Patient hs-cTn T measurements and modeled trajectories, color-coded by eGFR. The population average trajectory is given in black. eGFR indicates estimated glomerular filtration rate; hs-cTnT, high-sensitivity cardiac troponin T.

The effect of a 15 mL/min/1.73 m^2 lower eGFR on hs-cTnT was comparable both at baseline (23%) and over time (9%) to other factors known to be associated with elevated troponin levels (Figure S1). Men had 18% (95% CI, −1 to 34; *P*=0.07) higher baseline level of hs-cTnT and 5% (95% CI, 0–10; *P*=0.05) steeper slopes for hs-cTnT increase compared with women. Sex explained 11% of the variation in patient hs-cTnT values. Furthermore, patients with a history of myocardial infarct had 19% (95% CI, −10 to 40; *P*=0.18) higher baseline levels of hs-cTnT and 15% (95% CI, 6–22; *P*<0.0001) steeper slopes for hs-cTnT increase compared with those without and explained 10% of the variation in patient hs-cTnT values. Patients with diabetes mellitus had 19% (95% CI, −1 to 34; *P*=0.06) higher baseline levels of hs-cTnT and 4% (95% CI, −1 to 9; *P*=0.10) steeper slopes for hs-cTnT increase compared with those without. Diabetes mellitus explained 11% of the variation in patient hs-cTnT values.

Modification of the eGFR Effect on hs-cTnT Trajectory

We explored potential modifiers of the effect of eGFR on hs-cTnT baseline and slope. The effect of eGFR on hs-cTnT baseline (*P*=0.47) and slope (*P*=0.75) did not differ by sex, nor was there evidence of effect modification by the presence of chronic heart failure (baseline, *P*=0.85; slope, *P*=0.11), atrial fibrillation (baseline, *P*=0.11; slope, *P*=0.44) or cerebrovascular disease (baseline, *P*=0.18; slope=0.56). Interestingly, the presence of myocardial infarct strengthened the effect of eGFR on baseline hs-cTn T (*P*=0.01), but not on hs-cTnT slope (*P*=0.22), whereas the presence of diabetes mellitus (slope, *P*=0.007; baseline, *P*=0.15) or angina pectoris (baseline, *P*=0.18; slope, *P*=0.007) strengthened the effect of eGFR on hs-cTnT slope, but not on baseline hs-cTnT. We found no evidence of effect modification from other variables (Figure S2).

Table 2. The Univariable Association Between Patient Characteristics and Mean hs-cTnT, Given as the Percent Change in Mean hs-cTnT for Each Unit Increase in Determinant

	Percent Change in Mean TnT Per Unit Increase in Determinant	*P* Value
Demographics		
Age (per 5 y)	6% (−2% to 14%)	0.16
Male	24% (7–38%)	0.01
PRD		
Glomerular disease	Reference	
Diabetes mellitus	17% (−17% to 66%)	0.36
Hypertension	−1% (−27% to 36%)	0.96
Miscellaneous	−11% (−38% to 29%)	0.55
Tubulointerstitial disease	−33% (−58% to 7%)	0.10
Cardiovascular risk factors		
BMI, per 10 kg/m^2	−12% (−20% to −3%)	0.01
BP[3] diastolic, per 10 mm Hg	−2% (−4% to 0%)	0.07
BP systolic, per 10 mm Hg	−2% (−3% to −1%)	0.0002
Total cholesterol, per 1 mmol/L	−6% (−8% to −3%)	<0.0001
Diabetes mellitus	24% (6–38%)	0.01
Hb, per 1 g/L	−4% (−6% to −3%)	<0.0001
Current smoking	37% (−7% to 103%)	0.11
Renal function		
eGFR value (per 5-mL/min/1.73 m^2 increase)	−13% (−15% to −10%)	<0.0001
mGFR 24-h urine mL/min (per 5-mL/min/1.73 m^2 increase)	−5% (−7% to −3%)	<0.0001
ACR (per 100-mg/g increase)	2% (0–4%)	0.08
Preexisting CVD comorbidity		
Cerebrovascular	21% (−4% to 40%)	0.09
Myocardial infarct	33% (11–49%)	0.01
Angina	31% (9–48%)	0.01
Peripheral vascular	18% (−10% to 39%)	0.18
Atrial fibrillation	26% (4–43%)	0.03
Heart failure	34% (14–49%)	0.002
Left ventricular hypertrophy	12% (−15% to 34%)	0.34
Hypertension	34% (5–53%)	0.02

ACR indicates albumin creatinine ratio; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate (CKDEPI); Hb, hemoglobin; hs-cTnT, high-sensitivity cardiac troponin T; mGFR, measured glomerular filtration rate; PRD, primary renal disease; TnT, troponin T.

Effect of Starting Dialysis on hs-cTnT

We performed a sensitivity analysis including patients starting dialysis. Patients on dialysis had, on average, a 23% (95% CI, 13–34%; $P<0.0001$) higher hs-cTnT compared with patients not (yet) on dialysis, even after adjustment for patient demographics, cardiovascular risk factors, and preexisting cardiovascular comorbidities. We detected no difference in effect between patients starting dialysis on hemodialysis dialysis or peritoneal dialysis ($P=0.98$), but the sample size was small and confidence intervals wide.

