Supplemental Material for:

PCSK9 and Cardiovascular Disease in Individuals with Moderately Decreased Kidney Function

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Additional information on Material and Methods

GCKD Study Design

Further inclusion criteria were Caucasian ethnicity (due to the low prevalence of other ethnicities in Germany), absence of a solid organ or bone marrow transplantation or active malignancy 24 months prior to screening and absence of heart failure New York Heart Association Stage IV. Participants were excluded if they were under legal attendance or were unable to give consent. They were recruited between March 2010 and March 2012 throughout Germany via nine regional centers in a standardized procedure by trained personnel. Routine laboratory parameters were measured in a central laboratory. Serum and urine creatinine was measured using the CREA plus assay and urine albumin using the ALBU-XS assay (both Roche/Hitachi Diagnostics GmbH, Mannheim, Germany). The eGFR was calculated using the CKD-EPI equation. Systolic and diastolic blood pressure were calculated as the mean of up to three measurements per person, and hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or use of antihypertensive medications. Diabetes was defined as HbA1c ≥6.5% or use of at least one antidiabetic medication.

A written informed consent form was obtained from every participant. All methods were performed in accordance with approved guidelines and the Helsinki Declaration.

Time to event and censoring

GCKD participants are followed yearly, alternating between phone interviews and face-to-face visits. At the yearly visits the study nurses collected by structured interviews whether any event has occurred since the last visit. If this was the case, trained personnel collect data from hospital discharge letters, nephrologist out-patient letters and death certificates on hospitalizations, adverse health events and participants' medical history. An endpoint adjudication committee of four medical doctors centrally adjudicated all outcomes. In the Cox regression models we considered the time until the event of interest from the derived information. Any recorded event occurring before loss to follow-up or the end of the first 6.5 years of observation was included in the analysis. If there was no event, these participants were censored at the time loss to follow-up occurred or at the end of the first 6.5 years of observation.

Statistical Analysis

The baseline characteristics are provided for the entire study population as well as stratified by quartiles of PCSK9 concentration. To compare baseline parameters, Kruskal-Wallis and Chi-square tests were applied to continuous and categorical variables, respectively. Variables that are independently associated with PCSK9 concentration were determined by linear regression analysis (all variables included in a single model). To evaluate the relative importance of all included variables on PCSK9 concentrations, a proportional marginal variance decomposition metric (pmvd) was calculated using R package "relaimpo". This approach decomposes the total variance explained (R^2) into non-negative contributions that sum to the total R^2 of the model [1]. Based on these analyses, interaction analyses on the most relevant categorical variables were performed. A generalized linear model based on analysis of variance was applied to compare mean PCSK9 values between those with and without nephrotic range albuminuria (defined by UACR >2,220 mg/g as approximately equivalent to a nephrotic range proteinuria according to KDIGO [2]) adjusted for major confounders. High-sensitivity CRP (hs-CRP), Lp(a), and UACR were log-transformed due to their skewed distribution.

Logistic regression analysis was done to evaluate the association between PCSK9 and prevalent cardiovascular disease. Four different adjustment models were selected***: model 1***: age, sex, eGFR, log- urine albumin-creatinine ratio (UACR), ***model 1b***: as model 1 + statin treatment, ***model 2:*** as model 1 + HDL-cholesterol, log(Lp(a)), log(hs-CRP), statin treatment, diabetes mellitus, hypertension and smoking status, ***model 3:*** as model 2 + LDL-cholesterol. Model 3 is the main model (also called extended model) and is always reported unless stated otherwise. For better interpretability and to check for possible non-linear associations, odds ratio (OR) and 95% confidence intervals (CI) were not only given for each 100 ng/mL increase in PCSK9 levels, but also for quartile groups of PCSK9 (using quartile 1 as reference). To check on the linearity of the relationship between PCSK9 and prevalent and incident outcomes, the packages "mgcv" (function "gam") and survival" in R were used to calculate non-linear penalized splines.

For the analysis of the two endpoints 3-point-MACE and 4-point-MACE, the time from study entry to first event on study of the respective endpoint was calculated. Cox regression analysis for the first event on study was used to calculate hazard ratios (HR) and their 95% confidence intervals (95%CI). The proportional hazards assumption was tested by χ^2-test based on Schoenfeld residuals. Furthermore, sub-distribution HR from competing risks survival regression were calculated. Here, all other causes of death were treated as competing events.

Similar adjustment models as in the logistic regression were chosen, but with the addition of prevalent cardiovascular disease from model 2 onwards. In a further step the association of PCSK9 with major adverse incident cardiovascular disease outcomes during follow-up was examined by stratifying the cohort by prevalent cardiovascular disease status at baseline. To assess whether PCSK9 concentrations contribute to a better risk classification of individuals in terms of prevalent cardiovascular disease, the continuous net reclassification index (NRI) was applied based on the function *improveProb* in R. The continuous prospective NRI was calculated for incident 3-point-MACE with the function *nricens* in R. The continuous NRI has the advantage that it does not depend on the random choice of specific risk categories, and any change in predicted risk in the correct direction is deemed appropriate [3]. The NRI was considered significant when the empirically determined 95% confidence intervals excluded zero.

All statistical analyses were conducted using R 3.5.2. (Vienna, Austria, https://www.r-project.org/) and *p*-values <0.05 were considered as statistically significant.

Supplementary Figure 1: PCSK9 concentrations across Kidney Disease Improving Global Outcomes (KDIGO) risk categories[2] based on eGFR and urine albumin-creatinine ratio (UACR).

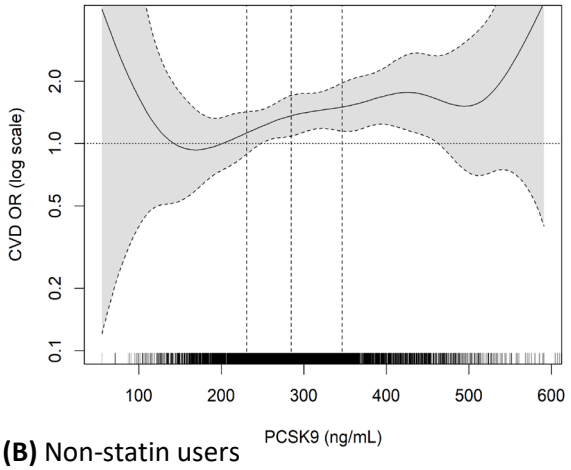
PCSK9 concentrations (mean± SD) of individuals at different stages of CKD are displayed: the first line in each cell represents the unadjusted values and the second line the values adjusted for HDL-cholesterol, Lp(a), hs-CRP, statin treatment, diabetes, hypertension, smoking, baseline cardiovascular diseases and LDL-cholesterol using a generalized linear model based on analysis of variance. The different shades of red represent nephrotic and non- nephrotic range (darker shade of red refers to participants with UACR above 2,220 mg/g classified as individuals with nephrotic syndrome).

