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ORIGINAL RESEARCH

Impact of Chronic Kidney Disease on the Associations of Cardiovascular Biomarkers With Adverse Outcomes in Patients With Suspected or Known Coronary Artery Disease: The EXCEED-J Study

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BACKGROUND: The impact of chronic kidney disease (CKD) on the prognostic utility of cardiovascular biomarkers in high-risk patients remains unclear.

METHODS AND RESULTS: We performed a multicenter, prospective cohort study of 3255 patients with suspected or known coronary artery disease (CAD) to investigate whether CKD modifies the prognostic utility of cardiovascular biomarkers. Serum levels of cardiovascular and renal biomarkers, including soluble fms-like tyrosine kinase-1 (sFlt-1), N-terminal pro-brain natriuretic peptide (NT-proBNP), high-sensitivity cardiac troponin-I (hs-cTnI), cystatin C, and placental growth factor, were measured in 1301 CKD and 1954 patients without CKD. The urine albumin to creatinine ratio (UACR) was measured in patients with CKD. The primary outcome was 3-point MACE (3P-MACE) defined as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. The secondary outcomes were all-cause death, cardiovascular death, and 5P-MACE defined as a composite of 3P-MACE, heart failure hospitalization, and coronary/peripheral artery revascularization. After adjustment for clinical confounders, sFlt-1, NT-proBNP, and hs-cTnI, but not other biomarkers, were significantly associated with 3P-MACE, all-cause death, and cardiovascular death in the entire cohort and in patients without CKD. These associations were still significant in CKD only for NT-proBNP and hs-cTnI. NT-proBNP and hs-cTnI were also significantly associated with 5P-MACE in CKD. The UACR was not significantly associated with any outcomes in CKD. NT-proBNP and hs-cTnI added incremental prognostic information for all outcomes to the model with potential clinical confounders in CKD.

CONCLUSIONS: NT-proBNP and hs-cTnI were the most powerful prognostic biomarkers in patients with suspected or known CAD and concomitant CKD.

Key Words: biomarker ■ cardiovascular events ■ chronic kidney disease ■ coronary artery disease ■ mortality ■ prospective cohort study

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CLINICAL PERSPECTIVE

What Is New?

- This is the first dedicated and large-scale prospective cohort study to demonstrate that higher levels of NT-proBNP (N-terminal pro-brain natriuretic peptide) and hs-cTnI (high-sensitivity cardiac troponin-I), but not those of sFlt-1 (soluble fms-like tyrosine kinase 1) or UACR (urine albumin to creatinine ratio), independently predicted cardiovascular events and mortality in patients with suspected or known coronary artery disease and concomitant chronic kidney disease.

What Are the Clinical Implications?

- Despite the possible chronic elevation of serum levels by renal insufficiency, NT-proBNP and hs-cTnI serve as powerful prognostic biomarkers beyond the other biomarkers, including sFlt-1 and UACR, in patients with suspected or known coronary artery disease and concomitant chronic kidney disease.

Nonstandard Abbreviations and Acronyms

3P-MACE	3-point major adverse cardiovascular events
5P-MACE	5-point major adverse cardiovascular events
CKD	chronic kidney disease
EXCEED-J	*E*stablishment of the method to extract a high-risk population employing novel biomarkers to predict car*d*iovascular events in *J*apan
Flt-1	fms-like tyrosine kinase 1
hs-cTnI	high-sensitivity cardiac troponin-I
IDI	integrated discrimination improvement
MACE	major adverse cardiovascular events
NGAL	neutrophil gelatinase-associated lipocalin
NHO	National Hospital Organization
NRI	net reclassification improvement
PlGF	placental growth factor
sFlt-1	soluble fms-like tyrosine kinase 1
UACR	urine albumin to creatinine ratio
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor

Chronic kidney disease (CKD) is a global public health problem due to its rising prevalence, poor outcomes, and high treatment cost.[1–4] It increases the risk of all-cause mortality, cardiovascular disease, and progression to kidney failure, independent of known coronary artery disease (CAD) risk factors such as hypertension, diabetes, and dyslipidemia.[5–8] Among subjects with CKD, cardiovascular disease is the leading cause of morbidity and mortality.[7]

Circulating levels of established cardiovascular biomarkers, ie, N-terminal pro-brain natriuretic peptide (NT-proBNP), high-sensitivity cardiac troponin-I (hs-cTnI), and high-sensitivity C-reactive protein (hs-CRP), can be chronically elevated by decreased renal clearance, and they are thus equally or less predictive for cardiovascular events in CKD than in non-CKD subjects in the general population.[9–11] However, the impact of CKD on the prognostic utility of established cardiovascular biomarkers in high-risk patients with suspected or known CAD remains unclear. In addition, there may be better predictors of cardiovascular events and mortality than established cardiovascular biomarkers in patients with suspected or known CAD and concomitant CKD.

The vascular endothelial growth factor (VEGF) family members, including VEGF, VEGF-B, VEGF-C, VEGF-D, and placental growth factor (PlGF), exhibit different patterns of binding to VEGF receptors (VEGFRs) on endothelial cells, and they differentially regulate blood and lymphatic vessel development and growth.[12] VEGF binds to VEGFR-1 (also called fms-like tyrosine kinase 1 [Flt-1]) and VEGFR-2.[13] While VEGF-VEGFR-2 signaling is essential for vascular development and maintenance, Flt-1 acts as an anti-angiogenic decoy receptor for VEGF and is required for proper vascular development.[14–16] A soluble truncated form of Flt-1 (sFlt-1) is secreted by endothelial cells by alternative splicing of the Flt-1 mRNA.[13] sFlt-1 has been shown to cause endothelial dysfunction, decrease angiogenesis, impair capillary repair, and increase proteinuria.[17,18]

A previous study found that increased sFlt-1 levels are associated with endothelial dysfunction in patients with CKD.[19] Since endothelial dysfunction, which is one of the initial pathological processes of atherosclerosis, is associated with an increased cardiovascular risk,[20,21] an increase in circulating sFlt-1 may be associated with cardiovascular risk in CKD. A relatively small-scale observational study showed that circulating sFlt-1 levels were associated with adverse outcomes in patients with CKD (stages 2–4).[22] However, whether sFlt-1 can predict cardiovascular events and mortality in patients with CKD should be confirmed in a larger cohort study.

Cystatin C and neutrophil gelatinase-associated lipocalin (NGAL) are renal biomarkers for acute kidney injury and CKD progression.[23,24] Cystatin C is a serum measure of renal function that appears to be

independent of age, sex, and lean muscle mass.[25] Cystatin C has been shown to be associated with all-cause death, cardiovascular death, and cardiovascular events in elderly persons living in the community.[25] In another study, the associations of cystatin C with all-cause death and cardiovascular death were independent of the glomerular filtration rate.[26] NGAL is a glycoprotein released by damaged renal tubular cells and is a sensitive marker of acute kidney injury.[23,24] Circulating levels of NGAL have been independently associated with all-cause death, cardiovascular death, and cardiovascular events in community-dwelling older adults.[27]

In the present study, therefore, we investigated whether possible novel biomarkers, including sFlt-1, and established cardiovascular biomarkers, ie, NT-proBNP, hs-cTnI, and hs-CRP, as well as renal biomarkers can predict cardiovascular events and mortality and whether CKD modifies the prognostic utility of these biomarkers in a large-scale, multicenter prospective cohort study of patients with suspected or known CAD.

METHODS

Study Population

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. Patients with suspected or known CAD (ie, stable angina, ischemic heart disease, chest pain, positive cardiac stress test) undergoing elective coronary angiography were recruited in the EXCEED-J (*E*stablishment of the method to extra*c*t a high risk population employing novel biomarkers to predict car*d*iovascular events in *J*apan) study (UMIN000018807): a nationwide, multicenter, prospective cohort study to determine whether sFlt-1 or other biomarkers can predict cardiovascular events in patients with CKD or other risk factors, and to establish the methods to efficiently extract high-risk patients. The EXCEED-J study group consists of 17 National Hospital Organization (NHO) institutions across Japan, and the present study was conducted by nationally certified cardiologists. The exclusion criteria included malignancy, inflammatory disease, heparin use, steroid or other hormone replacement therapy, inability to consent, scheduled follow-up angiography after coronary revascularization, and patients determined as ineligible by the attending physician. Between November 2013 and May 2017, a total of 3311 patients were consecutively enrolled. After excluding 47 patients who did not provide blood samples and 9 patients who withdrew consent, a total of 3255 (1301 CKD and 1954 non-CKD) patients were eligible. The estimated glomerular filtration rate (eGFR) was calculated with the new Japanese coefficient for the abbreviated Modification of Diet in the Renal Disease Study equation, including a correction factor of 0.739 for women.[28] CKD is defined as a creatinine-based eGFR <60 mL/min per 1.73 m^2.[1] The prevalence of risk factors for cardiovascular disease was determined by the examining physician (as described in Data S1). Data on demographic characteristics, smoking status, medical history, and medication use were collected from medical records. Submitted data were examined for completeness and accuracy by the coordinating center (Clinical Research Institute, Kyoto Medical Center, Kyoto, Japan), and data queries were sent to study sites. The study was approved by the central ethics committee of the NHO headquarters and each institution's ethical committee. All patients provided written informed consent.

Outcomes and Follow-Up

The primary outcome was 3-point major adverse cardiovascular events (3P-MACE) defined as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. The prespecified secondary outcomes were all-cause death, cardiovascular death, and 5P-MACE defined as a composite of 3P-MACE, heart failure hospitalization, and coronary/peripheral artery revascularization. The patients were monitored over 3 years (1080 days) for the occurrence of 3P-MACE, all-cause death, cardiovascular death, and/or 5P-MACE. The follow-up was performed by personnel blinded to the biomarker data through medical record/chart reviews, a survey letter, and/or telephone interviews.

Sudden death resulting from an unknown but presumed cardiovascular cause in high-risk patients was included in cardiovascular death. All deaths and MACE were recorded in the official medical chart of the hospitals where the patients received care. The reported deaths, myocardial infarctions, and strokes were reviewed and adjudicated by the expert committee (three independent and blinded cardiologists). The follow-up continued even after nonfatal myocardial infarction and/or nonfatal stroke had occurred. At the end of the follow-up (day 1080), the survival status and detailed information about MACE were available in 3220 patients (98.9%), and 35 patients (1.1%) were lost to follow-up.

Exposures, Sample Collection, and Biomarker Measurement

Heparin-free fasting blood samples for serum were collected from the peripheral vein before each patient's coronary angiography. The serum was stored at −80 °C for a mean of 4 months until it was assayed for sFlt-1, hs-CRP, cystatin C, neutrophil gelatinase-associated

lipocalin (NGAL), VEGF, and PlGF after one freeze-thaw cycle. The serum levels were measured with specific, commercially available, kits according to the manufacturers' instructions (Quantikine, R&D Systems, Minneapolis, MN, for sFlt-1, cystatin C, VEGF, and PlGF; CycLex, Medical & Biological Laboratories Co., Ltd. [MBL], Nagano, Japan for hs-CRP; BioPorto A/S, Hellerup, Denmark for NGAL). The sensitivity of the assay for sFlt-1 was 3.5 pg/mL. The inter-/intra-assay coefficients of variation of the ELISA for sFlt-1 were <10%/<4%. The sensitivities of the assays for hs-CRP, cystatin C, NGAL, VEGF, and PlGF were 0.0286 mg/L, 0.102 ng/mL, 4 pg/mL, 5 pg/mL, and 7 pg/mL, respectively. The inter-/intra-assay coefficients of variation of ELISAs for hs-CRP, cystatin C, NGAL, VEGF, and PlGF were <6%/<4%, ≤7%/<7%, 8.2%/3.0%, ≤7%/<5%, and <12%/≤7%, respectively. The assays were performed by an investigator blinded to the sources of the samples.