The Effect of mGFR on hs-cTnT Trajectory

In an additional sensitivity analysis, using the 24-hour urine collections from 171 patients (526 measurements), we investigated the effect of mGFR on hs-cTnT trajectory. We found a similar association as with eGFR; specifically, each 15 mL/min/1.73 m^2 lower mean mGFR was associated with a 16.3% (95% CI, 7.1–24.6; $P=0.009$) higher baseline hs-cTn T and a 5.5% (95% CI, 0.7–10.1; $P=0.03$) steeper increase in hs-cTnT.

Discussion

In this study of severe-stage CKD patients followed over 4 years in renal outpatient care, we found that hs-cTnT increased over time and was strongly associated with renal function both at baseline and during follow-up. The median hs-cTnT value in this CKD population was around 3 times higher than the 99th percentile of the reference population, which is currently used to diagnose AMI, and almost all patients in our cohort had at least 1 value above that limit during follow-up. The cross-sectional effect of eGFR per CKD stage (15 mL/min/1.73 m^2) at baseline was independently associated with hs cTnT and in the same range as other factors (sex, angina, and diabetes mellitus) previously known to be associated with higher troponin levels.[1] Over time, those with lower eGFRs had steeper increases in hs-cTnT, and this effect size was similar to that of patients with previous myocardial infarction. In addition, the variation of hs-cTnT explained by eGFR was relatively higher than that of other risk factors.

The interpretation of elevated hs-cTnT values in CKD patients is challenging in the setting of a suspected AMI. Patients with renal dysfunction are known to exhibit an elevated risk of cardiovascular disease and more often present with atypical symptoms.[11] Furthermore, in patients with chest pain and eGFR <45 mL/min/1.73 m^2 but no AMI, around 65% have elevated hs-cTnT levels.[12] The cause of stable troponin elevation in patients with CKD has been suggested to be either troponin retention or increased myocardial stress.[2] Reduced renal clearance could be 1

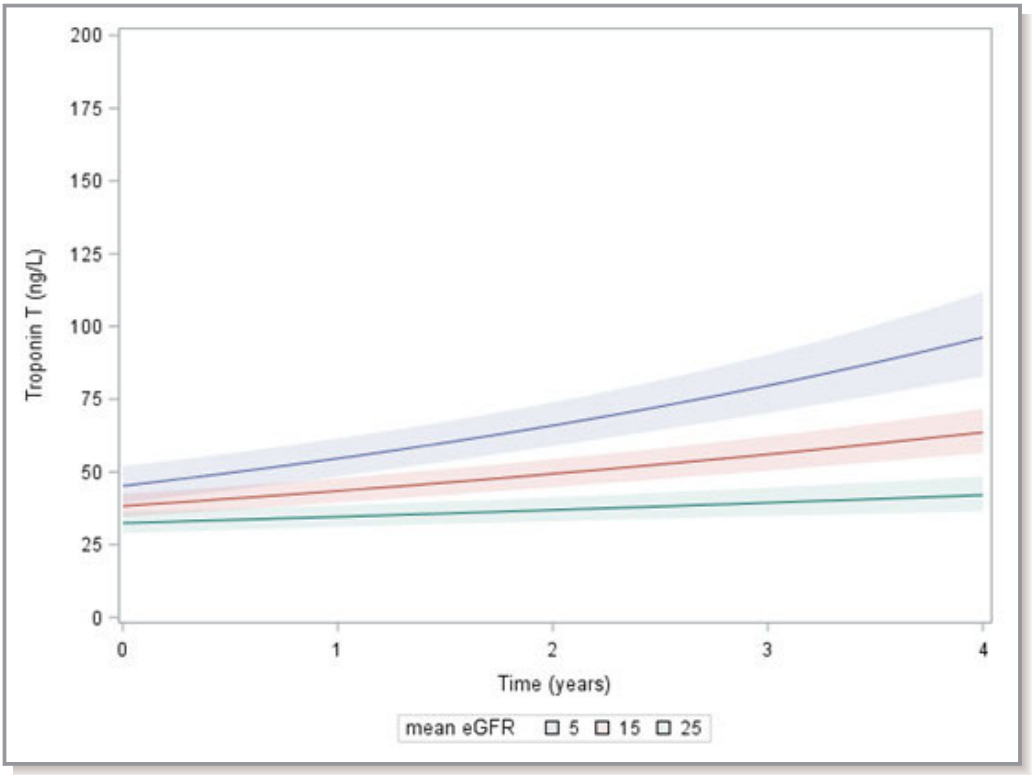

Figure 2. The unadjusted effect of mean eGFR (mL/min/1.73 m^2) on hs-cTn T trajectory.