GCKD Study					
eGFR (mL/min/1.73 m²)	**UACR (mg/g)**				
	<30	30-299	≥300-2,220	>2,220	Total (n)
60	285.4 ± 82.9 294.4 ± 78.9 (n=393)	295.2 ± 90.4 300.1 ± 78.8 (n=260)	297.2 ± 95.6 295.3 ±81.2 (n=335)	320.9 ± 92.9 294.6 ± 79.4 (n=57)	1,045
45-59	292.6 ± 79.4 293.3 ±78.8 (n=855)	284.8 ± 88.1 288.9 ±77.8 (n=457)	293.6 ± 89.7 294.6 ± 78.0 (n=284)	334.1 ± 116.4 310.1 ± 78.5 (n=52)	1,648
30-44	295.1 ± 82.0 293.4 ± 79.6 (n=756)	288.7 ± 83.5 291.6 ± 78.2 (n=587)	291.3 ± 86.2 288.9 ± 78.0 (n=417)	323.5 ± 98.6 311.6 ± 78.1 (n=73)	1,833
<30	302.4 ± 85.8 294.3 ± 78.5 (n=138)	294.4 ± 83.6 290.2 ±78.0 (n=162)	290.0 ± 89.5 289.8 ± 77.9 (n=139)	329.6 ± 123.6 306.2 ± 77.9 (n=45)	484
Total (n)	2,142	1,466	1,175	227	5,010

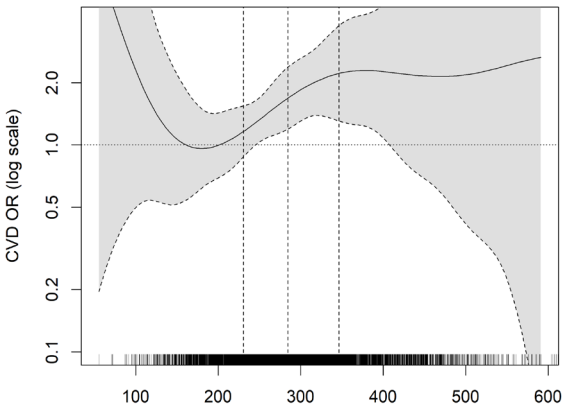
Supplementary Figure 2: Non-linear P-splines for prevalent cardiovascular disease

P-splines are shown for **(A)** all GCKD participants, **(B)** Non-statin users and **(C)** statin users from model with extended adjustments (model3). Odds ratio (OR) is given as log-scale on the y-axes. Vertical dotted lines refer to PCSK9 quartiles; the median value of PCSK9 quartile 1 (201.1 ng/mL) is set as a reference (OR=1; horizontal dashed line). The grey shades correspond to the 95% intervals. Rugplot at the bottom of the figures indicates the number of measurements.

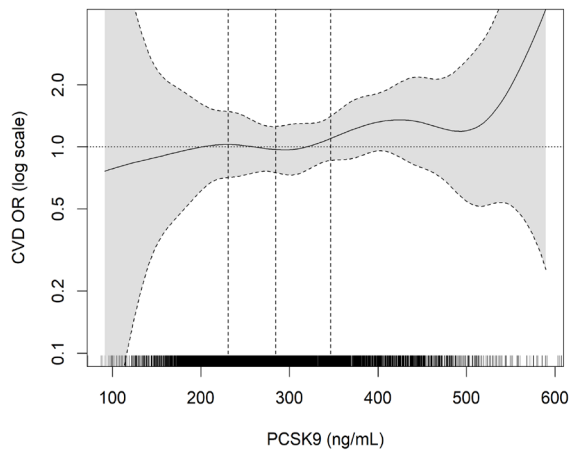
(A) All GCKD participants



(B) Non-statin users

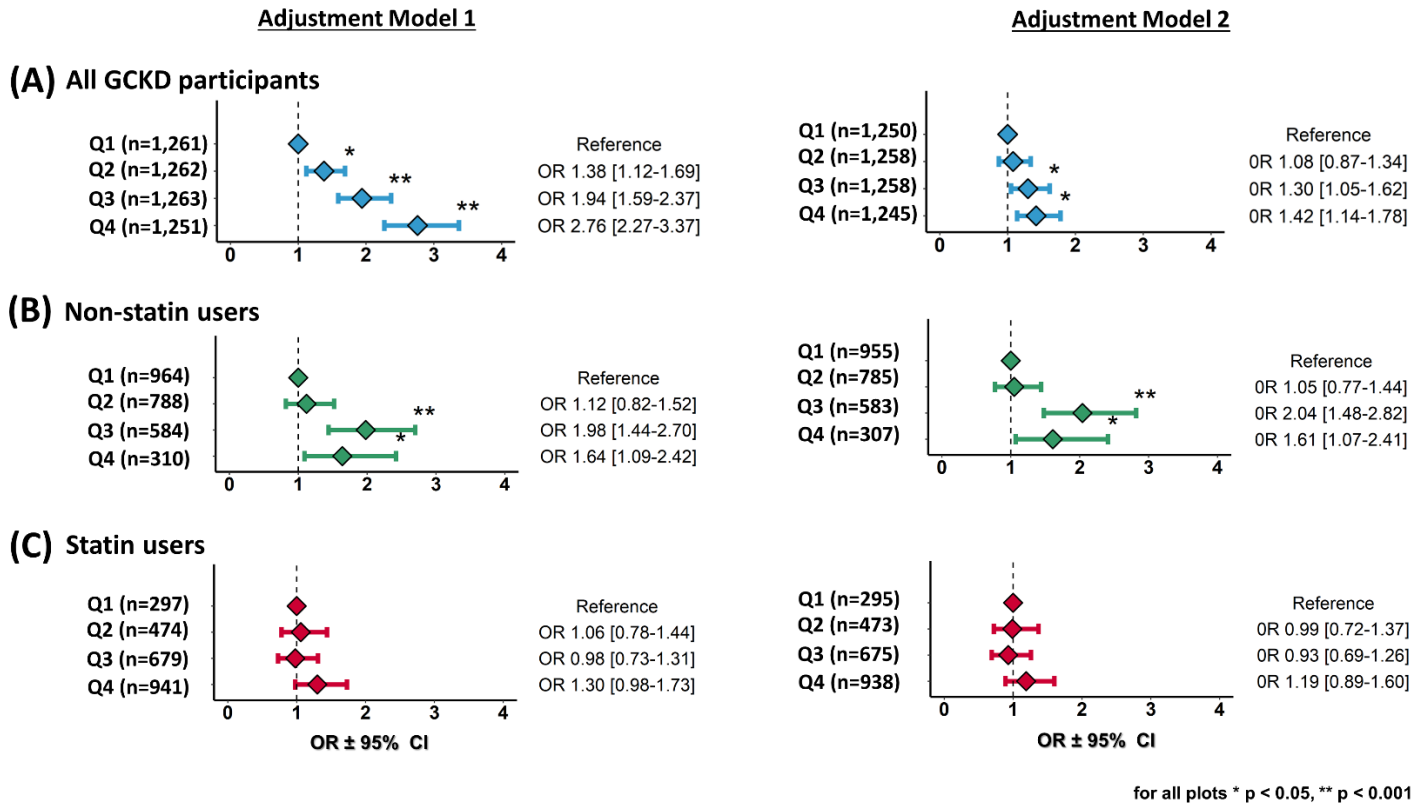


(C) Statin users



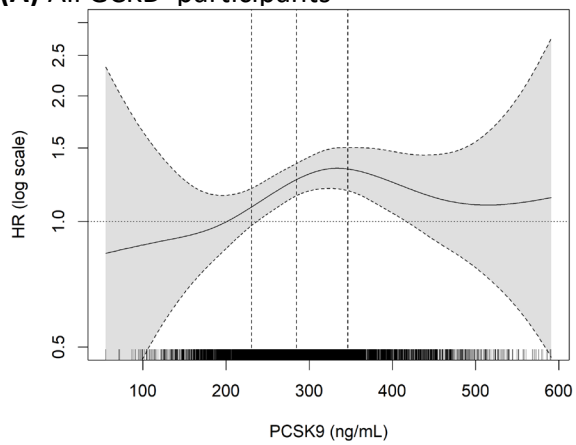
Supplementary Figure 3: Association of PCSK9 with prevalent cardiovascular disease presented for each PCSK9 quartile.