The details of the assay for NT-proBNP are described elsewhere.[29–31] Briefly, the serum levels of NT-proBNP were measured using a validated, sandwich electrochemiluminescence immunoassay (Elecsys; Roche Diagnostics, Indianapolis, IN). The sensitivity of the assay for NT-proBNP was 5 pg/mL, and the assay coefficient of variation at values of the measuring range (5–35 000 pg/mL) was <10%. The hs-cTnI values were measured using a cardiac troponin assay (Architect Stat High-Sensitive Troponin I; Abbott Laboratories, Abbot Park, IL, USA). The limit of detection in this assay is 1.9 pg/mL (range, 0–50 000 pg/mL) and the 99th percentile cut-off is 26.2 pg/mL. The urine albumin to creatinine ratio (UACR) was measured by the routine method. Additional details are described elsewhere.[29–31]

Statistical Analysis

We divided the patients into 2 groups according to the presence or absence of CKD. The baseline data were compared between CKD and non-CKD groups and significant differences were determined using the Wilcoxon and χ^2 tests. The relationships between sFlt-1 and other variables were assessed in simple and stepwise multiple linear regression analyses. Stepwise variable selection was performed in a forward direction with the Bayesian information criterion. Because sFlt-1, the Gensini score, NT-proBNP, hs-cTnI, hs-CRP, cystatin C, NGAL, VEGF, and PlGF were normally distributed after logarithmic transformation, the logarithms of these parameters were used in the linear regression analyses. The cumulative incidences of clinical outcomes were estimated by the Kaplan-Meier method. The relationships between the baseline biomarkers levels (as continuous variables, tertiles, and the top tertile [ie, tertile 3 versus tertiles 1 and 2]) and the outcomes were investigated with the use of Cox proportional hazard regression in models adjusted for potential clinical confounders (ie, age, sex, body mass index [BMI], hypertension, dyslipidemia, diabetes, current smoking, eGFR, the Gensini score, previous myocardial infarction, previous stroke, previous heart failure hospitalization, atrial fibrillation, anemia [defined as a hemoglobin level below 13 g/L in men and 12 g/L in women], antihypertensive drug use, statin use, and aspirin use). The biomarkers were log-transformed for use as continuous variables.

We evaluated the incremental predictive performance of selected biomarkers by calculating changes in the C-statistic, continuous net reclassification improvement (NRI), and integrated discrimination improvement (IDI) metrics.[32] We assessed the model calibration by comparing predicted probabilities with observed probabilities. A residual analysis was used to assess the model fit. Additional details are described in Data S1.

All statistical tests were two-sided, and $P<0.05$ was considered significant. Since all analyses were considered exploratory, the *P*-values were not adjusted for multiple comparisons. The analyses were performed using JMP13 (SAS, Cary, NC) and R, ver. 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics

The baseline characteristics of the entire cohort and those divided according to the presence or absence of CKD are shown in Table 1 and Table S1. The proportions of CKD stages were as follows: stage 3a, 64.1%; stage 3b, 24.8%; stage 4, 5.6%; and stage 5, 5.6% (Table S1). Patients with CKD had older age, higher rates of hypertension, diabetes, former smoking, obstructive CAD, previous stroke, previous heart failure hospitalization, atrial fibrillation, anemia and antihypertensive drug use, lower rate of current smoking, lower eGFR, and higher Gensini score. There were no significant differences in the rate of male sex, the BMI, or the rates of obesity, dyslipidemia, previous myocardial infarction, statin use, or aspirin use. Serum levels of sFlt-1, NT-proBNP, hs-cTnI, hs-CRP, cystatin C, and NGAL were significantly higher in patients with CKD than in those without CKD. Those of VEGF and PlGF were similar between the two groups. The sFlt-1/PlGF ratio was significantly higher in patients ith CKD than in patients without CKD. The baseline characteristics according to the tertiles of sFlt-1 levels in the entire cohort, patients with CKD, and patients without CKD are shown in Tables S2 through S4, respectively.

Figure S1 shows the comparison of sFlt-1 levels among patients without CKD and those with CKD stages 3a, 3b, 4, and 5. The sFlt-1 level increased in proportion to the severity of CKD. The correlations of sFlt-1 with other variables are shown in Table S5. Stepwise regression analysis revealed that higher sFlt-1 levels were independently associated with previous heart failure hospitalization, atrial fibrillation, absence of anemia, no use of statins, higher levels of NT-proBNP, hs-CRP and NGAL, and lower levels of cystatin C and VEGF.

Incidence of Outcomes

Incidences of prespecified outcomes in the entire cohort, patients with CKD, and patients without CKD are shown in Table 2. During the 3-year follow-up, 156 patients developed 3P-MACE (12 myocardial infarctions, 77 strokes, and 67 cardiovascular deaths), 215 died from any cause (82 cardiovascular and 133 noncardiovascular deaths), and 1361 developed 5P-MACE (156 3P-MACEs, 132 heart failure hospitalizations, and 1141 coronary/peripheral artery revascularizations).

Table 1. Baseline Characteristics in the Entire Cohort, Patients With CKD*, and Patients Without CKD

Baseline characteristics and incidence of events	Entire cohort (n=3255)	CKD (n=1301)	Non-CKD (n=1954)	*P* value†
Age, mean (SD), y	70.2 (10.4)	73.5 (8.5)	68.0 (11.0)	<0.001
Male	2272 (69.8)	892 (68.6)	1380 (70.6)	0.210
Body mass index, mean (SD)	24.5 (4.0)	24.5 (4.0)	24.5 (4.0)	0.673
Obesity‡	1311 (40.3)	538 (41.4)	773 (39.6)	0.307
Hypertension	2483 (76.3)	1112 (85.5)	1371 (70.2)	<0.001
Dyslipidemia	2480 (76.2)	1003 (77.1)	1477 (75.6)	0.323
Diabetes	1281 (39.4)	566 (43.5)	715 (36.6)	<0.001
Current smoker	591 (18.2)	189 (14.5)	402 (20.6)	<0.001
Former smoker	1390 (42.7)	594 (45.7)	796 (40.7)	0.005
eGFR, mean (SD), mL/min per 1.73 m^2	63 (20)	45 (13)	76 (14)	<0.001
Gensini score, median (IQR)§	10.5 (2.0–31.5)	13.0 (3.0–34.8)	9.5 (2.0–28.5)	<0.001
Obstructive coronary artery disease	1988 (61.1)	828 (63.6)	1160 (59.4)	0.014
Previous myocardial infarction	446 (13.7)	181 (13.9)	265 (13.6)	0.776
Previous stroke	385 (11.8)	185 (14.2)	200 (10.2)	<0.001
Previous heart failure hospitalization	285 (8.8)	173 (13.3)	112 (5.7)	<0.001
Atrial fibrillation	324 (10.0)	172 (13.2)	152 (7.8)	<0.001
Anemia‖	928 (28.5)	516 (39.7)	412 (21.1)	<0.001
Antihypertensive drug use	2684 (82.5)	1154 (88.7)	1530 (78.3)	<0.001
Statin use	1922 (59.1)	742 (57.0)	1180 (60.4)	0.057
Aspirin use	1714 (52.7)	674 (51.8)	1040 (53.2)	0.427
sFlt-1, median (IQR), pg/mL	108 (91–131)	112 (94–134)	105 (89–129)	<0.001
NT-proBNP, median (IQR), pg/mL	165 (65–598)	301 (106–1268)	115 (51–339)	<0.001
hs-cTnI, median (IQR), pg/mL	8 (4–16)	10 (6–23)	6 (4–13)	<0.001
hs-CRP, median (IQR), mg/L	0.6 (0.2–1.8)	0.7 (0.3–2.1)	0.5 (0.2–1.6)	<0.001
Cystatin C, median (IQR), mg/L	0.8 (0.7–1.0)	1.0 (0.8–1.2)	0.7 (0.6–0.9)	<0.001
NGAL, median (IQR), ng/mL	97 (68–139)	122 (85–178)	85 (62–117)	<0.001
VEGF, median (IQR), pg/mL	300 (184–468)	306 (190–477)	294 (180–462)	0.117
PlGF, median (IQR), pg/mL	14 (11–16)	14 (11–17)	14 (11–16)	0.371
sFlt-1/PlGF ratio, median (IQR)	7.9 (6.1–10.6)	8.1 (6.2–10.8)	7.8 (6.1–10.5)	0.036
UACR, median (IQR), mg/g¶	…	20 (8–83)	…	…

Values are expressed as number (percentage) unless otherwise indicated. CKD indicates chronic kidney disease; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; hs-cTnI, high-sensitivity cardiac troponin I; IQR, interquartile range; NGAL, neutrophil gelatinase-associated lipocalin; NT-proBNP, N-terminal pro-brain natriuretic peptide; PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase 1; UACR, urine albumin to creatinine ratio; and VEGF, vascular endothelial growth factor.

*CKD is defined as an estimated glomerular filtration rate of <60 mL/min per 1.73 m^2 of body surface area.

†The *P*-value represents a comparison of the differences between CKD and Non-CKD, and is based on the χ^2 test of independence for categorical variables, and the Wilcoxon test for continuous variables.

‡Obesity is defined as a body mass index of 25 or more.

§The Gensini score represents the angiographic severity of coronary artery disease employing a nonlinear points system for degree of luminal narrowing.

‖Anemia is defined as a hemoglobin level of <13 g/dL in men and <12 g/dL in women.

¶There are missing data for 223 patients.

Figure 1 shows the cumulative incidence of 3P-MACE according to the tertiles of sFlt-1 levels in the entire cohort (Figure 1A), patients with CKD (Figure 1B), and patients without CKD (Figure 1C). Patients in the top tertile of sFlt-1 had the greatest risk of 3P-MACE within the entire cohort, patients with CKD, and patients without CKD. Figures S2 through S4 show the cumulative incidence of all-cause death, cardiovascular death, and 5P-MACE according to the tertiles of sFlt-1 levels in the entire cohort, patients with CKD, and patients without CKD, respectively. The top tertile of sFlt-1 also had the greatest risks of all-cause death and cardiovascular death irrespective of the presence or absence of CKD. In contrast, there was no difference in the cumulative incidence of 5P-MACE among tertiles of sFlt-1. The incidences of prespecified outcomes according to tertiles of sFlt-1 levels in the entire cohort, patients with CKD, and patients without CKD are shown in Tables S2 through S4.

Multivariate Cox Regression Analyses

Figure 2 shows adjusted hazard ratios (HRs) of each biomarker level as (1) a natural log-transformed continuous variable (per 1-SD increase), (2) tertiles, and (3) the top tertile (ie, tertile 3 [versus tertiles 1 and 2]) for 3P-MACE in the entire cohort, patients with CKD, and patients without CKD. The tertiles of biomarker levels and numbers of patients are summarized in Table S6. After adjusting for potential clinical confounders (ie, age, sex, BMI, hypertension, dyslipidemia, diabetes, current smoking, eGFR, the Gensini score, previous myocardial infarction, previous stroke, previous heart failure hospitalization, atrial fibrillation, anemia, antihypertensive drug use, statin use, and aspirin use), the sFlt-1 level (as a continuous variable) was significantly associated with 3P-MACE in the entire cohort (HR, 1.26; 95% CI [95% CI], 1.11–1.43) and in patients without CKD (HR, 1.40; 95% CI, 1.18–1.65), but not in patients with CKD (HR, 1.13; 95% CI, 0.92–1.35). The tertile analysis of sFlt-1 levels revealed that there was an apparent threshold effect between tertile 2 and tertile 3 in the incidence of 3P-MACE. Thus, sFlt-1 was also modeled as a dichotomous variable by applying a threshold of the tertiles 1 and 2 versus tertile 3. The top tertile (ie, tertile 3 [versus tertiles 1 and 2]) of sFlt-1 was significantly associated with 3P-MACE in the entire cohort (HR, 1.63; 95% CI, 1.17–2.26) and in patients with CKD (HR, 1.78; 95% CI, 1.14–2.76), but not in patients without CKD (HR, 1.63; 95% CI, 0.99–2.68).