possible mechanism of hs-cTnT retention.[13] Although the intact molecule is too large (37 kDa) to be filtered through the glomerulus, measured hs-cTnT is degraded to fragments which could be affected by renal clearance.[14] In patients with CKD, heart failure, and AMI, around 60% to 80% of measured hs-cTnT had a molecular weight <17 kDa, small enough to pass through the glomerular membrane.[4] However, Fridén et al proposed that extrarenal clearance mechanisms (probably through scavenger receptors) were likely to be more important at the high troponin levels commonly observed in patients with AMI.[4] At the low, but stable, hs-cTnT levels observed in CKD patients, scavenger receptors are less likely to play an important role given that they do not have such high affinity for their target proteins. In these patients, a correlation between measured hs-cTnT and renal clearance could be expected in a steady-state situation.[13] Experimental data from their study support this hypothesis.[4] Clinical data suggest that acute changes in renal function correlate with changes in hs-cTnT down to the detection limit.[5] In addition, eGFR-adjusted hs-cTnT discriminates better between AMI and no AMI in the acute setting, and 1 study also observed improved predictive performance with eGFR-adjusted troponin.[4,6]

In CKD patients, however, troponin levels are higher than would be expected if only explained by reduced renal clearance.[13] Furthermore, other studies have indicated that mechanisms other than renal clearance play a larger role.[15,16] It has been proposed that cardiac troponin release is the

Table 3. Effect of 5 mL/min/1.73 m^2 Lower Mean eGFR on TnT Baseline and Progression Over Time Adjusted for Various Groups of Confounders (Following the Variables Listed in Table 2)

	Baseline		Slope	
Model	Estimate (95% CI)	*P* Value	Estimate (95% CI)	*P* Value
Unadjusted	8.2% (4.8–11.5%)	<0.0001	3.0% (1.6–4.5%)	<0.0001
Demographics	9.0% (5.6–12.2%)	<0.0001	2.5% (1.0–4.0%)	0.001
Cardiovascular risk factors	8.1% (4.6–11.5%)	<0.0001	1.8% (0.4–3.3%)	0.01
Cardiovascular comorbidities	8.0% (4.4–11.4%)	<0.0001	3.2% (1.7–4.6%)	<0.0001

eGFR indicates estimated glomerular filtration rate; TnT, troponin T.

result of inflammation and chronic myocardial injury associated with renal dysfunction.[17] The interindividual variability of hs-cTnT is large, also in stable hemodialysis patients, and elevated levels are associated with worse prognosis, also in patients without reduced renal function.[18] Elevated troponins are associated with mortality and cardiovascular disease in CKD patients, both with and without dialysis.[19]

The independent association between baseline eGFR and hs-cTnT in our study, together with a relatively high explained variation of hs-cTnT by eGFR (14%), could mean that renal clearance per se may influence hs-cTnT levels. However, the observational methods of our study do not allow us to separate the attributable effect of renal clearance from that of, for example, reduced degradation or indirect effects associated with advanced CKD. In addition, our results show that hs-cTnT increased over time, and that a reduction in eGFR by 15 mL/min/1.73 m^2 resulted in a 9% steeper increase in hs-cTnT, remaining statistically significant after adjusting for other important risk factors. One interpretation of increasing troponin over time is that it is a sign of myocardial stress, which, in turn, could be linked to the CKD state. In our study, the magnitude of this effect is somewhat lower to that of a previous myocardial infarction (15% steeper increase), but somewhat higher than the effect of diabetes mellitus (4% steeper increase). Several risk factors are likely to contribute to and mediate the increased myocardial stress and uremic cardiomyopathy. Decreasing renal function causes neurohormonal activation, which leads to both fluid and sodium retention with extracellular volume expansion. Several studies have demonstrated that heart diseases, such as heart failure and left ventricular hypertrophy, have a high prevalence in CKD patients.[20,21] The CRIC (Chronic Renal Insufficiency Cohort) study found that echocardiographic findings of structural heart damage worsened over time with progressive CKD.[22] In the same cohort, a high-sensitivity troponin in the highest quartile was associated with a higher risk of incident heart failure.[23] Thus, the rise in troponin over time in our study could reflect a subclinical development of heart disease, although additional data on cardiac imaging would be required to confirm this mechanism. Other mechanisms could also contribute to the development of heart disease and heart failure in CKD patients. Some of these factors are metabolic abnormalities, such as alterations in mineral metabolism and increased levels of phosphate and fibroblast growth factor 23, anemia, metabolic acidosis, and myocardial stunning, previously associated with hemodialysis treatment.[24]

Interestingly, our results indicate that increases in various cardiovascular risk factors (systolic blood pressure, body mass index, and cholesterol) were negatively associated with hs-cTnT. In exploratory analyses (not presented), we found inverse trends between the presence of preexisting cardiovascular comorbidities and these risk factors, suggesting that the relationship between hs-cTnT and the risk factors are confounded by the severity of the underlying disease (ie, a low systolic blood pressure caused by heart failure is associated with higher troponin levels).