Forest plots of odds ratios (OR) and 95% confidence intervals (CI) are provided for **(A)** the entire cohort **(B)** individuals without statin treatment and **(C)** individuals treated with statins. Plots represent data of the adjustment model 1 (adjusted for age, sex, eGFR, and UACR) and model 2 (adjusted additionally for smoking, HDL-cholesterol, Lp(a), hs-CRP, diabetes mellitus, hypertension, and statin treatment where applicable (panel A)).

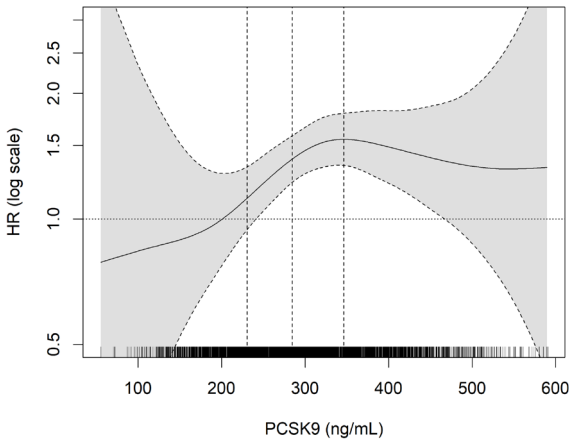


Supplementary Figure 4: Non-linear P-splines demonstrating the association between PCSK9 and incident 3-point-MACE.
P-splines are shown for **(A)** the entire GCKD study, **(B)** those with cardiovascular disease at baseline and **(C)** those without cardiovascular disease at baseline in model with extended adjustments (model3). Hazard ratio (HR) is given as log-scale on the y-axes. Vertical dotted lines refer to PCSK9 quartiles; the median value of PCSK9 quartile 1 (201.1 ng/mL) is set as reference (HR=1; horizontal dashed line). The grey shades correspond to the 95% intervals. Rugplot at the bottom of the figures indicates the number of measurements.

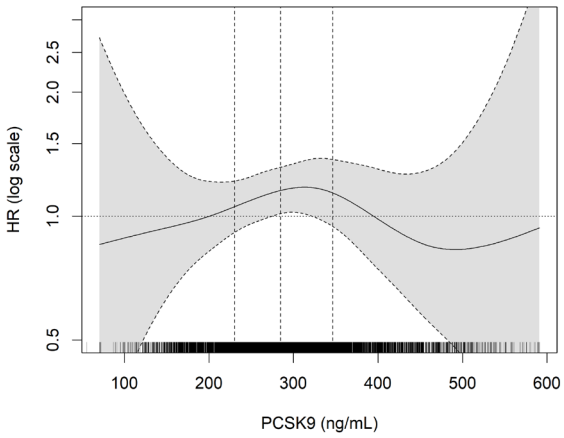
(A) All GCKD participants



(B) With Cardiovascular disease at baseline

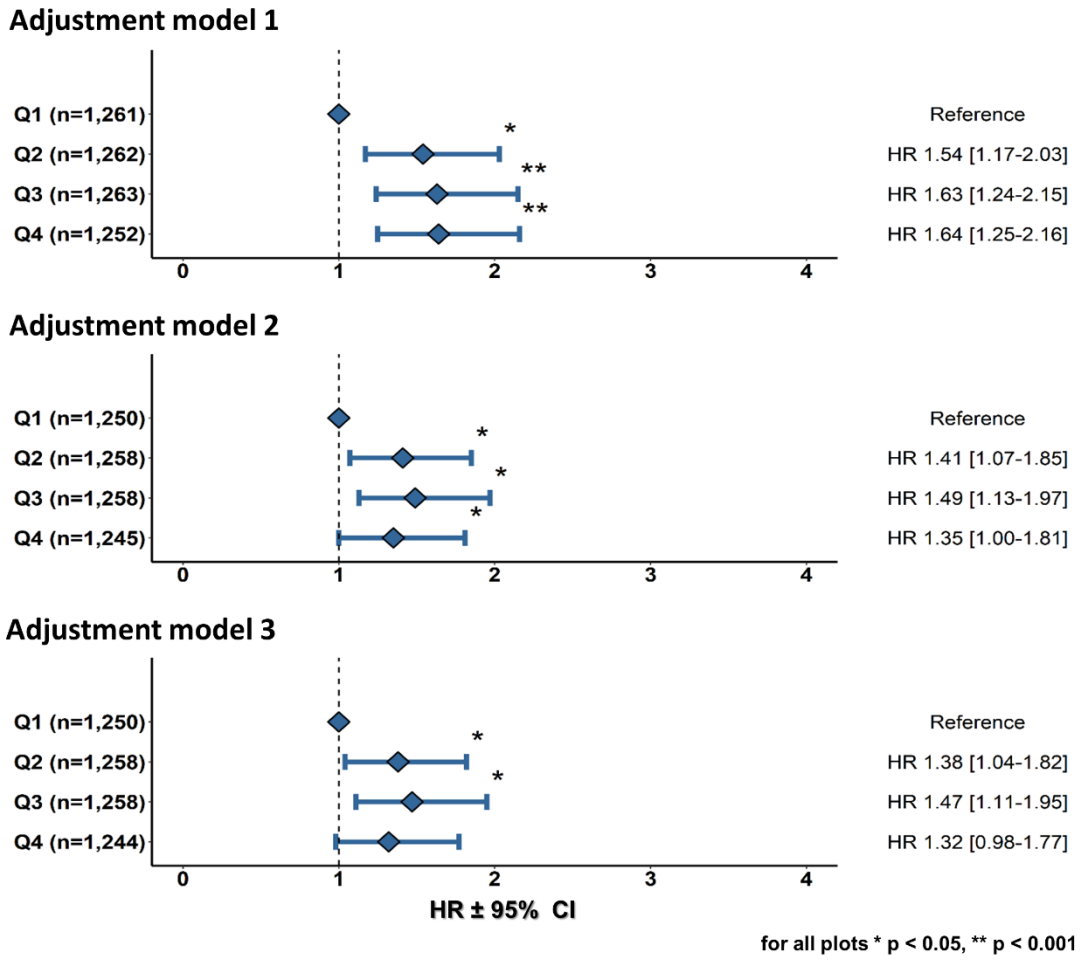


(C) Without Cardiovascular disease at baseline



Supplementary Figure 5: Association of PCSK9 with incident 3-point-MACE during a median follow up of 6.5 years presented for each PCSK9 quartile.