Serum levels of NT-proBNP and hs-cTnI (as continuous variables) were significantly associated with 3P-MACE in the entire cohort (NT-proBNP: HR, 1.90; 95% CI, 1.58–2.28; hs-cTnI: HR, 1.44; 95% CI, 1.28–1.63), patients with CKD (NT-proBNP: HR, 1.98; 95% CI, 1.50–2.61; hs-cTnI: HR, 1.51; 95% CI, 1.25–1.79), and patients without CKD (NT-proBNP: HR, 1.81; 95% CI, 1.39–2.36; hs-cTnI: HR, 1.38; 95% CI, 1.17–1.64). Among other biomarkers, only cystatin C levels (as a continuous variable) were significantly associated with 3P-MACE in the entire cohort, and no biomarkers including UACR were significantly associated with 3P-MACE in patients with CKD.

Adjusted HRs of each biomarker level for all-cause death, cardiovascular death, and 5P-MACE are shown in Figures S5 through S7, respectively. After adjusting for potential clinical confounders, the sFlt-1 level (as a continuous variable) was significantly associated with all-cause death in the entire cohort (HR, 1.23; 95% CI, 1.10–1.37), patients with CKD (HR, 1.19; 95% CI, 1.03–1.38), and patients without CKD (HR, 1.29; 95% CI, 1.09–1.53) (Figure S5), whereas it was significantly associated with cardiovascular death in the entire cohort (HR, 1.34; 95% CI, 1.14–1.56) and in patients without

Table 2. Incidence of Outcomes in the Entire Cohort, Patients With CKD, and Patients Without CKD

Type of outcomes	Entire cohort (n=3255)	CKD (n=1301)	Non-CKD (n=1954)
3-point MACE*	156 (16.8)	88 (24.2)	68 (12.0)
All-cause death	215 (22.9)	128 (34.6)	87 (15.2)
Cardiovascular death	82 (8.7)	50 (13.5)	32 (5.6)
5-point MACE†	1361 (226.8)	595 (261.3)	766 (205.7)
Myocardial infarction	12 (1.3)	5 (1.4)	7 (1.2)
Stroke	77 (8.3)	42 (11.5)	35 (6.2)
Heart failure hospitalization	179 (19.5)	107 (30.1)	72 (12.8)
Revascularization for coronary/peripheral artery disease	1151 (183.2)	477 (196.4)	674 (174.9)
PCI	936 (137.1)	365 (135.3)	571 (138.2)
CABG	137 (15.1)	74 (21.1)	63 (11.4)
Peripheral artery disease	134 (14.7)	62 (17.4)	72 (13.0)

Values are expressed as number (/1000 person-years). CABG indicates coronary artery bypass grafting; MACE, major adverse cardiovascular events; and PCI, percutaneous coronary intervention.

*3-point MACE is defined as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.

†5-point MACE is defined as a composite of 3-point MACE, heart failure hospitalization, and revascularization for coronary/peripheral artery disease.

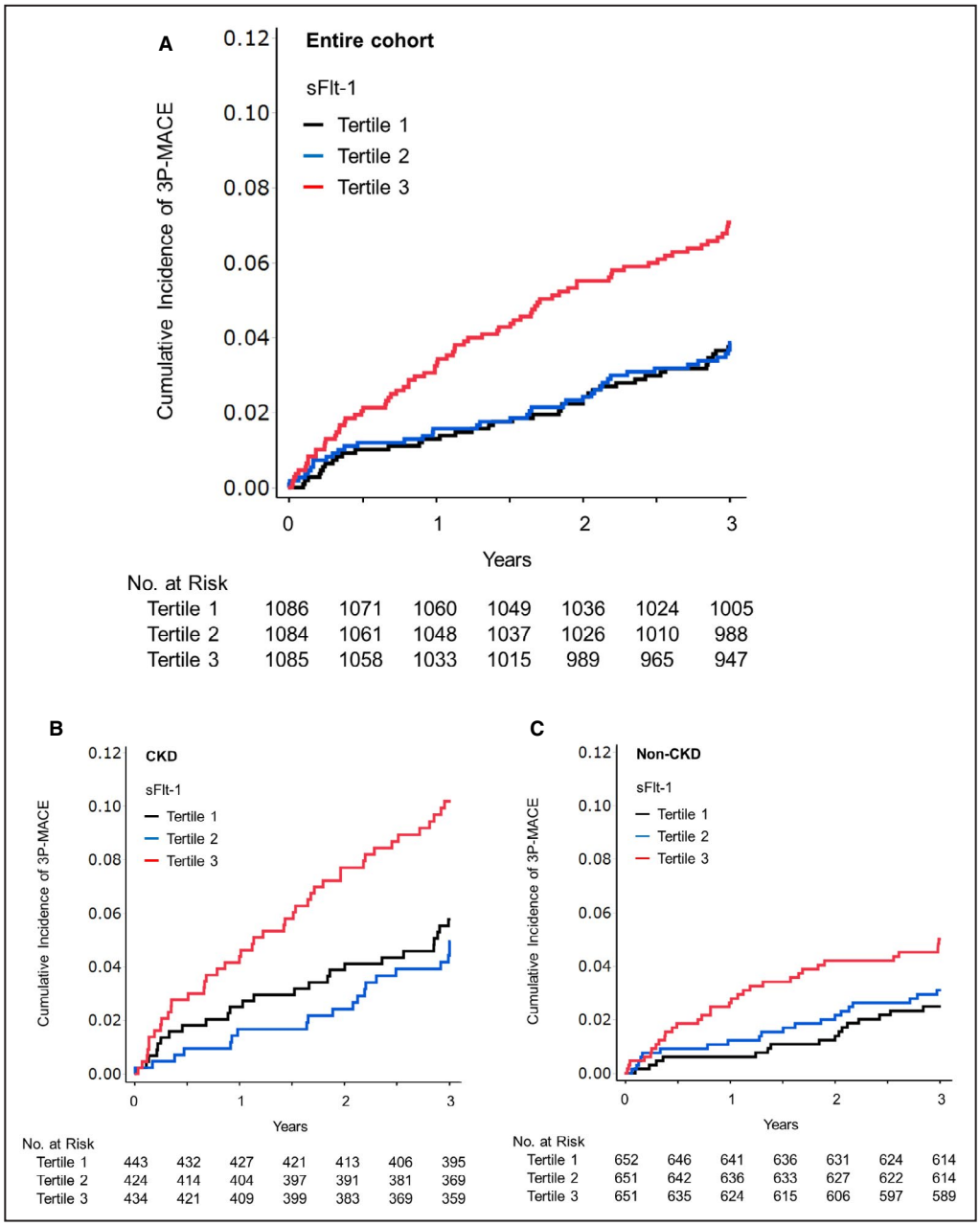
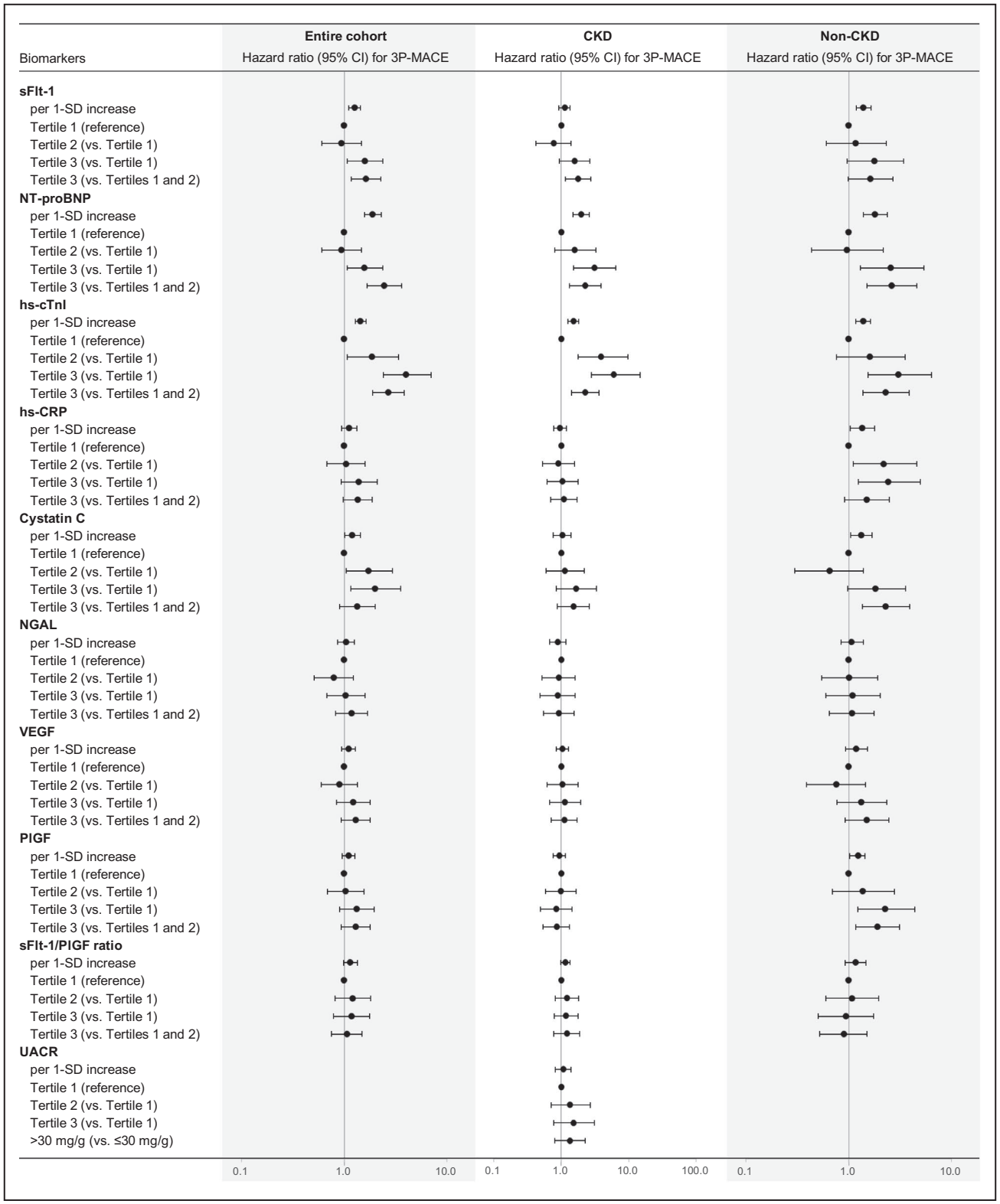


Figure 1. Cumulative incidence of 3P-MACE in the entire cohort (A), patients with CKD (B), and patients without CKD (C) according to the serum sFlt-1 level at baseline.
Follow-up results are truncated after 3 years. 3P-MACE is defined as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. CKD is defined as an estimated glomerular filtration rate of <60 mL/min per 1.73 m^2 of body surface area. The tertiles of sFlt-1 levels were as follows: (**A**) tertile 1, ≤96.59; tertile 2, 96.59<, ≤121.17; tertile 3, >121.17 pg/mL; (**B**) tertile 1, ≤100.00; tertile 2, 100.00<, ≤124.91; tertile 3, >124.91 pg/mL; (**C**) tertile 1, ≤94.45; tertile 2, 94.45<, ≤119.69; tertile 3, >119.69 pg/mL. 3P-MACE indicates 3-point major adverse cardiovascular events; CKD, chronic kidney disease; and sFlt-1, soluble fms-like tyrosine kinase 1.

CKD (HR, 1.55; 95% CI, 1.24–1.93), but not in patients with CKD (HR, 1.20; 95% CI, 0.96–1.50) (Figure S6). In contrast, the sFlt-1 level was not significantly associated with 5P-MACE either as a continuous variable or the top tertile in the entire cohort, patients with CKD or patients without CKD (Figure S7).