Our study has many strengths. First, the cohort represents stable CKD patients referred to nephrology. The patients were incident, included when eGFR dropped below a predefined level, which minimizes the selection of healthier survivors. The cohort is well characterized and had rich information on variables collected both at baseline and during the 4-year follow-up. Unlike most other cohort studies, hs-cTnT was measured prospectively throughout follow-up. Although hs-cTnT was measured at different laboratories, the instruments used were similar and showed equal limit of detection and coefficient of variation. There are also some limitations. First, because of the observational nature of our study, we are unable to infer causality to our findings. Furthermore, most patients were whites, and therefore our results may not be generalizable to other populations. Because of our inclusion criteria, there were only a limited number of patients in CKD stage 3, and we cannot rule out that the eGFR/hs-CTnT association is different when renal function is more preserved. However, earlier cross-sectional studies indicate that the association between eGFR and cardiac troponins is present in the whole spectrum of CKD stages.[6] In addition, we lack data on cardiac imaging, which is required to verify the influence of myocardial strain on hs-CTnT concentrations. Last, our sample size may have been too small to rule out type 2 errors in our subanalyses, especially when looking at effect modification.

In summary, this observational study of a stable nondialysis CKD population shows that there is an independent association between GFR and hs-cTnT levels. More important, hs-cTnT increases independently over time in those with lower eGFR, suggesting that CKD may contribute to chronic myocardial stress in the same range as established cardiovascular disease, although additional data on cardiac imaging would be required to confirm this mechanism.

Appendix

The EQUAL Study Investigators

Adamasco Cupisti, Adelia Sagliocca, Alberto Ferraro, Aleksandra Musiała, Alessandra Mele, Alessandro Naticchia, Alex Còsaro, Alistair Woodman, Andrea Ranghino, Andrea Stucchi, Andreas Jonsson, Andreas Schneider, Angelo Pignataro, Anita Schrander, Anke Torp, Anna McKeever, Anna Szymczak, Anna-Lena Blom, Antonella De Blasio, Antonello Pani, Aris Tsalouichos, Asad Ullah, Barbara McLaren, Bastiaan van Dam, Beate Iwig, Bellasi Antonio, Biagio Raffaele Di Iorio, Björn Rogland, Boris Perras, Butti Alessandra, Camille Harron, Carin

Wallquist, Carl Siegert, Carla Barrett, Carlo Gaillard, Cataldo Abaterusso, Charles Beerenhout, Charlotte O'Toole, Chiara Somma, Christian Marx, Christiane Drechsler, Christina Summersgill, Christof Blaser, Christoph Wanner, Claudia D'alessandro, Claudia Emde, Claudia Torino, Claudia Zullo, Claudio Pozzi, Colin Geddes, Cornelis Verburgh, Cynthia Janmaat, Daniela Bergamo, Daniele Ciurlino, Daria Motta, Deborah Glowski, Deborah McGlynn, Denes Vargas, Detlef Krieter, Domenico Russo, Dunja Fuchs, Dympna Sands, Ellen Hoogeveen, Ellen Irmler, Emöke Dimény, Enrico Favaro, Eva Platen, Ewelina Olczyk, Ewout Hoorn, Federica Vigotti, Fergus Caskey, Ferruccio Ansali, Ferruccio Conte, Francesca Cianciotta, Francesca Giacchino, Francesco Cappellaio, Francesco Pizzarelli, Fredrik Sundelin, Fredrik Uhlin, Friedo Dekker, Gaetano Greco, Geena Roy, Gaetana Porto, Giada Bigatti, Giancarlo Marinangeli, Gianfranca Cabiddu, Gillian Hirst, Giordano Fumagalli, Giorgia Caloro, Giorgina Piccoli, Giovanbattista Capasso, Giovanni Gambaro, Giuliana Tognarelli, Giuseppe Bonforte, Giuseppe Conte, Giuseppe Toscano, Goffredo Del Rosso, Gunilla Welander, Hanna Augustyniak-Bartosik, Johannes Boots, Hans Schmidt-Gürtler, Hayley King, Helen McNally, Hendrik Schlee, Henk Boom, Holger Naujoks, Houda Masri-Senghor, Hugh Murtagh, Hugh Rayner, Ilona Miśkowiec-Wiśniewska, Ines Schlee, Irene Capizzi, Sabine Cäsar, Isabel Bascaran Hernandez, Ivano Baragetti, Jacek Manitius, Jane Turner, Jan-Willem Eijgenraam, Jeroen Kooman, Joachim Beige, Joanna Pondel, Joanne Wilcox, Jocelyn Berdeprado, Jochen Röthele, Jonathan Wong, Joris Rotmans, Joyce Banda, Justyna Mazur, Kai Hahn, Kamila Jędrzejak, Katarzyna Nowańska, Katja Blouin, Katrin Neumeier, Kirsteen Jones, Kirsten Anding-Rost, Kitty Jager, Knut-Christian Gröntoft, Lamberto Oldrizzi, Lesley Haydock, Liffert Vogt, Lily Wilkinson, Loreto Gesualdo, Lothar Schramm, Luigi Biancone, Łukasz Nowak, Maarten Raasveld, Maciej Szymczak, Magdalena Durlik, Manuela Magnano, Marc Vervloet, Marco Ricardi, Margaret Carmody, Maria Di Bari, Maria Laudato, Maria Luisa Sirico, Maria Stendahl, Maria Svensson, Maria Weetman, Marie Evans, Marjolijn van Buren, Martin Joinson, Martina Ferraresi, Mary Dutton, Maurizio Postorino, Merel van Diepen, Michael Matthews, Michele Provenzano, Monika Hopf, Moreno Malaguti, Nadja Wuttke, Neal Morgan, Nicholas Chesnaye, Nicola Palmieri, Nikolaus Frischmuth, Nina Bleakley, Olof Heimburger, Paola Murrone, Paul Cockwell, Paul Leurs, Paul Roderick, Pauline Voskamp, Pavlos Kashioulis, Pawlos Ichtiaris, Peter Blankestijn, Petra Kirste, Petra Schulz, Phil Mason, Philip Kalra, Pietro Cirillo, Pietro Dattolo, Pina Acampora, Rincy Sajith, Rita Nigro, Roberto Boero, Roberto Scarpioni, Rosa Sicoli, Rosella Malandra, Sabine Aign, Sadie van Esch, Sally Chapman, Sandra Biribauer, Santee Navjee, Sarah Crosbie, Sharon Brown, Sheila Tickle, Sherin Manan, Silke Röser, Silvana Savoldi, Silvio Bertoli, Silvio Borrelli, Siska Boorsma, Stefan Heidenreich, Stefan Melander, Stefania Maxia, Stefano Maffei, Stefano Mangano, Stephanie Palm, Constantijn Konings, Suresh Mathavakkannan, Susanne Schwedler, Sylke Delrieux, Sylvia Renker, Sylvia Schättel, Szyszkowska Dorota, Teresa Cicchetti, Teresa Nieszporek, Theresa Stephan, Thomas Schmiedeke, Thomas Weinreich, Til Leimbach, Tiziana Rappa, Tora Almquist, Torsten Stövesand, Udo Bahner, Ulrika Jensen, Valentina Palazzo, Walter De Simone, Wolfgang Seeger, Ying Kuan, Zbigniew Heleniak, Zeynep Aydin.