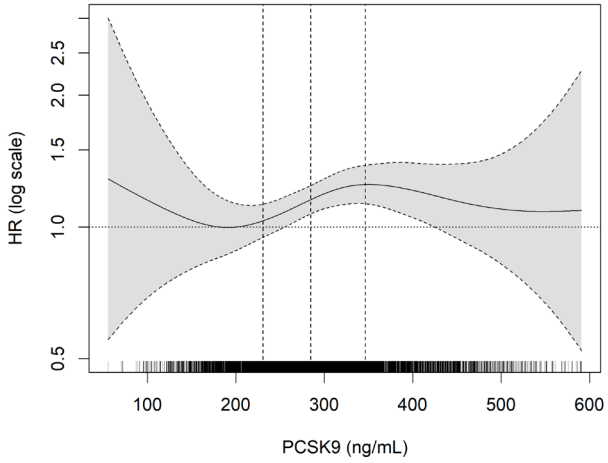
Forest plots representing hazard ratios (HR) and 95% confidence intervals (CI) for PCSK9 quartiles in the entire GCKD cohort during a median follow-up of 6.5 years. Model 1 is adjusted for age, sex, eGFR and UACR, model 2 is additionally adjusted for HDL-cholesterol, Lp(a), hs-CRP, statin treatment, diabetes, hypertension, smoking and baseline cardiovascular disease. The fully adjusted model 3 (additionally adjusted for LDL-cholesterol) is also provided in Figure 3 (panel A) of the main manuscript and is included here for completeness of data.



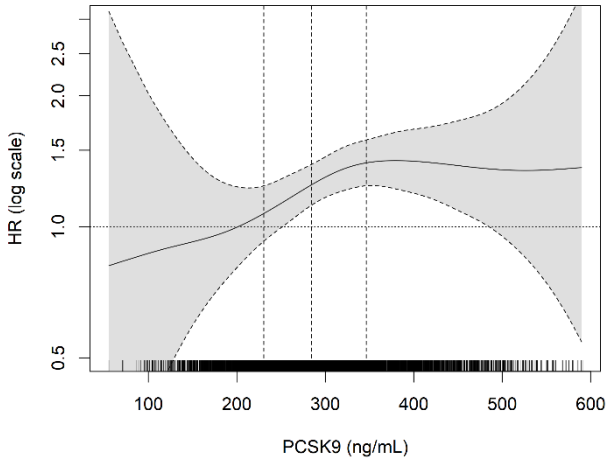
Supplementary Figure 6: Non-linear P-splines demonstrating the association between PCSK9 and incident 4-point-MACE.

P-splines are shown for **(A)** the entire GCKD study, **(B)** those with cardiovascular disease at baseline and **(C)** those without cardiovascular disease at baseline in model with extended adjustments (model3). Hazard ratio (HR) is given as log-scale on the y-axes. Vertical dotted lines refer to PCSK9 quartiles; the median value of PCSK9 quartile 1 (201.1 ng/mL) is set as reference (HR=1; horizontal dashed line). The grey shades correspond to the 95% intervals. Rugplot at the bottom of the figures indicates the number of measurements.