Serum levels of NT-proBNP and hs-cTnI (as continuous variables) were significantly associated with all-cause death in the entire cohort (NT-proBNP: HR, 1.68; 95% CI, 1.43–1.98; hs-cTnI: HR, 1.25; 95% CI, 1.12–1.41), patients with CKD (NT-proBNP: HR, 1.75; 95% CI, 1.38–2.22; hs-cTnI: HR, 1.32; 95% CI,



1.12–1.56), and patients without CKD (NT-proBNP: HR, 1.53; 95% CI, 1.20–1.96; hs-cTnI: HR, 1.20; 95% CI, 1.01–1.43) (Figure S5); and with cardiovascular death in the entire cohort (NT-proBNP: HR, 2.42; 95% CI, 1.87–3.12; hs-cTnI: HR, 1.53; 95% CI, 1.30–1.79), patients with CKD (NT-proBNP: HR, 2.76; 95% CI, 1.88–4.07; hs-cTnI: HR, 1.70; 95% CI, 1.34–2.15), and patients without CKD (NT-proBNP: HR, 2.31; 95% CI, 1.56–3.43; hs-cTnI: HR, 1.42; 95% CI, 1.12–1.80) (Figure S6). Those of hs-cTnI were also significantly associated

Figure 2. Adjusted hazard ratios of the biomarker levels for 3P-MACE in the entire cohort, patients with CKD, and patients without CKD.
The data were adjusted for age, sex, body mass index, hypertension, dyslipidemia, diabetes, current smoking, estimated glomerular filtration rate, the Gensini score, previous myocardial infarction, previous stroke, previous heart failure hospitalization, atrial fibrillation, anemia, antihypertensive drug use, statin use and aspirin use. CKD is defined as an estimated glomerular filtration rate of <60 mL/min per 1.73 m^2 of body surface area. The biomarkers are modeled as (1) continuous variables, (2) tertiles, and (3) the top tertile (ie, tertile 3 vs tertiles 1 and 2), and are natural log-transformed for use as continuous variables. NT-proBNP indicates N-terminal pro-brain natriuretic peptide; hs-cTnI, high-sensitivity cardiac troponin I; hs-CRP, high-sensitivity C-reactive protein; NGAL, neutrophil gelatinase-associated lipocalin; VEGF, vascular endothelial growth factor; PlGF, placental growth factor; and UACR: urine albumin to creatinine ratio. Other abbreviations used in this figure are the same as in Figure 1. The tertiles of biomarker levels and number of patients are summarized in Table S6.

with 5P-MACE in the entire cohort, patients with CKD and patients without CKD, while those of NT-proBNP were significantly associated with 5P-MACE in the entire cohort and in patients with CKD, but not in patients without CKD (Figure S7).

Among other biomarkers, the serum levels of hs-CRP, cystatin C, and PlGF (as continuous variables) were significantly associated with all-cause death and 5P-MACE in the entire cohort and in patients without CKD. However, the serum levels of hs-CRP, but not those of cystatin C or PlGF, were significantly associated with all-cause death, and those of hs-CRP and cystatin C, but not those of PlGF, were significantly associated with 5P-MACE in patients with CKD (Figures S5 and S7). Only the serum levels of cystatin C were significantly associated with cardiovascular death in the entire cohort and in patients without CKD, but not in patients with CKD (Figure S6). UACR, either as a continuous variable or at values of 30 mg/g or more, was not significantly associated with all-cause death, cardiovascular death, or 5P-MACE in patients with CKD (Figures S5 through S7).

Discrimination, Reclassification, and Calibration

Table 3 shows the incremental predictive performance of selected biomarkers for 3P-MACE in the entire cohort, patients with CKD and patients without CKD. The C statistics for 3P-MACE by the model with potential clinical confounders (base model) were 0.712 in the entire cohort, 0.673 in patients with CKD and 0.735 in patients without CKD. The addition of sFlt-1 (as a continuous variable) to the base model significantly improved the prediction of 3P-MACE in the entire cohort (P=0.006 for NRI, P=0.027 for IDI) and in patients without CKD (P=0.032 for NRI, P<0.050 for IDI), but not in patients with CKD (P=0.093 for NRI, P=0.169 for IDI). On the other hand, the addition of the top tertile (versus tertiles 1 and 2) of sFlt-1 to the base model significantly improved the prediction of 3P-MACE in the entire cohort (P<0.001 for NRI, P=0.014 for IDI) and in patients with CKD (P=0.002 for NRI, P=0.013 for IDI), but not in patients without CKD (P=0.022 for NRI, P=0.163 for IDI).

Table S7 shows the incremental predictive performance of selected biomarkers for all-cause death in the entire cohort, patients with CKD, and patients without CKD. The addition of sFlt-1 (as a continuous variable) to the base model significantly improved the prediction of all-cause death in the entire cohort (P<0.001 for NRI, P=0.024 for IDI), but not in patients with CKD (P=0.004 for NRI, P=0.064 for IDI) or patients without CKD (P<0.001 for NRI, P=0.132 for IDI). However, the addition of the top tertile (versus tertiles 1 and 2) of sFlt-1 to the base model significantly improved the prediction of all-cause death in the entire cohort (P<0.001 for NRI, P=0.023 for IDI) and in patients with CKD (P=0.001 for NRI, P=0.019 for IDI), but not in patients without CKD (P<0.001 for NRI, P=0.133 for IDI).

Table S8 shows the incremental predictive performance of selected biomarkers for cardiovascular death in the entire cohort, patients with CKD, and patients without CKD. The addition of sFlt-1 (as a continuous variable) to the base model significantly improved the prediction of cardiovascular death in the entire cohort (P=0.002 for NRI, P=0.042 for IDI), but not in patients with CKD (P=0.050 for NRI, P=0.306 for IDI) or patients without CKD (P=0.023 for NRI, P=0.070 for IDI). The addition of the top tertile (versus tertiles 1 and 2) of sFlt-1 to the base model significantly improved the prediction of cardiovascular death in the entire cohort (P<0.001 for NRI, P=0.013 for IDI), but not in patients with CKD (P=0.003 for NRI, P=0.066 for IDI) or patients without CKD (P=0.008 for NRI, P=0.090 for IDI).

Notably, the addition of either NT-proBNP or hs-cTnI significantly improved the prediction of 3P-MACE, all-cause death, and cardiovascular death not only in the entire cohort, but also in patients with CKD (Table 3 and Tables S7, S8). Moreover, the addition of either NT-proBNP or hs-cTnI significantly improved the prediction of 5P-MACE in patients with CKD (Table S9). Calibration of the models with or without each biomarker showed no evidence of lack of fit.

DISCUSSION

This is the first dedicated and large-scale prospective cohort study to demonstrate that higher levels of NT-proBNP and hs-cTnI, but not those of sFlt-1 or UCAR, independently predicted cardiovascular events and mortality in patients with suspected or known CAD

Table 3. Incremental Predictive Performance of Selected Biomarkers for 3-Point MACE in the Entire Cohort, Patients With CKD, and Patients Without CKD

Subgroups and prediction models	C statistics	ΔC statistics	Continuous NRI, 95% CI	*P* value	IDI, 95% CI	*P* value
Entire cohort						
Base model*	0.712	…	…		…	
Base+sFlt-1†	0.724	0.012	0.227 (0.067 to 0.388)	0.006	0.005 (0.001 to 0.009)	0.027
Base+sFlt-1 (top tertile)†	0.721	0.009	0.310 (0.150 to 0.470)	<0.001	0.004 (0.001 to 0.006)	0.014
Base+NT-proBNP†	0.748	0.037	0.384 (0.225 to 0.543)	<0.001	0.021 (0.011 to 0.031)	<0.001
Base+hs-cTnI†	0.751	0.039	0.393 (0.233 to 0.554)	<0.001	0.011 (0.005 to 0.017)	<0.001
CKD						
Base model*	0.673	…	…		…	
Base+sFlt-1†	0.673	0.000	0.186 (−0.031 to 0.402)	0.093	0.002 (−0.001 to 0.005)	0.169
Base+sFlt-1 (top tertile)†	0.686	0.014	0.333 (0.117 to 0.548)	0.002	0.007 (0.001 to 0.012)	0.013
Base+NT-proBNP†	0.719	0.046	0.484 (0273 to 0.696)	<0.001	0.023 (0.010 to 0.036)	<0.001
Base+hs-cTnI†	0.714	0.041	0.538 (0.325 to 0.751)	<0.001	0.016 (0.006 to 0.025)	0.001
Non-CKD						
Base model*	0.735	…	…		…	
Base+sFlt-1†	0.758	0.023	0.264 (0.023 to 0.504)	0.032	0.014 (0.000 to 0.028)	0.050
Base+sFlt-1 (top tertile)†	0.743	0.008	0.282 (0.041 to 0.523)	0.022	0.003 (−0.001 to 0.007)	0.163
Base+NT-proBNP†	0.776	0.041	0.410 (0.171 to 0.649)	<0.001	0.015 (0.002 to 0.029)	0.027
Base+hs-cTnI†	0.777	0.042	0.371 (0.130 to 0.611)	0.003	0.006 (−0.002 to 0.014)	0.146

Follow-up results are truncated after 3 years. The biomarkers are natural log-transformed and are modeled as continuous variables unless otherwise indicated. The ΔC statistic, continuous NRI and IDI show the change in model performance from the base model. hs-cTnI indicates high-sensitivity cardiac troponin I; IDI, integrated discrimination improvement; MACE, major adverse cardiovascular events; NRI, net reclassification improvement; NT-proBNP, N-terminal pro-brain natriuretic peptide; and sFlt-1, soluble fms-like tyrosine kinase 1.

*The base model is based on age, sex, body mass index, hypertension, dyslipidemia, diabetes, current smoking, estimated glomerular filtration rate, the Gensini score, previous myocardial infarction, previous stroke, previous heart failure hospitalization, atrial fibrillation, anemia, antihypertensive drug use, statin use, and aspirin use.

†The change of model performance was evaluated against the base model.

and concomitant CKD. The strengths of our investigation include the large sample size, multi-center prospective design, inclusion of both CKD and non-CKD patient data, and high follow-up rate (98.9%).