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Chesnaye, Evans, and Magin drafted the manuscript. Evans, Wanner, Dekker, and Jager contributed to the conception and design of the study. Chesnaye performed the statistical analysis, and all authors interpreted the data, contributed and revised the manuscript, and approved the final version of the manuscript for publication. The EQUAL Study Investigators collected data.

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Disclosures

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Supplemental Material

Data S1.

Definitions

Cerebrovascular disease; patients with a history of cerebrovascular accident with minor or no residual symptoms and transient ischemic attacks.

Peripheral arterial disease; intermittent claudication or bypass for arterial insufficiency, those with gangrene or acute arterial insufficiency, and those with untreated thoracic or abdominal aneurysm (6 cm or more).

Myocardial infarction; ST and non-ST elevation myocardial infarction, includes patients with one or more definite of probable myocardial infarctions, these patients had ECG and/or enzyme changes. Patients with ECG changes alone were not designated as having had a myocardial infarction.

Angina pectoris; chronic exertional angina, or coronary artery bypass graft, and those admitted with unstable angina.

Congestive heart failure; exertional or paroxysmal nocturnal dyspnea, or responded symptomatically to digitalis, diuretics, or afterload reducing agents. It does not include patients on medication but have had no symptomatic response, and no evidence of improvement of physical signs.

Left ventricular hypertrophy; confirmed by echo or ECG.

Hypertension; sustained blood pressure of >140/90 or using antihypertensives.

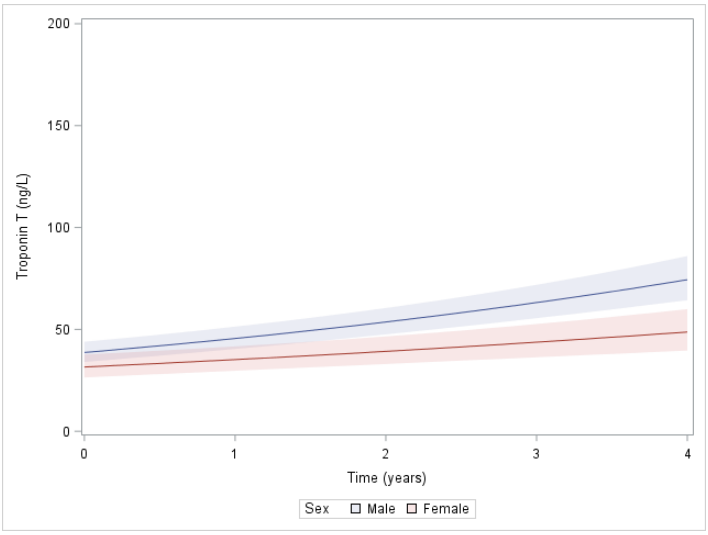
Cardiac arrhythmias; includes arrhythmias, patient with chronic atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias requiring chronic treatment.