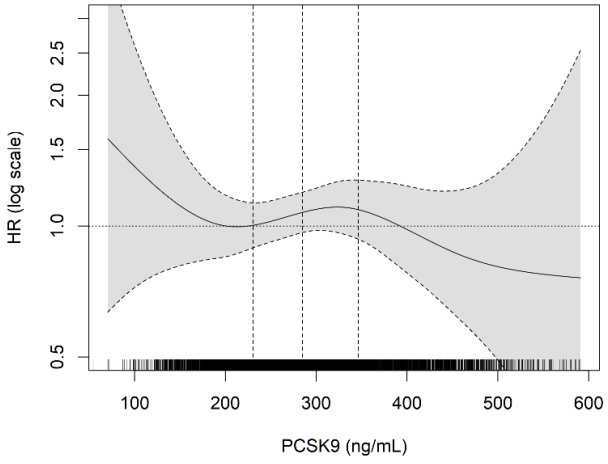
(A) All GCKD participants



(B) With Cardiovascular disease at baseline

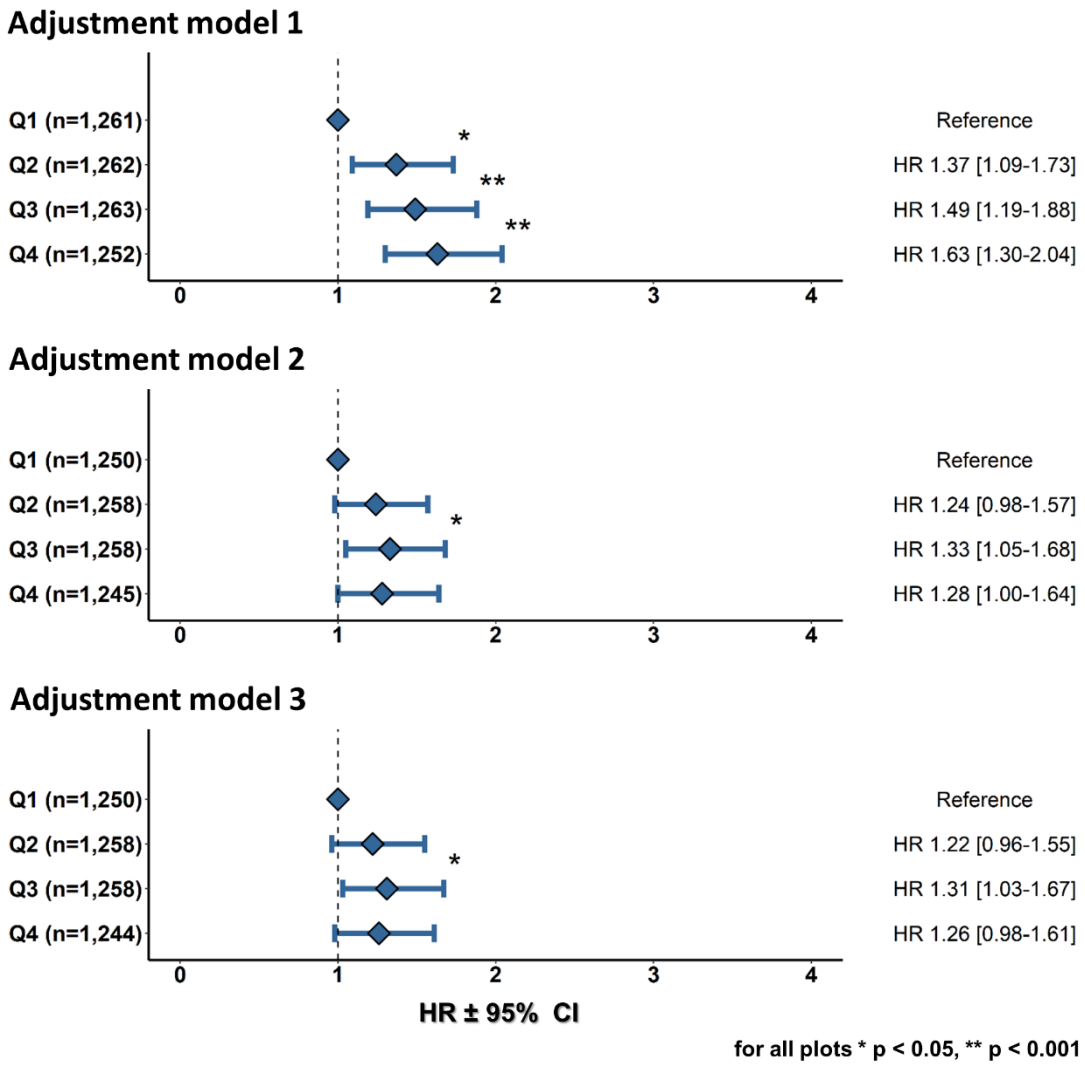


(C) Without Cardiovascular disease at baseline



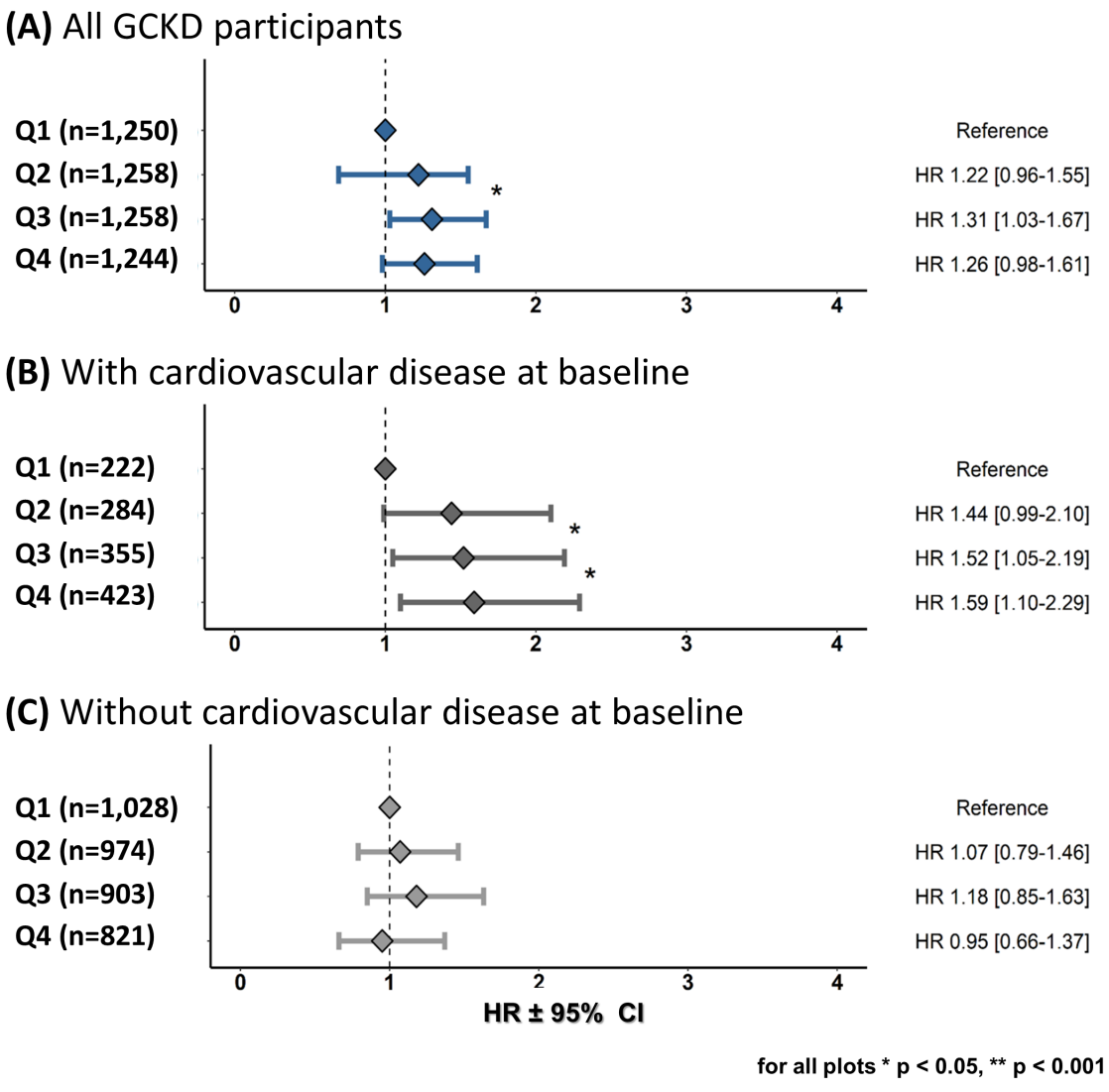
Supplementary Figure 7: Association of PCSK9 with incident 4-point-MACE during a median follow up of 6.5 years presented for each PCSK9 quartile.

Forest plots representing hazard ratios (HR) and 95% confidence intervals (CI) for PCSK9 quartiles in the entire GCKD cohort during a median follow-up of 6.5 years. Model 1 is adjusted for age, sex, eGFR and UACR, model 2 is additionally adjusted for HDL-cholesterol, Lp(a), hs-CRP, statin treatment, diabetes, hypertension, smoking and baseline cardiovascular disease. The fully adjusted model 3 (additionally adjusted for LDL-cholesterol) is also provided in Figure 3 (panel A) of the main manuscript and is included here for completeness of data.



Supplementary Figure 8: Association of PCSK9 concentrations with incident 4-point-MACE during a median follow up of 6.5 years.

Forest plots representing hazard ratios (HR) and 95% confidence intervals (CI) from the extended adjustment model 3. GCKD participants were stratified based on presence or absence of baseline cardiovascular disease (cardiovascular disease). The association between serum PCSK9 quartiles and 4-point-MACE during a median follow-up of 6.5 years is shown in **(A)** the entire GCKD study (650 events), **(B)** those with cardiovascular disease at baseline (335 events) and **(C)** those without cardiovascular disease at baseline (315 events).