Many clinical studies have evaluated novel biomarkers due to the importance of improving risk stratification and supporting clinical decision making in patients with CKD.[33] To date, however, only a few biomarkers, including eGFR and proteinuria, have been approved for large-scale clinical application.[34]

NT-proBNP has previously been shown to be predictive of cardiovascular morbidity and mortality in the general population,[35] and among patients with acute coronary syndrome, those with heart failure, and those with stable CAD.[36–40] Pre-proBNP is synthesized within the cardiac myocytes in response to ventricular wall stress and stretch.[41] After removal of a signaling peptide within the cytosol, proBNP is further cleaved into an inactive form (NT-proBNP) and an active form (brain natriuretic peptide [BNP]) at the time of release from the myocytes or in the circulation.[41] NT-proBNP is more stable, with a longer half-life, and may be a better biomarker for chronic volume expansion or stress than BNP.[41] The clearance of NT-proBNP is predominantly renal, and NT-proBNP levels are inversely correlated with eGFR, and are often elevated in asymptomatic patients with CKD.[9,41,42] Since circulating NT-proBNP levels are mostly determined by the cardiac myocyte production and renal clearance, the coexistence of ventricular wall stress/stretch and renal insufficiency obscures the implications of elevated NT-proBNP: the largest determinant of NT-proBNP elevation depends on which is more severe, the ventricular wall stress/stretch or renal insufficiency. In any case, higher NT-proBNP levels can be a cardiorenal comprehensive prognostic biomarker, because both abnormal cardiac ventricular stress/stretch and renal insufficiency are associated with the risks of cardiovascular events and mortality.

hs-cTnI has also been shown to be a predictor of cardiovascular morbidity and mortality in the general population,[43] and among patients with acute coronary syndrome, those with heart failure, and those with stable CAD.[44–46] Cardiac troponin I (cTnI) and T (cTnT) are components of the contractile apparatus of myocardial cells and are expressed almost exclusively in the heart.[47,48] An increase in cTnI values has not been reported to occur following injury to non-cardiac tissues, whereas injured skeletal muscle expresses proteins that are detected by the cTnT assay.[44] cTnI and cTnT are the preferred biomarkers for the evaluation

of myocardial injury, and hs-cTnI and hs-cTnT assays are recommended for routine clinical use.[44,48] hs-cTnI was significantly and inversely associated with eGFR.[49] Increased hs-cTnI levels were common in CKD without acute coronary syndrome, and are influenced by both underlying cardiac and renal disease[49]: troponin elevation does not necessarily indicate acute ischemia from coronary atherosclerosis but may be due to decreased renal clearance or chronic myocardial injury.[9] Our findings that NT-proBNP and hs-cTnI serve as prognostic biomarkers even in the presence of CKD in high-risk patients with suspected or known CAD have extended the findings of the previous study in the general population.[10]

The Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference reported that albuminuria (defined as an UACR of 30 mg/g or more) was independently associated with all-cause death and cardiovascular death in the general population, among high-risk patients (ie, those with hypertension, diabetes, clinical cardiovascular disease, or a history of kidney disease), and among patients with CKD.[50] Albuminuria was also independently associated with incident atherosclerotic vascular disease events and death in patients with CKD without a history of cardiovascular disease.[51] By contrast, UACR was not independently associated with cardiovascular events or mortality in the present study. Among the very high-risk patients with overlapping risks of CAD and CKD, the impact of UACR on poor prognosis may be relatively reduced. Further investigation is necessary to confirm these findings.

sFlt-1 has been shown to be independently associated with adverse outcomes among patients with chronic heart failure[52,53] and among patients with CKD stages 2–4.[22] PlGF, a specific ligand for Flt-1, has been suggested to be independently associated with all-cause death in the general population[54]; with cardiovascular events among patients with suspected and definite acute coronary syndrome[55,56]; with all-cause death and cardiovascular death among patients with acute heart failure[57]; and with all-cause death and cardiovascular events among patients with CKD.[58] The sFlt1/PlGF ratio has been shown to predict adverse outcomes among women with suspected preeclampsia[59,60] and among pregnant women with hypertension.[61] In the present study, sFlt-1 was independently associated with hard end points (3P-MACE, all-cause death, and cardiovascular, and cardiovascular death), but not with soft end points (5P-MACE), among patients with suspected or known CAD (ie, in the entire cohort). However, these associations were attenuated in the subgroup of CKD. PlGF was independently associated with all-cause death and 5P-MACE, but not with 3P-MACE or cardiovascular death, in the entire cohort. These associations were attenuated in the subgroup of CKD. The sFlt-1/PlGF ratio was independently associated with cardiovascular death, but not with 3P-MACE, all-cause death or 5P-MACE, in the entire cohort. This association was attenuated in the subgroup of CKD as well. These findings suggest that sFlt-1, PlGF, and the sFlt-1/PlGF ratio were less predictive for poor prognosis in patients with CKD than in patients without CKD among patients with suspected or known CAD. However, the addition of sFlt-1 to the base model with potential clinical confounders significantly improved the prediction of 3P-MACE, all-cause death, and cardiovascular death, but not that of 5P-MACE, in the entire cohort. Further investigation will clarify whether there are subgroups in which sFlt-1 shows better prognostic utility than established biomarkers such as NT-proBNP and hs-cTnI.

We recently demonstrated that serum levels of VEGF were not independently associated with all-cause death, cardiovascular death, or 3P-MACE in patients with suspected or known CAD.[29] In the present study, we observed similar results in the entire cohort, patients with CKD, and patients without CKD.

hs-CRP has been shown to be predictive of cardiovascular events and mortality in the general population, among patients with acute coronary syndrome, and among patients with stable CAD.[62] In the present study, hs-CRP was significantly associated with: 3P-MACE in patients without CKD, but not in the entire cohort or in patients with CKD; cardiovascular death in the entire cohort and in patients without CKD, but not in patients with CKD; and all-cause death and 5P-MACE in the entire cohort, patients with CKD, and patients without CKD. The addition of hs-CRP to the base model with potential clinical confounders significantly improved the prediction of all-cause death, but not that of cardiovascular death or 5P-MACE, in the entire cohort, patients with CKD, and patients without CKD. Thus, hs-CRP is a very powerful predictor of all-cause death irrespective of the presence or absence of CKD, but seems to be less predictive of cardiovascular events and cardiovascular death than NT-proBNP and hs-cTnI in patients with suspected or known CAD, especially in the presence of CKD.

In the present study, cystatin C was significantly associated with 3P-MACE and all-cause death even after adjustment for potential clinical confounders, including creatinine-based eGFR, in the entire cohort and in patients without CKD, but not in patients with CKD. Cystatin C was independently associated with 5P-MACE in the entire cohort, patients with CKD, and patients without CKD. The addition of cystatin C to the model with potential clinical confounders including creatinine-based eGFR further improved the prediction of 5P-MACE in the entire cohort and in patients without CKD, but not in patients with CKD. In contrast, the addition of cystatin C did not further improve the prediction of any hard end points (3P-MACE, all-cause death, or cardiovascular death) in patients with suspected or

known CAD, regardless of the presence or absence of CKD. These findings may suggest that cystatin C is a powerful predictor of atherosclerotic cardiovascular events, but is less predictive of hard cardiovascular events and mortality than NT-proBNP and hs-cTnI in patients with suspected or known CAD, especially in the presence of CKD.

The sFlt-1 levels in the top tertile of the present study were >121.17 pg/mL. A previous study reported that the sFlt-1 levels in the top tertile among patients with CAD, including both patients with stable angina pectoris and those with acute coronary syndrome, were >160.0 pg/mL.[63] In the same study, the sFlt-1 levels were higher in patients with acute coronary syndrome than in patients with stable angina pectoris. The present study included patients with suspected or known CAD undergoing elective coronary angiography, but not those with acute coronary syndrome requiring urgent coronary intervention. Thus, the difference in the sFlt-1 levels in the top tertile could be explained by the inclusion rate of patients with acute coronary syndrome. The NT-proBNP and hs-cTnI levels in the top tertiles in the present study were >352 pg/mL and >11.8 pg/mL, respectively. A previous study reported that the NT-proBNP levels in the third quartile among patients with stable CAD were 170 to 455 pg/mL.[39] These values of NT-proBNP are similar to those in the present study. Another study showed that the hs-cTnI levels in the third quartile among patients with stable CAD were 4.6 to 7.3 pg/mL in men and 4.0 to 6.3 pg/mL in women.[46] Although these values of hs-cTnI are lower than those in the present study, the difference could be explained by the inclusion of a small number of unstable patients with CAD not requiring urgent coronary intervention in the present study.

Limitations

First, we did not include patients with stages 1 to 2 CKD as defined by albuminuria with preserved glomerular filtration rate in the CKD subgroup, because we had no collected data on UACR in patients with eGFR ≥60 mL/min per 1.73 m^2. We also did not include patients with severe CKD who had not been introduced to dialysis and would be discouraged from using contrast media. Second, we had no collected cardiovascular imaging data, such as echocardiography (especially, left ventricular ejection fraction and valvular disease), cardiovascular magnetic resonance, computed tomography, intravascular ultrasound/optical coherence tomography, or nuclear imaging data. Third, we had no collected data of a history of COPD. Fourth, this was an observational study, and other unmeasured confounding factors may have existed. Finally, because the EXCEED-J study cohort consists exclusively of Asian individuals with suspected or known CAD, our results may not be generalizable to general Asian populations, or to other ethnic groups.

CONCLUSIONS

Nevertheless, our results clearly demonstrate that higher serum levels of NT-proBNP and hs-cTnI, but not those of sFlt-1 or UACR, independently augmented the prediction of both cardiovascular events and mortality achieved by potential clinical confounders in patients with suspected or known CAD and concomitant CKD undergoing elective coronary angiography.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

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SUPPLEMENTAL MATERIAL

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Data S1.

SUPPLEMENTAL METHODS

Study population

Dyslipidemia was defined as a fasting low-density lipoprotein cholesterol level of 140 mg/dL or more, high-density lipoprotein cholesterol level of less than 40 mg/dL, triglycerides level of 150 mg/dL or more, or the use of lipid-lowering drugs. Hypertension was defined as a clinic systolic blood pressure of 140 mmHg or more, diastolic blood pressure of 90 mmHg or more, or the use of anti-hypertensive drugs. Diabetes was defined as fasting glucose of 126 mg/dL or more, glycosylated hemoglobin of 6.5% or more, or the use of oral hypoglycemic drugs or insulin. The presence of coronary artery disease (CAD), multi-vessel disease, and left main trunk disease was assessed using a modified American Heart Association/American College of Cardiology classification.[64] The severity of CAD was quantified using the Gensini score. [65]

Sample collection and biomarker measurement

Serum contemporary sensitive cardiac troponin-I (cTnI) was measured with the ADVIA Centaur Troponin I Ultra assay (Siemens Healthcare Diagnostics, Los Angeles, CA). The sensitivity of the assay for cTnI was 6 pg/mL, and the assay CV at the 99th percentile reference value of 40 pg/mL (potential range, 20–60 pg/mL) was <10%. The hemoglobin and the hematocrit levels, plasma hemoglobin A1c levels, and fasting serum levels of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, glucose, creatinine, and uric acid were measured by routine methods.

Statistical analyses

In our prior exploratory study of 490 consecutive outpatients, 94 had CKD. In the CKD patients, the incidence of MACE over a 3-year follow-up period was 36.1% in a high sFlt-1 group (above the cut-off value determined by receiver operating curve analysis, n=36) and 12.1% in a low sFlt-1 group (n=58). To realize 99.9% power for MACE, we estimated that a sample size of 503 CKD patients was required. Because this was an all-comers study, we expected that a total of 2622 (503 CKD and 2119 non-CKD) patients would be enrolled during the registration period. We increased this sample size by 25% to account for potential loss to follow-up, arriving at a final sample size of 3280 patients.

Table S1. Baseline characteristics in the entire cohort, CKD patients, and non-CKD patients.