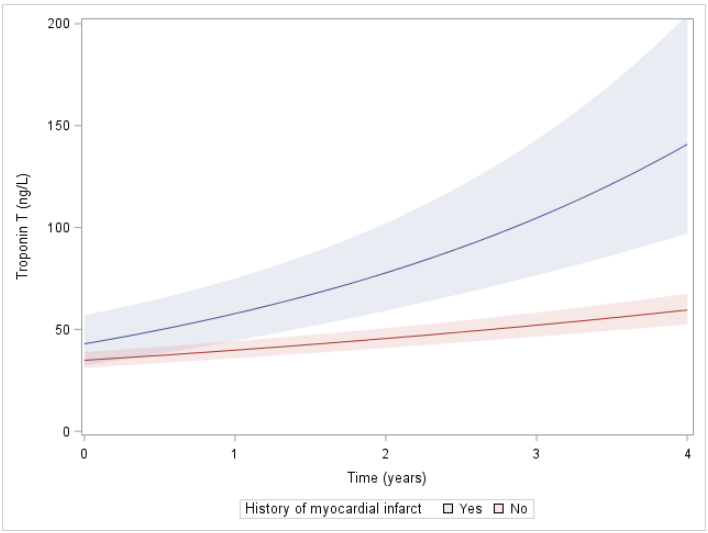
Diabetes; includes patient with retinopathy, neuropathy, or nephropathy, patients who had previous hospitalizations for ketoacidosis, hyperosmolar coma, or control, and those with juvenile onset, or brittle diabetes, or patients treated with insulin or oral hypoglycemic, but not diet alone.

Table S1. Missing values.

Variable	Measurements missing	% Missing
eGFR	100	12%
mGFR iohexol (patients)	85	50%
mGFR 24-hour urine	283	34%
ACR	298	36%
BMI	122	15%
Cholesterol	138	17%
Diastolic blood pressure	119	14%
Systolic blood pressure	119	14%
Hb	100	12%

Figure S1. The univariable effect of sex, myocardial infarct, and diabetes on hs-cTn T trajectory.





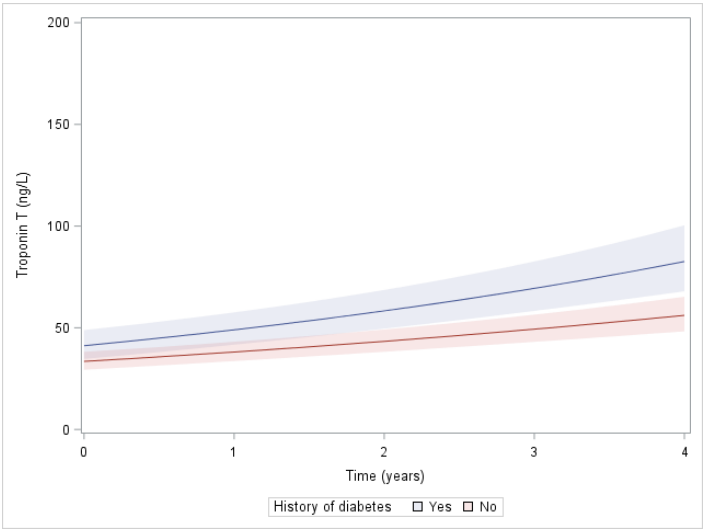


Figure S2A. The modifying effect of sex on the effect eGFR - hs-cTn T. Although men had higher levels of hs-cTn T , the effect of eGFR on hs-cTn T was similar in both sexes.