for all plots * p < 0.05, ** p < 0.001

Supplementary Table 1: Literature on PCSK9 and kidney function

Study	Study participants	Findings related to kidney function
Non-dialysis CKD		
Kwakernaak et al., 2013 *Atherosclerosis* [4]	Case-control study (Netherlands) • **39** Caucasian proteinuric patients (eGFR 61 -29 mL/min/1.73 m^2, proteinuria 1.9 [0.9-3.3] g/day) (19 of them were under statin treatment) • **39** Caucasian healthy controls matched for age and sex	• Proteinuric patients had significantly higher PCSK9 compared to controls. • PCSK9 correlated with proteinuria at baseline and at maximal antiproteinuric treatment. • No correlation of eGFR with PCSK9 levels in patients and controls. • No significant reduction in PCSK9 when proteinuria was decreased.
Rogacev et al., 2016 *PLOS One* [5]	Two independent studies (Germany) • 1-CARE FOR HOME Study with **443** CKD patients with eGFR categories 2-4 (15 to 90 ml/min/1.73 m^2) • 2- LURIC (Ludwigshafen Risk and Cardiovascular Health Study) with **1,462** participants referred for coronary angiography and eGFR of 15 to 90 ml/min/1.73 m^2.	• In both studies, plasma PCSK9 concentrations did not correlate with eGFR. Same was also observed when patients were stratified based on statin treatment.
Elewa et al., 2016 *Eur. J. Clin. Invest.* [6]	Cross-sectional study (Spain) **134** diabetic kidney disease patients (eGFR G1-G4 and albuminuria A1-A3)	• PCSK9 levels did not vary across eGFR and albuminuria categories. • Combination of lipid lowering therapy (fibrates plus statin) resulted in higher PCSK9 concentrations.
Haas et al., 2016 *Circulation* [7]	Prospective Study (USA) **50** patients with nephrotic syndrome: Plasma samples were taken once with disease active (UACR ≥1 mg/mg) and once on remission (UACR <0.5 mg/mg).	• Significant 14% reduction in PCSK9 concentrations when patients were on remission.
Morena et al., 2017 *J.Clin.Lipidol.* [8]	Cross-sectional study (France) **94** nondiabetic non-dialysis CKD patients. CKD was defined as either kidney damage or eGFR <60 mL/min/1.73 m^2 for at least 3 months. Excluded were patients with nephrotic syndrome, diabetes mellitus and statin treatment	• No correlation between PCSK9 concentration and eGFR and proteinuria. • No difference in PCSK9 concentrations between different stages
Zhang et al., 2018 *Cardiorenal.Med.* [9]	Single-center study (China) • **1,205** subjects with eGFR ≥90 mL/min/1.73 m^2 • **884** patients with eGFR <90 mL/min/1.73 m^2 All subjects were without lipid-lowering treatment and had normal serum creatinine levels (<133 µmol/L)	• No significant associations of PCSK9 with eGFR in the entire study population and in various subgroups.
Didas et al., 2020 *Int.Urol.Nephrol.* [10]	Cross-sectional Study in patients with type 2 diabetes mellitus (Thailand) • 87 CKD patients (eGFR <60 mL/min/1.73 m^2 for at least 3 months) • 93 non-CKD patients	• PCSK9 levels did not vary between CKD and non-CKD patients. • Multivariate logistic regression analysis, did not show any significant association between PCSK9 levels and CKD in T2DM patients.
Dounousi et al., 2021 *Oxid. Med.Cell. Longev.* [11]	Cross-sectional observational study (Greece) • 92 patients with CKD stages II-IV (mean eGFR=47.3 mL/min/1.73m^2.) • 20 controls	• CKD patients had significantly higher PCSK9 levels compared to controls. • No association between PCSK9 and kidney function parameters.

Vlad et al., 2021 *Int.Urol.Nephrol.* [12]	Prospective Study (Romania) • 110 Caucasian patients with CKD stages 2-4 **58** patients defined as G2-G3 (mean eGFR of 47.9 mL/min/1.73m^2. **52** patients CKD G4 patients (mean eGFR of 21.1 mL/min/1.73m^2. Patients were followed up at two time points 6 and 12 months after the initiation of the study	• PCSK9 levels were not significantly different between CKD stages. • 54 patients had kidney disease progression (defined as doubling of serum creatinine, renal replacement therapy, and an eGFR decrease ≥30%): those with progression had a significant increase in PCSK9 levels after 6 and 12 months when compared to those without progression. • Kaplan Meier curves showed that patients with PCSK9 >220 ng/ml and hs-CRP >3 mg/L have a progression of CKD in a shorter period of time when compared to patients with lower levels of these 2 variables.
Dialysis and Non-dialysis (mixed)		
Abujrad et al., 2014 *Atherosclerosis* [13]	Cross-sectional study (Canada) • 66 hemodialysis patients on dialysis <2 years: 32 patients were non-statin and n=34 were statin-treated patients • 178 non-CKD control patients (eGFR ≥60 mL/min/1.73 m^2) • Additional 13 CKD patients were examined pre and post-hemodialysis.	• PCSK9 was lower in hemodialysis patients compared to controls. • No significant difference between patients with and without statins. • PCSK9 levels did not vary significantly pre- and post-hemodialysis.
Jin et al., 2014, *Am.J.Kidney Dis.* [14]	Cross-sectional study (South Korea) • **15** patients with nephrotic-range proteinuria (≥3.5 g/24 h) • **15** peritoneal dialysis (PD) patients • **15** hemodialysis (HD) patients • **15** healthy controls	• Very low plasma PCSK9 concentration reported (roughly 10-15 ng/mL measured by Cell Biolabs ELISA assay). • Nephrotic and PD patients had significantly higher PCSK9 than controls. • No significant difference between HD patients and controls.
Konarzewski et al., 2014 *Am.J.Nephrol.* [15]	Cross-sectional study (Poland) • **44** CKD stages III and IV (eGFR <60 ml/min/1.72 m^2) • **29** hemodialysis patients • **20** kidney transplant patients (eGFR >60 ml/min/1.72 m^2) • **34** hospital-based controls (eGFR >60 ml/min/1.72 m^2)	• Significantly elevated levels of serum PCSK9 in CKD patients • PCSK9 showed a negative correlation with eGFR • A significant reduction in PCSK9 by hemodialysis resulted in similar PCSK9 levels compared to controls and kidney transplant patients.
Bermudez-Lopez et al., 2019 *Expert.Opin.Ther.Targets* [16]	Cross-sectional study (Spain) • **86** CKD stage III patients • **71** CKD stage IV-V patients • **52** dialysis patients • **186** controls Subjects with diabetes and treated with statin were excluded.	• PCSK9 concentration was highest in the controls when compared to the other groups. • PCSK9 was lower in advanced CKD stages.
Rasmussen et al., 2020 *Nephrol.Dial.Transplant.* [17]	Observational prospective study (Denmark) • **151** kidney transplant candidates of whom 44% were on dialysis (20 peritoneal dialysis and 45 hemodialysis). Median eGFR in pre-dialysis patients was 12mL/min/1.73m^2. Only candidates with end-stage kidney disease and those with the need of cardiac evaluation were included. • **79** controls (random samples of individuals with no history of cardiac or kidney diseases and no use of statins)	• There was no difference in PCSK9 levels of non-statin treated kidney transplant candidates and the controls. • In the non-statin subgroup, there was no difference in the PCSK9 concentration in the pre-dialysis, peritoneal dialysis and hemodialysis patients. • In pre-dialysis patients, PCSK9 and eGFR did not correlate.