Baseline characteristics	Entire cohort		CKD		Non-CKD		*P* value*
	No.	Value	No.	Value	No.	Value	
Stages of chronic kidney disease †	3255		1301		1954		<0.001
Stage 3a		834 (25.6)		834 (64.1)		0 (0.0)	
Stage 3b		323 (9.9)		323 (24.8)		0 (0.0)	
Stage 4		73 (2.2)		73 (5.6)		0 (0.0)	
Stage 5		71 (2.2)		71 (5.5)		0 (0.0)	
Dialysis	3255	67 (2.1)	1301	67 (5.2)	1954	0 (0.0)	<0.001
Multivessel or LMT disease	3255	1094 (33.6)	1301	475 (36.5)	1954	619 (31.7)	0.004
NYHA class III or IV	3255	219 (6.7)	1301	125 (9.6)	1954	94 (4.8)	<0.001
Previous PCI	3255	845 (26.0)	1301	372 (28.6)	1954	473 (24.2)	0.005
Previous CABG	3255	111 (3.4)	1301	68 (5.2)	1954	43 (2.2)	<0.001
Previous CAD (MI, PCI, or CABG)	3255	931 (28.6)	1301	414 (31.8)	1954	517 (26.5)	<0.001
Previous cardiovascular events‡	3255	1479 (45.4)	1301	673 (51.7)	1954	806 (41.3)	<0.001
Family history of cardiovascular events	3255	719 (22.1)	1301	323 (24.8)	1954	396 (20.3)	0.002
Previous malignancies	3255	297 (9.1)	1301	146 (11.2)	1954	151 (7.7)	<0.001
Systolic blood pressure, mean (SD), mmHg	3255	128 (19)	1301	129 (19)	1954	127 (18)	0.017
Diastolic blood pressure, mean (SD), mmHg	3255	72 (13)	1301	71 (13)	1954	73 (13)	0.002
Pulse rate, mean (SD), beats per minute	3255	70 (13)	1301	71 (14)	1954	70 (13)	0.029
LDL-cholesterol, mean (SD), mg/dL	3238	108 (34)	1291	108 (34)	1947	109 (34)	0.179
HDL-cholesterol, mean (SD), mg/dL	3226	53 (16)	1288	51 (15)	1938	54 (16)	<0.001
Triglycerides, median (IQR), mg/dL	3225	116 (84-171)	1286	119 (87-173)	1939	114 (82-170)	0.015

Fasting glucose, median (IQR), mg/dL	3205	108 (95-132)	1277	108 (95-134)	1928	108 (96-131)	0.850
Hemoglobin A1c, median (IQR), %	3165	6.0 (5.6-6.7)	1268	6.1 (5.7-6.8)	1897	6.0 (5.6-6.7)	0.001
Creatinine, median (IQR), mg/dL	3255	0.9 (0.7-1.0)	1301	1.1 (1.0-1.3)	1954	0.8 (0.7-0.9)	<0.001
Hemoglobin, mean (SD), g/dL	3255	13.4 (1.8)	1301	13.0 (1.9)	1954	13.7 (1.6)	<0.001
Hematocrit, mean (SD), %	3254	40 (5)	1300	39 (5)	1954	41 (5)	<0.001
Uric acid, mean (SD), mg/dL	3208	5.9 (1.8)	1277	6.4 (1.7)	1931	5.6 (1.8)	<0.001
cTnI, median (IQR), ng/mL	3255	0.008 (0.001-0.020)	1301	0.011 (0.004-0.025)	1954	0.006 (0.000-0.016)	<0.001
Antihypertensive drug use							
RASI	3255	1883 (57.9)	1301	851 (65.4)	1954	1032 (52.8)	<0.001
ACEI	3255	503 (15.5)	1301	200 (15.4)	1954	303 (15.5)	0.918
ARB	3255	1407 (43.2)	1301	656 (50.4)	1954	751 (38.4)	<0.001
β-blocker	3255	1263 (38.8)	1301	549 (42.2)	1954	714 (36.5)	0.001
Any lipid-lowering drug use	3255	2043 (62.8)	1301	799 (61.4)	1954	1244 (63.7)	0.193
Any hypoglycemic drug use	3255	1031 (31.7)	1301	473 (36.4)	1954	558 (28.6)	<0.001
Oral hypoglycemic drugs	3255	900 (27.7)	1301	408 (31.4)	1954	492 (25.2)	<0.001
Insulin	3255	277 (8.5)	1301	135 (10.4)	1954	142 (7.3)	0.002
Any antiplatelet drug use	3255	1993 (61.2)	1301	799 (61.4)	1954	1194 (61.1)	0.859
Any anticoagulant drugs	3255	454 (14.0)	1301	230 (17.7)	1954	224 (11.5)	<0.001
Warfarin	3255	217 (6.7)	1301	121 (9.3)	1954	96 (4.9)	<0.001

Values are expressed as number (percentage) unless otherwise indicated. LMT indicates left main trunk; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; SD, standard deviation; LDL, low-density lipoprotein; HDL, high-density lipoprotein; IQR, interquartile range; cTnI, contemporary sensitive cardiac troponin I; RASI, renin angiotensin system inhibitors; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers.

* The *p*-value represents a comparison of the differences between CKD and Non-CKD, and is based on the χ^2 test of independence for categorical variables, and the Wilcoxon test for continuous variables.

†Chronic kidney disease is defined as an estimated glomerular filtration rate (eGFR) of less than 60 ml/min/1.73 m^2 of body surface area. eGFRs of stages 3a, 3b, 4, and 5 are defined as follows: stage 3a, 45–59 ml/min/1.73 m^2; stage 3b, 30–44 ml/min/1.73 m^2; stage 4, 15–29 ml/min/1.73 m^2; stage 5, ≤14 ml/min/1.73 m^2.

‡ Previous cardiovascular events include myocardial infarction, stroke, heart failure hospitalization, and coronary revascularization.

Table S2. Baseline characteristics and incidence of outcomes according to tertiles of sFlt-1 levels in the entire cohort.

Baseline characteristics and incidence of events	Tertile 1		Tertile 2		Tertile 3		*P* value*
	No.	Value	No.	Value	No.	Value	
Baseline characteristics							
Age, mean (SD), y	1086	69.2 (10.5)	1084	70.6 (10.0)	1085	70.8 (10.7)	<0.001
Male	1086	743 (68.4)	1084	774 (71.4)	1085	755 (69.6)	0.312
Body mass index, mean (SD)	1086	24.7 (3.9)	1084	24.5 (3.9)	1085	24.3 (4.2)	0.013
Obesity†	1086	459 (42.3)	1084	441 (40.7)	1085	411 (37.9)	0.108
Hypertension	1086	834 (76.8)	1084	853 (78.7)	1085	796 (73.4)	0.013
Dyslipidemia	1086	879 (80.9)	1084	843 (77.8)	1085	758 (69.9)	<0.001
Diabetes	1086	431 (39.7)	1084	411 (37.9)	1085	439 (40.5)	0.461
Current smoker	1086	227 (20.9)	1084	182 (16.8)	1085	182 (16.8)	0.016
Former smoker	1086	436 (40.2)	1084	481 (44.4)	1085	473 (43.6)	0.106
eGFR, mean (SD), ml/min/1.73 m^2	1086	66 (20)	1084	62 (19)	1085	62 (20)	<0.001
Chronic kidney disease ‡	1086	374 (34.4)	1084	453 (41.8)	1085	474 (43.7)	<0.001
Stages of chronic kidney disease ‡	1086		1084		1085		<0.001
Stage 3a		247 (22.7)		298 (27.5)		289 (26.6)	
Stage 3b		95 (8.8)		106 (9.8)		122 (11.2)	
Stage 4		18 (1.7)		23 (2.1)		32 (3.0)	
Stage 5		14 (1.3)		26 (2.4)		31 (2.9)	
Dialysis	1086	15 (1.4)	1084	23 (2.1)	1085	29 (2.7)	0.104
Gensini score, median (IQR) §	1086	12.0 (3.0-32.0)	1084	11.3 (2.5-32.0)	1085	9.0 (1.0-28.0)	<0.001
Obstructive CAD	1086	671 (61.8)	1084	689 (63.6)	1085	628 (57.9)	0.021

Multivessel or LMT disease	1086	379 (34.9)	1084	367 (33.9)	1085	348 (32.1)	0.371
NYHA class III or IV	1086	41 (3.8)	1084	64 (5.9)	1085	114 (10.5)	<0.001
Atrial fibrillation	1086	39 (3.6)	1084	98 (9.0)	1085	187 (17.2)	<0.001
Anemia ‖	1086	316 (29.1)	1084	300 (27.7)	1085	312 (28.8)	0.746
Previous MI	1086	169 (15.6)	1084	160 (14.8)	1085	117 (10.8)	0.003
Previous PCI	1086	321 (29.6)	1084	292 (26.9)	1085	232 (21.4)	<0.001
Previous CABG	1086	33 (3.0)	1084	49 (4.5)	1085	29 (2.7)	0.043
Previous CAD (MI, PCI, or CABG)	1086	343 (31.6)	1084	333 (30.7)	1085	255 (23.5)	<0.001
Previous stroke	1086	138 (12.7)	1084	141 (13.0)	1085	106 (9.8)	0.036
Previous heart failure hospitalization	1086	54 (5.0)	1084	81 (7.5)	1085	150 (13.8)	<0.001
Previous cardiovascular events #	1086	495 (45.6)	1084	509 (47.0)	1085	475 (43.8)	0.329
Family history of cardiovascular events	1086	236 (21.7)	1084	247 (22.8)	1085	236 (21.8)	0.795
Previous malignancies	1086	99 (9.1)	1084	100 (9.2)	1085	98 (9.0)	0.988
Systolic blood pressure, mean (SD), mmHg	1086	128 (18)	1084	129 (19)	1085	126 (19)	0.010
Diastolic blood pressure, mean (SD), mmHg	1086	72 (13)	1084	73 (13)	1085	72 (14)	0.409
Pulse rate, mean (SD), beats per minute	1086	69 (12)	1084	70 (13)	1085	72 (15)	<0.001
LDL-cholesterol, mean (SD), mg/dL	1082	108 (35)	1079	108 (33)	1077	109 (34)	0.462
HDL-cholesterol, mean (SD), mg/dL	1077	53 (16)	1074	53 (16)	1075	53 (16)	0.470
Triglycerides, median (IQR), mg/dL	1078	120 (85-181)	1075	115 (85-169)	1072	114 (81-162)	0.014
Fasting glucose, median (IQR), mg/dL	1071	107 (95-128)	1066	108 (96-134)	1068	110 (96-134)	0.148
Hemoglobin A1c, median (IQR), %	1054	6.0 (5.6-6.6)	1054	6.0 (5.6-6.7)	1057	6.0 (5.6-6.8)	0.148
Creatinine, median (IQR), mg/dL	1086	0.8 (0.7-1.0)	1084	0.9 (0.7-1.0)	1085	0.9 (0.7-1.1)	<0.001
Hemoglobin, mean (SD), g/dL	1086	13.3 (1.7)	1084	13.4 (1.7)	1085	13.5 (1.9)	0.039

Hematocrit, mean (SD), %	1086	40 (5)	1083	40 (5)	1085	41 (6)	<0.001
Uric acid, mean (SD), mg/dL	1074	5.7 (1.4)	1063	5.9 (2.1)	1071	6.1 (1.8)	<0.001
sFlt-1, median (IQR), pg/mL	1086	85 (77-91)	1084	108 (102-114)	1085	145 (131-175)	<0.001
NT-proBNP, median (IQR), pg/mL	1086	113 (51-304)	1084	157 (65-517)	1085	307 (88-1174)	<0.001
hs-cTnI, median (IQR), pg/mL	1086	6 (4-13)	1084	7 (4-15)	1085	9 (5-22)	<0.001
cTnI, median (IQR), ng/mL	1086	0.007 (0.001-0.016)	1084	0.007 (0.001-0.018)	1085	0.009 (0.002-0.027)	<0.001
hs-CRP, median (IQR), mg/L	1086	0.5 (0.2-1.6)	1084	0.6 (0.2-1.7)	1085	0.7 (0.3-2.3)	<0.001
Cystatin C, median (IQR), mg/L	1086	0.79 (0.67-0.97)	1084	0.82 (0.69-1.02)	1085	0.82 (0.68-1.02)	0.005
NGAL, median (IQR), ng/mL	1086	91 (64-127)	1084	99 (70-144)	1085	101 (72-149)	<0.001
VEGF, median (IQR), pg/mL	1086	304 (184-460)	1084	292 (182-447)	1085	303 (184-502)	0.442
PlGF, median (IQR), pg/mL	1086	14 (12-16)	1084	14 (12-16)	1085	13 (11-16)	0.129
sFlt-1/PlGF ratio, median (IQR)	1086	6.0 (4.9-7.2)	1084	7.9 (6.6-9.3)	1085	11.4 (8.9-14.8)	<0.001
UACR, median (IQR), mg/g	313	18 (7-59)	382	17 (7-77)	383	22 (9-104)	0.060
Antihypertensive drug use	1086	891 (82.0)	1084	890 (82.1)	1085	903 (83.2)	0.717
RASI	1086	636 (58.6)	1084	625 (57.7)	1085	622 (57.3)	0.833
ACEI	1086	171 (15.8)	1084	154 (14.2)	1085	178 (16.4)	0.348
ARB	1086	487 (44.8)	1084	477 (44.0)	1085	443 (40.8)	0.138
β-blocker	1086	388 (35.7)	1084	411 (37.9)	1085	464 (42.8)	0.003
Any lipid-lowering drug use	1086	754 (69.4)	1084	698 (64.4)	1085	591 (54.5)	<0.001
Statin use	1086	714 (65.8)	1084	656 (60.5)	1085	552 (50.9)	<0.001
Any hypoglycemic drug use	1086	362 (33.3)	1084	342 (31.6)	1085	327 (30.1)	0.276
Oral hypoglycemic drugs	1086	316 (29.1)	1084	302 (27.9)	1085	282 (26.0)	0.265
Insulin	1086	101 (9.3)	1084	89 (8.2)	1085	87 (8.0)	0.514