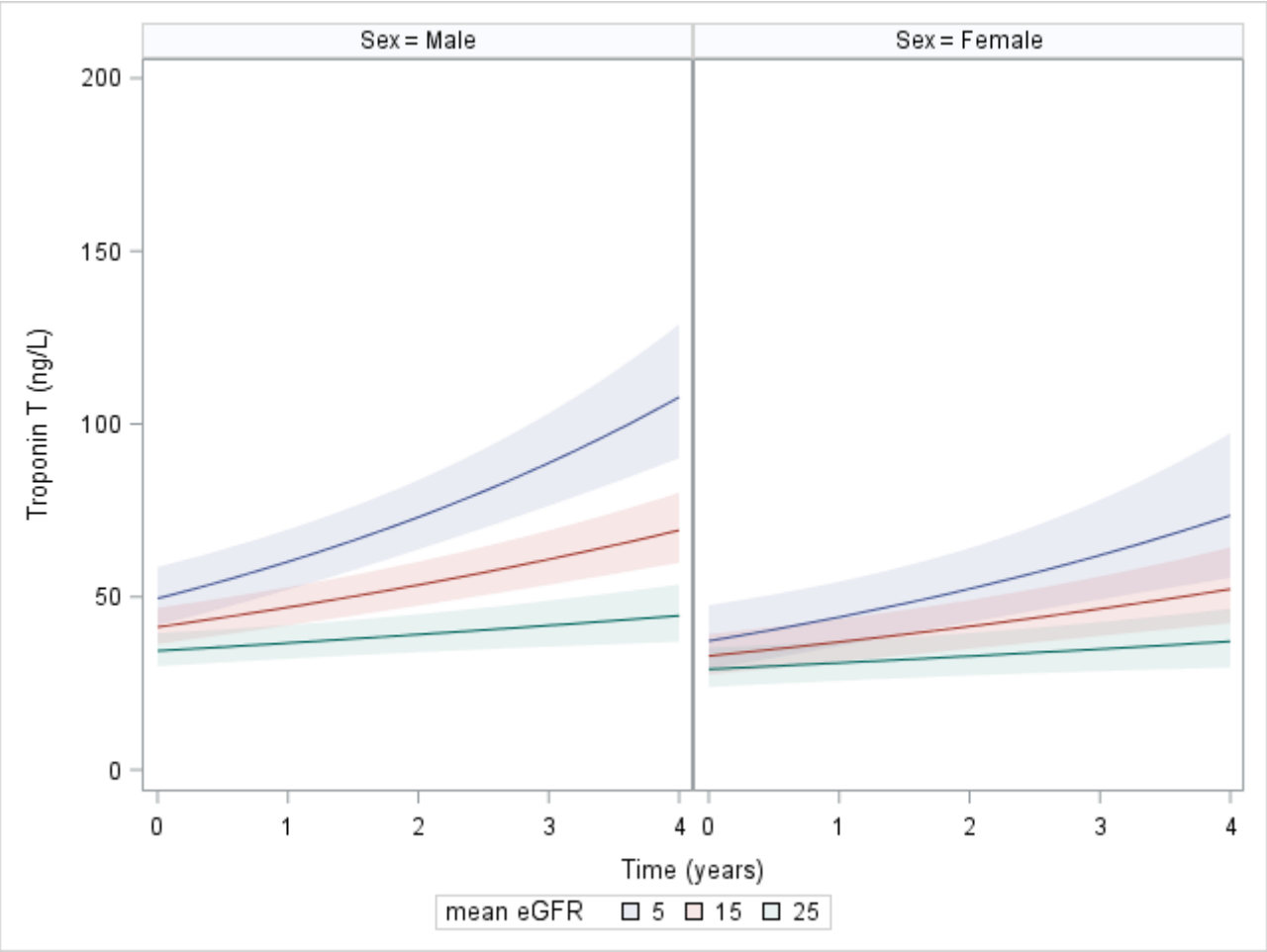


Figure S2B. The modifying effect of angina on the effect eGFR - hs-cTn T.