Supplementary Table 2: Literature on PCSK9 in CKD patients and cardiovascular outcomes

Study	Study participants	Study type	Number and type of events	Main findings
Rogacev et al, 2015 *PLOS One* [5]	1-CARE FOR HOME • **443** CKD patients with reduced GFR (15-90 ml/min/1.73 m^2) • Median follow-up of **3 years** 2- LURIC • **1,450** participants with eGFR between 90 and 15 ml/min/1.73 m^2. • Median follow-up of **10 years**	Two independent cohorts (Germany)	1 - CARE FOR HOME • **91 events:** acute MI; interventional coronary, cerebrovascular or PAD revascularization; stroke with symptoms ≥24 hours, amputation above the ankle; or death of any cause. 2 - LURIC • **335 patients died** due to cardiovascular disease causes (sudden death, MI, congestive heart failure, intervention to treat CHD, fatal stroke, and other causes of death due to CHD)	• In both studies, there was no significant association between PCSK9 tertiles and cardiovascular disease outcome in the entire cohort and also in statin or non-statin stratified groups. • PCSK9 concentrations were also not significantly associated with outcomes in multivariate Cox regression analyses.
Eisenga et al. 2017 *Diabetes care* [18]	• 453 renal transplant recipients (baseline on average 6 yrs. after transplantation) • Median 9.6 year follow-up	Prospective study (Netherlands)	**51 cases** with cardiovascular mortality (ICD-9 codes 410–447)	• No association of PCSK9 concentrations with cardiovascular disease mortality
Hwang et al., 2020 *J.Clin.Med.* [19]	• 353 hemodialysis patients • Average 29 months follow-up	Prospective study (Korea)	**60 CV events** (CAD, heart failure, ventricular arrhythmia, cardiac arrest, cerebral infarction, and PAD requiring intervention)	• Tertile 3 vs. 1: HR=2.31 (95%CI 1.17-4.59) • Concentrations with 36.6±20.3 ng/mL very low.
Rasmussen et al., 2020 *Nephrol.Dial.Transplant.* [17]	• **151** kidney transplant candidates of whom 44% were on dialysis (20 PD and 45 HD); Median eGFR in pre-dialysis patients: 12mL/min/1.73m² • Median follow up of **3.7 years**.	Observational prospective study (Denmark)	• Coronary artery calcification score at baseline • **32 MACE** and 29 death events during follow-up.	• No association between either PCSK9 and the degree of CAD at baseline or combined MACE and mortality risk during follow-up
Vlad et al., 2021 *Int.Urol.Nephrol.* [12]	• 110 patients in CKD stage G2-G4 • 72.9% with history of atherosclerotic cardiovascular disease at baseline • 12 months of follow-up	Prospective study (Romania)	**44 patients developed new events** (19 CHD, 15 PAD, 10 stroke)	• Significant association of higher PCSK9 concentrations with outcomes. However, statistical modelling is unclear (e.g. OR=97.7 for PCSK9 >220 ng/ml)

Note: Studies which did not provide estimates for cardiovascular outcomes (e.g. only all-cause mortality) are not considered in this table (e.g. reference [20]). Furthermore, the study by Kajinglu et al. [21] could not be judged since PCSK9 concentrations in the middle tertile were between 9560 and 23100 ng/mL which is quite unusual.

Supplementary Table 3: Association of PCSK9 with prevalent cardiovascular disease in the total GCKD population and stratified based on statin treatment.

Data presented were obtained from logistic regression analyses.

	OR per 100 ng/mL	95% CI	*p*-value
All GCKD participants (1289 out of 5037 participants with events)			
Model 1	1.56	1.44-1.69	< 0.001
Model 1b	1.21	1.11-1.32	<0.001
Model 2	1.19	1.09-1.30	<0.001
Model 3	1.22	1.12-1.34	<0.001
Participants without statin treatment (336 out of 2646 participants with events)			
Model 1	1.38	1.18-1.62	<0.001
Model 2*	1.38	1.17-1.61	<0.001
Model 3*	1.38	1.18-1.62	<0.001
Participants with statin treatment (953 out of 2391 participants with events)			
Model 1	1.15	1.04-1.28	0.01
Model 2*	1.12	1.01-1.25	0.04
Model 3*	1.16	1.04-1.29	0.008

Model 1: adjusted for age, sex, eGFR and UACR

Model 1b: adjusted for age, sex, eGFR, UACR and statin treatment

Model 2: adjusted for age, sex, eGFR, UACR, statin treatment, HDL-cholesterol, Lp(a), hs-CRP, diabetes mellitus, hypertension and smoking.

Model 3: adjusted for age, sex, eGFR, UACR, statin treatment, HDL-cholesterol, Lp(a), hs-CRP, diabetes mellitus, hypertension, smoking and LDL-cholesterol

cardiovascular disease, cardiovascular disease; OR, odds ratio; CI, confidence interval

*Due to statin stratification, these models do not include statin treatment as confounders.

Supplementary Table 4: Association of PCSK9 with incident 3-point-MACE during a median follow-up of 6.5 years in all GCKD participants and stratified based on statin treatment.

Results of Cox regression analyses are presented.

	For each increase of PCSK9 by 100 ng/mL		
	HR	**95% CI**	***p*-value**
All GCKD participants (474 out of 5038 participants with events)			
Model 1	1.18	1.06-1.30	0.002
Model 1b	1.15	1.03-1.28	0.01
Model 2	1.07	0.96-1.20	0.23
Model 3	1.06	0.95-1.19	0.29
Participants without statin treatment (194 out of 2646 participants with events)			
Model 1	1.28	1.07-1.53	0.007
Model 2*	1.16	0.97-1.39	0.11
Model 3*	1.15	0.96-1.38	0.14
Participants with statin treatment (280 out of 2392 participants with events)			
Model 1	1.08	0.94-1.24	0.28
Model 2*	1.03	0.89-1.18	0.71
Model 3*	1.02	0.89-1.17	0.78

Model 1: adjusted for age, sex, eGFR, and UACR.

Model 1b: adjusted for age, sex, eGFR, UACR and statin treatment.

Model 2: adjusted for age, sex, eGFR, UACR, statin treatment, HDL-cholesterol, Lp(a), hs-CRP, diabetes mellitus, hypertension, smoking and baseline cardiovascular diseases.

Model 3: adjusted for age, sex, eGFR, UACR, statin treatment, HDL-cholesterol, Lp(a), hs-CRP, diabetes mellitus, hypertension, smoking, baseline cardiovascular diseases and LDL-cholesterol.

*Due to statin stratification, these models do not include statin treatment as confounders.

MACE, major adverse cardiovascular events; HR, hazard ratio; CI, confidence interval

Supplementary Table 5: Association of PCSK9 with incident 4-point-MACE during a median follow-up of 6.5 years in all GCKD participants and stratified based on statin treatment.

The presented data are results from Cox regression analyses.

	For each increase of PCSK9 by 100 ng/mL		
	HR	**95% CI**	***p*-value**
All GCKD participants (653 out of 5038 participants with events)			
Model 1	1.18	1.09-1.29	<0.001
Model 1b	1.13	1.03-1.24	0.01
Model 2	1.05	0.96-1.16	0.27
Model 3	1.05	0.95-1.15	0.34
Participants without statin treatment (252 out of 2646 participants with events)			
Model 1	1.18	1.00-1.39	0.04
Model 2*	1.08	0.92-1.27	0.36
Model 3*	1.07	0.90-1.26	0.44
Participants with statin treatment (401 out of 2392 participants with events)			
Model 1	1.10	0.98-1.23	0.11
Model 2*	1.04	0.93-1.17	0.49
Model 3*	1.04	0.92-1.17	0.54

Model 1: adjusted for age, sex, eGFR, and UACR.

Model 1b: adjusted for age, sex, eGFR, UACR and statin treatment.

Model 2: adjusted for age, sex, eGFR, UACR, statin treatment, HDL-cholesterol, Lp(a), hs-CRP, diabetes mellitus, hypertension, smoking and baseline cardiovascular diseases.