Any antiplatelet drug use	1086	735 (67.7)	1084	692 (63.8)	1085	566 (52.2)	<0.001
Aspirin use	1086	643 (59.2)	1084	595 (54.9)	1085	476 (43.9)	<0.001
Any anticoagulant drugs	1086	81 (7.5)	1084	139 (12.8)	1085	234 (21.6)	<0.001
Warfarin	1086	42 (3.9)	1084	68 (6.3)	1085	107 (9.9)	<0.001
Incidence of outcomes, no. (/1000 person-years)							
3-point MACE**	1086	40 (12.7)	1084	41 (13.2)	1085	75 (24.7)	–
All-cause death	1086	47 (14.8)	1084	62 (19.7)	1085	106 (34.4)	–
Cardiovascular death	1086	19 (6.0)	1084	17 (5.4)	1085	46 (14.9)	–
5-point MACE††	1086	445 (221.7)	1084	465 (237.1)	1085	451 (222.0)	–
MI	1086	7 (2.2)	1084	2 (0.6)	1085	3 (1.0)	–
Stroke	1086	18 (5.7)	1084	26 (8.3)	1085	33 (10.9)	–
Heart failure hospitalization	1086	31 (9.9)	1084	52 (16.9)	1085	96 (32.5)	–
Revascularization for coronary/peripheral artery disease	1086	403 (195.1)	1084	402 (196.4)	1085	346 (159.5)	–
PCI	1086	321 (141.1)	1084	335 (151.3)	1085	280 (119.7)	–
CABG	1086	50 (16.4)	1084	36 (11.8)	1085	51 (17.3)	–
Peripheral artery disease	1086	47 (15.3)	1084	48 (15.8)	1085	39 (13.0)	–

Values are expressed as number (percentage) unless otherwise indicated. The tertiles of sFlt-1 levels were as follows: tertile 1, ≤96.59; tertile 2, 96.59<, ≤121.17; tertile 3, >121.17 pg/mL. sFlt-1 indicates soluble fms-like tyrosine kinase1; SD, standard deviation; eGFR, estimated glomerular filtration rate; IQR, interquartile range; CAD, coronary artery disease; NYHA, New York Heart Association; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; LDL, low-density lipoprotein; HDL, high-density lipoprotein; NT-proBNP, N-terminal pro-brain natriuretic peptide; hs-cTnI, high-sensitivity cardiac troponin I; cTnI, contemporary sensitive cardiac troponin I; hs-CRP, high-sensitivity C-reactive protein; NGAL, neutrophil gelatinase-associated lipocalin; VEGF, vascular endothelial growth factor; PlGF, placental growth factor; UACR, urine albumin to

creatinine ratio; RASI, renin angiotensin system inhibitors; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; and MACE, major adverse cardiovascular events.

*The *P* value is for comparison between groups, and is based on the χ^2 test of independence for categorical variables, and the Kruskal-Wallis test for continuous variables.

†Obesity is defined as a body mass index of 25 or more.

‡Chronic kidney disease is defined as an eGFR of less than 60 ml/min/1.73 m^2 of body surface area. eGFRs of stages 3a, 3b, 4, and 5 are defined as follows: stage 3a, 45–59 ml/min/1.73 m^2; stage 3b, 30–44 ml/min/1.73 m^2; stage 4, 15–29 ml/min/1.73 m^2; stage 5, ≤14 ml/min/1.73 m^2.

§The Gensini score represents the angiographic severity of coronary artery disease employing a nonlinear points system for degree of luminal narrowing.

‖Anemia is defined as a hemoglobin level of less than 13 g/dL in men and less than 12 g/dL in women.

#Previous cardiovascular events include myocardial infarction, stroke, heart failure hospitalization, and coronary revascularization.

**3-point MACE is defined as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.

††5-point MACE is defined as a composite of 3-point MACE, heart failure hospitalization, and revascularization for coronary/peripheral artery disease.

Table S3. Baseline characteristics and incidence of outcomes according to tertiles of sFlt-1 levels in CKD patients.

Baseline characteristics and incidence of events	Tertile 1		Tertile 2		Tertile 3		*P* value*
	No.	Value	No.	Value	No.	Value	
Baseline characteristics							
Age, mean (SD), y	443	73.4 (8.1)	424	73.2 (8.7)	434	74.0 (8.8)	0.394
Male	443	293 (66.1)	424	303 (71.5)	434	296 (68.2)	0.236
Body mass index, mean (SD)	443	24.9 (3.7)	424	24.5 (3.9)	434	24.1 (4.2)	0.002
Obesity†	443	210 (47.4)	424	170 (40.1)	434	158 (36.4)	0.003
Hypertension	443	386 (87.1)	424	368 (86.8)	434	358 (82.5)	0.096
Dyslipidemia	443	355 (80.1)	424	334 (78.8)	434	314 (72.4)	0.014
Diabetes	443	204 (46.1)	424	181 (42.7)	434	181 (41.7)	0.396
Current smoker	443	70 (15.8)	424	60 (14.2)	434	59 (13.6)	0.628
Former smoker	443	194 (43.8)	424	206 (48.6)	434	194 (44.7)	0.325
eGFR, mean (SD), ml/min/1.73 m^2	443	46 (12)	424	45 (13)	434	44 (13)	0.108
Dialysis	443	16 (3.6)	424	25 (5.9)	434	26 (6.0)	0.196
Gensini score, median (IQR)‡	443	14.0 (5.0-35.0)	424	15.0 (2.5-38.8)	434	10.0 (2.0-30.3)	0.010
Obstructive CAD	443	283 (63.9)	424	278 (65.6)	434	267 (61.5)	0.465
Multivessel or LMT disease	443	165 (37.3)	424	163 (38.4)	434	147 (33.9)	0.352
NYHA class III or IV	443	29 (6.6)	424	31 (7.3)	434	65 (15.0)	<0.001
Atrial fibrillation	443	26 (5.9)	424	45 (10.6)	434	101 (23.3)	<0.001
Anemia§	443	185 (41.8)	424	167 (39.4)	434	164 (37.8)	0.481
Previous MI	443	65 (14.7)	424	61 (14.4)	434	55 (12.7)	0.654
Previous PCI	443	137 (30.9)	424	119 (28.1)	434	116 (26.7)	0.372

Previous CABG	443	22 (5.0)	424	24 (5.7)	434	22 (5.1)	0.885
Previous CAD (MI, PCI, or CABG)	443	148 (33.4)	424	139 (32.8)	434	127 (29.3)	0.367
Previous stroke	443	67 (15.1)	424	70 (16.5)	434	48 (11.1)	0.059
Previous heart failure hospitalization	443	39 (8.8)	424	43 (10.1)	434	91 (21.0)	<0.001
Previous cardiovascular events‖	443	218 (49.2)	424	223 (52.6)	434	232 (53.5)	0.412
Family history of cardiovascular events	443	121 (27.3)	424	107 (25.2)	434	95 (21.9)	0.173
Previous malignancies	443	54 (12.2)	424	49 (11.6)	434	43 (9.9)	0.544
Systolic blood pressure, mean (SD), mmHg	443	130 (18)	424	129 (20)	434	127 (20)	0.223
Diastolic blood pressure, mean (SD), mmHg	443	71 (13)	424	71 (13)	434	72 (14)	0.582
Pulse rate, mean (SD), beats per minute	443	69 (13)	424	71 (14)	434	73 (15)	<0.001
LDL-cholesterol, mean (SD), mg/dL	441	107 (35)	422	109 (34)	428	108 (35)	0.473
HDL-cholesterol, mean (SD), mg/dL	440	51 (14)	422	51 (15)	426	52 (15)	0.550
Triglycerides, median (IQR), mg/dL	439	123 (88-181)	421	118 (88-170)	426	115 (86-169)	0.282
Fasting glucose, median (IQR), mg/dL	435	108 (94-132)	418	109 (96-136)	424	108 (93-133)	0.599
Hemoglobin A1c, median (IQR), %	430	6.1 (5.7-6.8)	416	6.1 (5.7-6.8)	422	6.1 (5.7-6.8)	0.898
Creatinine, median (IQR), mg/dL	443	1.1 (1.0-1.2)	424	1.1 (1.0-1.3)	434	1.1 (1.0-1.3)	0.053
Hemoglobin, mean (SD), g/dL	443	12.8 (1.8)	424	12.9 (1.7)	434	13.2 (2.2)	0.086
Hematocrit, mean (SD), %	443	38 (5)	423	39 (5)	434	40 (6)	0.001
Uric acid, mean (SD), mg/dL	436	6.1 (1.5)	414	6.3 (1.6)	427	6.7 (1.8)	<0.001
sFlt-1, median (IQR), pg/mL	443	88 (80-95)	424	112 (106-117)	434	148 (134-179)	<0.001
NT-proBNP, median (IQR), pg/mL	443	200 (78-620)	424	264 (105-1181)	434	678 (181-2313)	<0.001
hs-cTnI, median (IQR), pg/mL	443	8 (5-18)	424	10 (6-21)	434	12 (7-33)	<0.001
cTnI, median (IQR), ng/mL	443	0.010 (0.003-0.022)	424	0.010 (0.003-0.023)	434	0.015 (0.004-0.041)	<0.001

hs-CRP, median (IQR), mg/L	443	0.7 (0.3-1.9)	424	0.6 (0.3-2.0)	434	0.9 (0.3-2.7)	0.011
Cystatin C, median (IQR), mg/L	443	0.99 (0.82-1.22)	424	1.01 (0.82-1.22)	434	0.99 (0.83-1.26)	0.808
NGAL, median (IQR), ng/mL	443	112 (79-161)	424	124 (87-179)	434	131 (91-194)	<0.001
VEGF, median (IQR), pg/mL	443	309 (192-460)	424	311 (194-471)	434	301 (182-514)	0.797
PlGF, median (IQR), pg/mL	443	14 (12-17)	424	14 (12-17)	434	13 (11-17)	0.069
sFlt-1/PlGF ratio, median (IQR)	443	6.1 (5.1-7.4)	424	8.1 (6.7-9.5)	434	11.7 (9.3-15.3)	<0.001
UACR, median (IQR), mg/g	372	18 (7-58)	354	18 (7-89)	352	22 (9-103)	0.060
Antihypertensive drug use	443	385 (86.9)	424	382 (90.1)	434	387 (89.2)	0.311
RASI	443	306 (69.1)	424	267 (63.0)	434	278 (64.1)	0.129
ACEI	443	70 (15.8)	424	53 (12.5)	434	77 (17.7)	0.099
ARB	443	243 (54.9)	424	210 (49.5)	434	203 (46.8)	0.052
β-blocker	443	161 (36.3)	424	174 (41.0)	434	214 (49.3)	<0.001
Any lipid-lowering drug use	443	298 (67.3)	424	272 (64.2)	434	229 (52.8)	<0.001
Statin use	443	277 (62.5)	424	250 (59.0)	434	215 (49.5)	<0.001
Any hypoglycemic drug use	443	179 (40.4)	424	156 (36.8)	434	138 (31.8)	0.029
Oral hypoglycemic drugs	443	159 (35.9)	424	129 (30.4)	434	120 (27.7)	0.028
Insulin	443	49 (11.1)	424	48 (11.3)	434	38 (8.8)	0.395
Any antiplatelet drug use	443	294 (66.4)	424	266 (62.7)	434	239 (55.1)	0.002
Aspirin use	443	258 (58.2)	424	216 (50.9)	434	200 (46.1)	0.001
Any anticoagulant drugs	443	41 (9.3)	424	67 (15.8)	434	122 (28.1)	<0.001
Warfarin	443	22 (5.0)	424	35 (8.3)	434	64 (14.8)	<0.001
Incidence of outcomes, no. (/1000 person-years)							