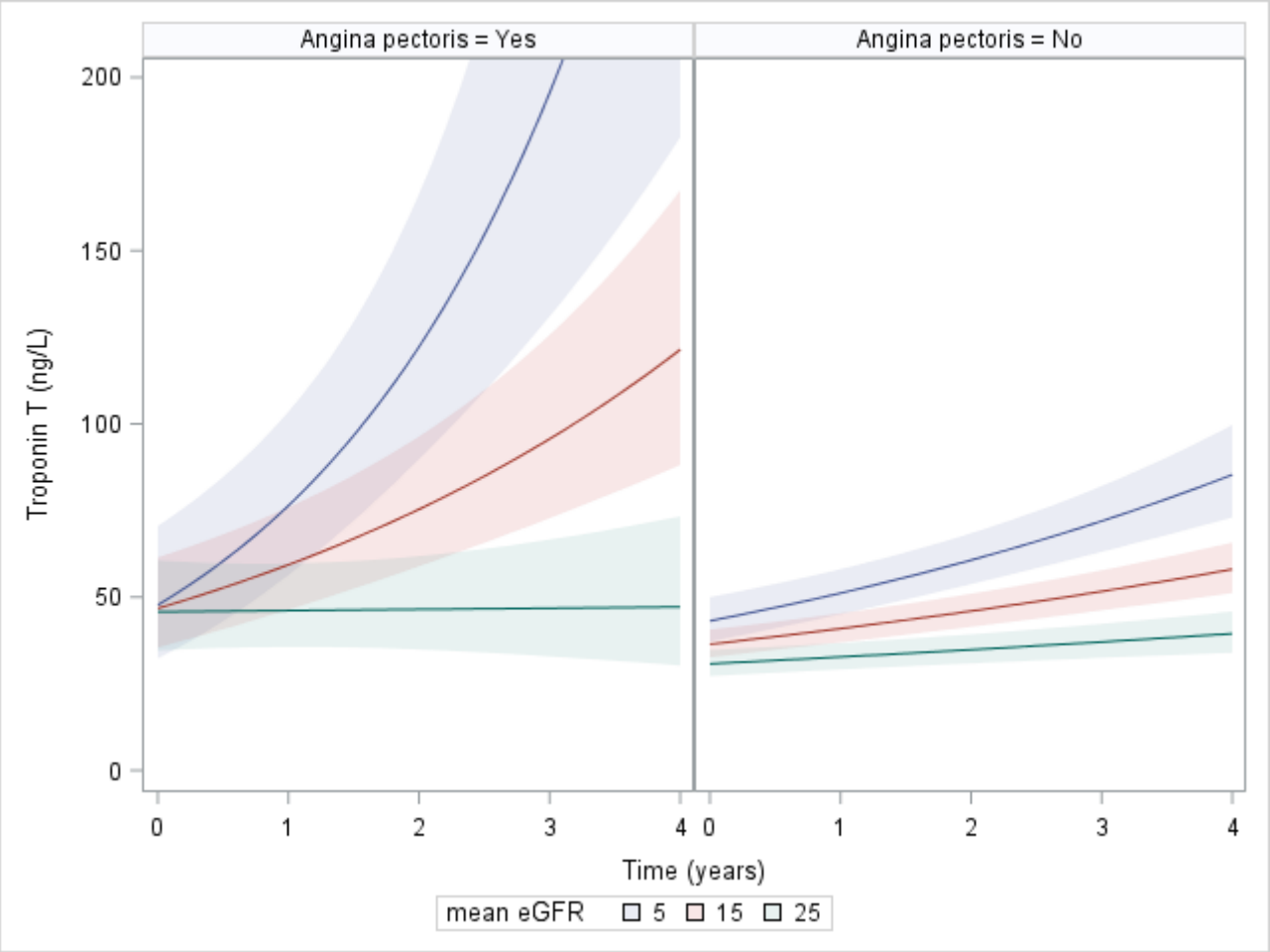


Figure S2C. The modifying effect of myocardial infarct on the effect eGFR - hs-cTn T.

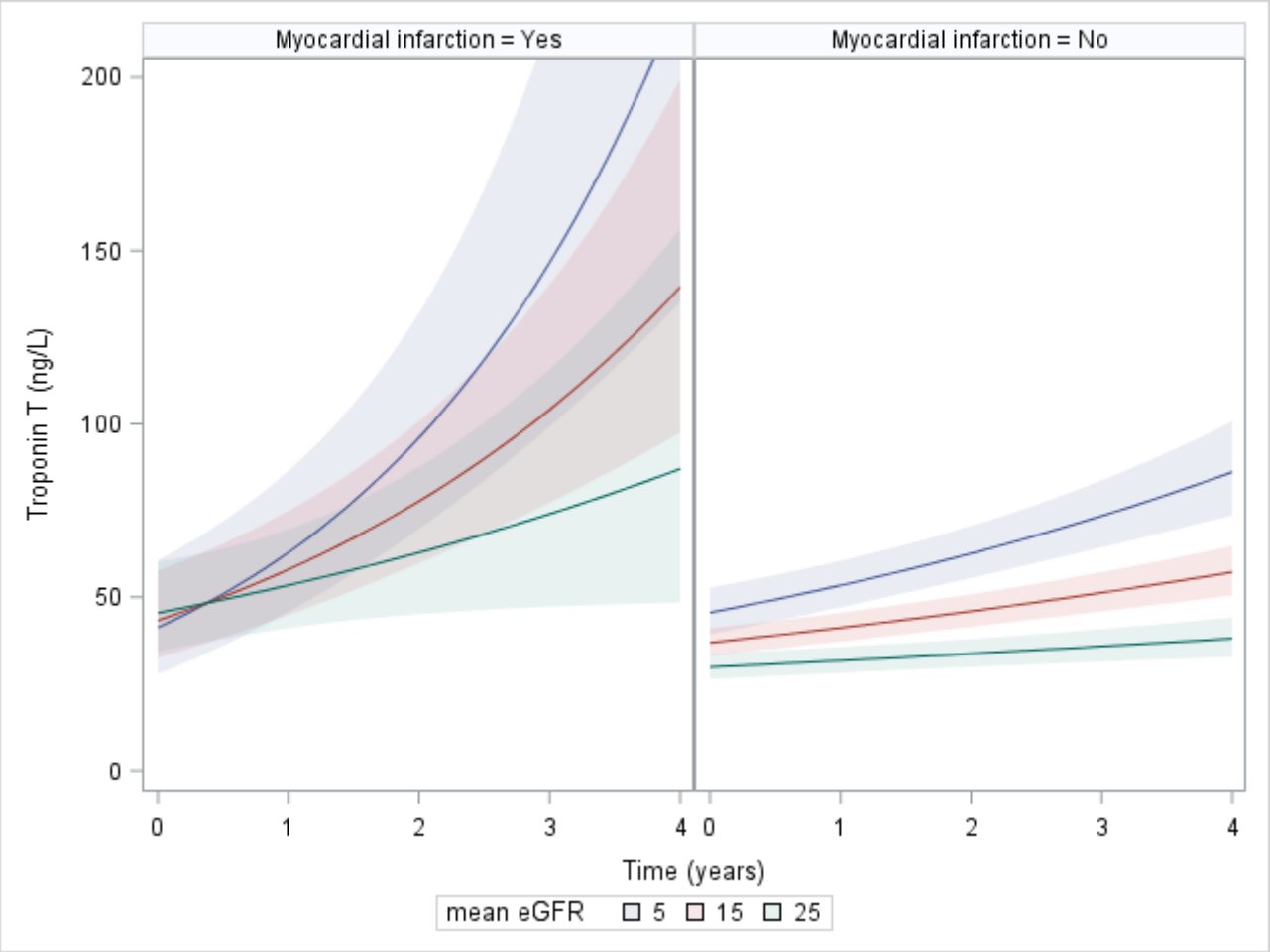


Figure S2D. The modifying effect of diabetes on the effect eGFR - hs-cTn T.