Model 3: adjusted for age, sex, eGFR, UACR, statin treatment, HDL-cholesterol, Lp(a), hs-CRP, diabetes mellitus, hypertension, smoking, baseline cardiovascular diseases and LDL-cholesterol .

*Due to statin stratification, these models do not include statin treatment as confounders.

MACE, major adverse cardiovascular events; HR, hazard ratio; CI, confidence interval

Supplementary Table 6: Association of PCSK9 quartiles with incident 3-point-MACE during a median follow-up of 6.5 years based on sub-distribution HR adjustment models.
For easier comparison also results from the Cox regression models (HR[95% CI]) are provided.

PCSK9 Quartiles	N	HR [95% CI]	p-value	Sub-distribution HR [95% CI]	*p*-value
Model 1: adjusted for age, sex, eGFR, and UACR					
Quartile 1	1,261				
Quartile 2	1,262	1.54 [1.17;2.03]	0.002	1.55 [1.18;2.04]	0.002
Quartile 3	1,263	1.63 [1.24;2.15]	<0.001	1.62 [1.24;2.13]	<0.001
Quartile 4	1,252	1.64 [1.25-2.16]	<0.001	1.66 [1.26;2.18]	<0.001
Model 1b: as model 1 plus adjustment for statin treatment					
Quartile 1	1,261				
Quartile 2	1,262	1.51 [1.15;2.00]	0.003	1.52 [1.15;2.00]	0.003
Quartile 3	1,263	1.58 [1.19;2.09]	0.001	1.56 [1.18;2.07]	0.002
Quartile 4	1,252	1.56 [1.16;2.09]	0.003	1.57 [1.17;2.10]	0.003
Model 2: as model 1b plus adjustment for HDL-cholesterol, Lp(a), hs-CRP, diabetes mellitus, hypertension, smoking and baseline cardiovascular disease.					
Quartile 1	1,250				
Quartile 2	1,258	1.41 [1.07;1.85]	0.02	1.41 [1.07;1.85]	0.02
Quartile 3	1,258	1.49 [1.13;1.97]	0.005	1.47 [1.11;1.94]	0.007
Quartile 4	1,245	1.35 [1.00;1.81]	0.05	1.38 [1.03;1.85]	0.03
Model 3: as model 2 plus adjustment for LDL-cholesterol					
Quartile 1	1,250				
Quartile 2	1,258	1.38 [1.04;1.82]	0.02	1.38 [1.05;1.82]	0.02
Quartile 3	1,258	1.47 [1.11;1.95]	0.007	1.45 [1.10;1.92]	0.009
Quartile 4	1,244	1.32 [0.98;1.77]	0.07	1.35 [1.00;1.81]	0.05

Supplementary Table 7: Association of PCSK9 quartiles with incident 4-point-MACE during a median follow-up of 6.5 years based on sub-distribution HR adjustment models.
For easier comparison also results from the Cox regression models (HR[95% CI]) are provided.

PCSK9 Quartiles	**N**	**HR [95% CI]**	**p-value**	Sub-distribution **HR [95% CI]**	**p-value**
Model 1: adjusted for age, sex, eGFR, and UACR					
Quartile 1	1,261				
Quartile 2	1,262	1.37 [1.09;1.73]	0.008	1.38 [1.09;1.74]	0.007
Quartile 3	1,263	1.49 [1.19;1.88]	<0.001	1.49[1.18;1.87]	<0.001
Quartile 4	1,252	1.63 [1.30;2.04]	<0.001	1.65 [1.32;2.07]	<0.001
Model 1b: as model 1 plus adjustment for statin treatment					
Quartile 1	1,261				
Quartile 2	1,262	1.32 [1.05;1.67]	0.02	1.33 [1.05;1.68]	0.02
Quartile 3	1,263	1.38 [1.09;1.75]	0.008	1.37 [1.08;1.74]	0.009
Quartile 4	1,252	1.45 [1.14;1.85]	0.003	1.47 [1.15;1.87]	0.002
Model 2: as model 1b plus adjustment for HDL-cholesterol, Lp(a), hs-CRP, diabetes mellitus, hypertension, smoking and baseline cardiovascular disease.					
Quartile 1	1,250				
Quartile 2	1,258	1.24 [0.98;1.57]	0.07	1.24 [0.98;1.58]	0.07
Quartile 3	1,258	1.33 [1.05;1.68]	0.02	1.31 [1.03;1.67]	0.03
Quartile 4	1,245	1.28 [1.00;1.64]	0.05	1.31 [1.03;1.68]	0.03
Model 3: as model 2 plus adjustment for LDL-cholesterol					
Quartile 1	1,250				
Quartile 2	1,258	1.22 [0.96;1.55]	0.10	1.22 [0.97;1.55]	0.10
Quartile 3	1,258	1.31 [1.03;1.67]	0.03	1.30 [1.02;1.65]	0.03
Quartile 4	1,244	1.26 [0.98;1.61]	0.07	1.29 [1.00;1.65]	0.05

Supplementary Table 8: Frequency counts of clinical incident 3-point-MACE events (only the first event occurred has been counted).

Types of events	Events (n)
Myocardial Infarction	227
Non-fatal stroke	161
Fatal myocardial Infarction	9
Fatal coronary heart disease	32
Sudden cardiac death	39
Others	6

Supplementary Table 9: Association of PCSK9 quartiles with incident 3-point-MACE when excluding recurrent events (model3).

For easier comparison, results from the Cox regression without exclusion are also included.

	3-point-MACE (without exclusion)			Exclusion of recurrent events (myocardial infarction and stroke)		
	All GCKD (473 events)			All GCKD (377 events)		
Quartiles	**N**	**HR [95%CI]**	**p-value**	**N**	**HR [95%CI]**	**p-value**
Quartile 1	1,250	1.00		1,240	1.00	
Quartile 2	1,258	1.38 [1.04-1.82]	0.02	1,232	1.30 [0.96-1.75]	0.09
Quartile 3	1,258	1.47 [1.11-1.95]	0.01	1,233	1.46 [1.07-1.98]	0.02
Quartile 4	1,244	1.32 [0.98-1.77]	0.07	1,209	1.22 [0.88-1.69]	0.24
	With cardiovascular disease at baseline (247 events)			With cardiovascular disease at baseline (151 events)		
Quartile 1	222	1.00		212	1.00	
Quartile 2	284	1.79 [1.14-2.82]	0.01	258	1.70 [0.96-3.00]	0.07
Quartile 3	355	1.79 [1.15-2.80]	0.01	330	1.84 [1.06-3.21]	0.03
Quartile 4	423	1.76 [1.13-2.76]	0.01	388	1.69 [0.96-2.97]	0.07

Supplementary Table 10: Continuous net reclassification index (NRI) based on PCSK9 quartiles calculated for model 3

All GCKD participants	
Prevalent cardiovascular disease	
Overall NRI	0.27 [0.20-0.33]
Non-cases	0.08 [0.05-0.12]
Cases	0.18 [0.13-0.23]
Incident 3-point-MACE	
Overall NRI	0.10 [0.008-0.21]
Non-cases	-0.21 [-0.38-0.34]
Cases	0.31 [-0.27-0.55]

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