3-point MACE[#]	443	25 (19.9)	424	20 (16.7)	434	43 (36.2)	–
All-cause death	443	30 (23.5)	424	38 (31.5)	434	60 (49.4)	–
Cardiovascular death	443	15 (11.8)	424	8 (6.6)	434	27 (22.2)	–
5-point MACE[**]	443	198 (250.8)	424	194 (267.1)	434	203 (266.7)	–
MI	443	3 (2.4)	424	1 (0.8)	434	1 (0.8)	–
Stroke	443	10 (7.9)	424	11 (9.2)	434	21 (17.7)	–
Heart failure hospitalization	443	25 (20.2)	424	27 (23.0)	434	55 (48.2)	–
Revascularization for coronary/peripheral artery disease	443	169 (204.7)	424	166 (217.7)	434	142 (168.8)	–
PCI	443	125 (134.1)	424	132 (157.2)	434	108 (116.5)	–
CABG	443	23 (18.9)	424	22 (19.1)	434	29 (25.4)	–
Peripheral artery disease	443	27 (22.2)	424	20 (17.2)	434	15 (12.6)	–

Values are expressed as number (percentage) unless otherwise indicated. The tertiles of sFlt-1 levels were as follows: tertile 1, ≤100.00; tertile 2, 100.00<, ≤124.91; tertile 3, >124.91 pg/mL. CKD is defined as an eGFR of less than 60 ml/min/1.73 m^2 of body surface area. sFlt-1 indicates soluble fms-like tyrosine kinase1; CKD, chronic kidney disease; SD, standard deviation; eGFR, estimated glomerular filtration rate; IQR, interquartile range; CAD, coronary artery disease; NYHA, New York Heart Association; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; LDL, low-density lipoprotein; HDL, high-density lipoprotein; NT-proBNP; N-terminal pro-brain natriuretic peptide; hs-cTnI, high-sensitivity cardiac troponin I; cTnI, contemporary sensitive cardiac troponin I; hs-CRP, high-sensitivity C-reactive protein; NGAL, neutrophil gelatinase-associated lipocalin; VEGF, vascular endothelial growth factor; PlGF, placental growth factor; UACR, urine albumin to creatinine ratio; RASI, renin angiotensin system inhibitors; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; and MACE, major adverse cardiovascular events.

*The *P* value is for comparison between groups, and is based on the χ^2 test of independence for categorical variables, and the Kruskal-Wallis test for continuous variables.

[†]Obesity is defined as a body mass index of 25 or more.

[‡]The Gensini score represents the angiographic severity of coronary artery disease employing a nonlinear points system for degree of luminal narrowing.

[§]Anemia is defined as a hemoglobin level of less than 13 g/dL in men and less than 12 g/dL in women.

[‖]Previous cardiovascular events include myocardial infarction, stroke, heart failure hospitalization, and coronary revascularization.

[#]3-point MACE is defined as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.

[**]5-point MACE is defined as a composite of 3-point MACE, heart failure hospitalization, and revascularization for coronary/peripheral artery disease.

Table S4. Baseline characteristics and incidence of outcomes according to tertiles of sFlt-1 levels in non-CKD patients.

Baseline characteristics and incidence of events	Tertile 1		Tertile 2		Tertile 3		*P* value*
	No.	Value	No.	Value	No.	Value	
Baseline characteristics							
Age, mean (SD), y	652	66.8 (11.0)	651	68.6 (10.5)	651	68.5 (11.3)	0.002
Male	652	466 (71.5)	651	453 (69.6)	651	461 (70.8)	0.750
Body mass index, mean (SD)	652	24.6 (3.9)	651	24.4 (4.0)	651	24.4 (4.2)	0.433
Obesity†	652	260 (39.9)	651	259 (39.8)	651	254 (39.0)	0.941
Hypertension	652	462 (70.9)	651	474 (72.8)	651	435 (66.8)	0.055
Dyslipidemia	652	536 (82.2)	651	495 (76.0)	651	446 (68.5)	<0.001
Diabetes	652	236 (36.2)	651	229 (35.2)	651	250 (38.4)	0.466
Current smoker	652	151 (23.2)	651	124 (19.1)	651	127 (19.5)	0.132
Former smoker	652	259 (39.7)	651	264 (40.6)	651	273 (41.9)	0.714
eGFR, mean (SD), ml/min/1.73 m^2	652	77 (15)	651	75 (13)	651	75 (13)	0.001
Gensini score, median (IQR)‡	652	11.0 (2.0-32.0)	651	9.5 (2.0-28.0)	651	8.0 (1.0-28.0)	0.006
Obstructive CAD	652	404 (62.0)	651	389 (59.8)	651	367 (56.4)	0.118
Multivessel or LMT disease	652	226 (34.7)	651	190 (29.2)	651	203 (31.2)	0.099
NYHA class III or IV	652	17 (2.6)	651	31 (4.8)	651	46 (7.1)	<0.001
Atrial fibrillation	652	16 (2.5)	651	47 (7.2)	651	89 (13.7)	<0.001
Anemia§	652	141 (21.6)	651	132 (20.3)	651	139 (21.4)	0.820
Previous MI	652	104 (16.0)	651	95 (14.6)	651	66 (10.1)	0.006
Previous PCI	652	194 (29.8)	651	163 (25.0)	651	116 (17.8)	<0.001
Previous CABG	652	12 (1.8)	651	25 (3.8)	651	6 (0.9)	0.001

Previous CAD (MI, PCI, or CABG)	652	206 (31.6)	651	183 (28.1)	651	128 (19.7)	<0.001
Previous stroke	652	70 (10.7)	651	67 (10.3)	651	63 (9.7)	0.818
Previous heart failure hospitalization	652	20 (3.1)	651	33 (5.1)	651	59 (9.1)	<0.001
Previous cardiovascular events‖	652	287 (44.0)	651	273 (41.9)	651	246 (37.8)	0.067
Family history of cardiovascular events	652	128 (19.6)	651	137 (21.0)	651	131 (20.1)	0.813
Previous malignancies	652	51 (7.8)	651	47 (7.2)	651	53 (8.1)	0.819
Systolic blood pressure, mean (SD), mmHg	652	126 (17)	651	130 (18)	651	126 (19)	0.001
Diastolic blood pressure, mean (SD), mmHg	652	72 (13)	651	74 (12)	651	72 (13)	0.189
Pulse rate, mean (SD), beats per minute	652	69 (12)	651	70 (13)	651	71 (14)	0.016
LDL-cholesterol, mean (SD), mg/dL	650	109 (35)	647	108 (33)	650	110 (34)	0.581
HDL-cholesterol, mean (SD), mg/dL	645	54 (16)	644	55 (16)	649	54 (16)	0.122
Triglycerides, median (IQR), mg/dL	648	121 (83-182)	645	113 (84-167)	646	111 (79-160)	0.018
Fasting glucose, median (IQR), mg/dL	644	108 (95-128)	642	107 (96-131)	642	111 (97-133)	0.123
Hemoglobin A1c, median (IQR), %	632	6.0 (5.6-6.6)	634	6.0 (5.6-6.7)	631	6.0 (5.6-6.8)	0.259
Creatinine, median (IQR), mg/dL	652	0.8 (0.6-0.9)	651	0.8 (0.7-0.9)	651	0.8 (0.7-0.9)	0.225
Hemoglobin, mean (SD), g/dL	652	13.6 (1.6)	651	13.7 (1.6)	651	13.8 (1.7)	0.148
Hematocrit, mean (SD), %	652	40 (4)	651	41 (4)	651	41 (5)	<0.001
Uric acid, mean (SD), mg/dL	646	5.5 (1.3)	641	5.6 (2.4)	644	5.7 (1.7)	0.059
sFlt-1, median (IQR), pg/mL	652	83 (76-89)	651	105 (100-112)	651	142 (128-171)	<0.001
NT-proBNP, median (IQR), pg/mL	652	84 (44-209)	651	116 (52-289)	651	174 (64-605)	<0.001
hs-cTnI, median (IQR), pg/mL	652	6 (3-10)	651	6 (4-12)	651	7 (4-15)	<0.001
cTnI, median (IQR), ng/mL	652	0.005 (0.000-0.014)	651	0.005 (0.000-0.015)	651	0.007 (0.000-0.021)	0.006
hs-CRP, median (IQR), mg/L	652	0.5 (0.2-1.5)	651	0.5 (0.2-1.4)	651	0.7 (0.3-2.0)	<0.001

Cystatin C, median (IQR), mg/L	652	0.72 (0.64-0.84)	651	0.74 (0.63-0.86)	651	0.72 (0.62-0.84)	0.374
NGAL, median (IQR), ng/mL	652	83 (57-114)	651	85 (62-120)	651	86 (65-118)	0.024
VEGF, median (IQR), pg/mL	652	302 (182-463)	651	285 (177-436)	651	303 (182-485)	0.471
PlGF, median (IQR), pg/mL	652	14 (12-16)	651	14 (12-16)	651	14 (11-16)	0.585
sFlt-1/PlGF ratio, median (IQR)	652	5.9 (4.9-7.1)	651	7.7 (6.5-9.2)	651	11.3 (8.9-14.4)	<0.001
UACR, median (IQR), mg/g							
Antihypertensive drug use	652	520 (79.8)	651	496 (76.2)	651	514 (79.0)	0.262
RASI	652	347 (53.2)	651	342 (52.5)	651	343 (52.7)	0.967
ACEI	652	99 (15.2)	651	106 (16.3)	651	98 (15.1)	0.797
ARB	652	263 (40.3)	651	245 (37.6)	651	243 (37.3)	0.470
β-blocker	652	239 (36.7)	651	223 (34.3)	651	252 (38.7)	0.248
Any lipid-lowering drug use	652	465 (71.3)	651	418 (64.2)	651	361 (55.5)	<0.001
Statin use	652	445 (68.3)	651	397 (61.0)	651	338 (51.9)	<0.001
Any hypoglycemic drug use	652	196 (30.1)	651	178 (27.3)	651	184 (28.3)	0.543
Oral hypoglycemic drugs	652	169 (25.9)	651	165 (25.4)	651	158 (24.3)	0.785
Insulin	652	55 (8.4)	651	40 (6.1)	651	47 (7.2)	0.281
Any antiplatelet drug use	652	446 (68.4)	651	416 (63.9)	651	332 (51.0)	<0.001
Aspirin use	652	391 (60.0)	651	365 (56.1)	651	284 (43.6)	<0.001
Any anticoagulant drugs	652	43 (6.6)	651	70 (10.8)	651	111 (17.1)	<0.001
Warfarin	652	20 (3.1)	651	34 (5.2)	651	42 (6.5)	0.017
Incidence of outcomes, no. (/1000 person-years)							
3-point MACE[#]	652	16 (8.4)	651	20 (10.5)	651	32 (17.3)	–

All-cause death	652	20 (10.4)	651	22 (11.5)	651	45 (24.1)	–
Cardiovascular death	652	5 (2.6)	651	9 (4.7)	651	18 (9.6)	–
5-point MACE**	652	258 (210.5)	651	254 (204.0)	651	254 (202.9)	–
MI	652	4 (2.1)	651	1 (0.5)	651	2 (1.1)	–
Stroke	652	8 (4.2)	651	13 (6.8)	651	14 (7.6)	–
Heart failure hospitalization	652	9 (4.7)	651	24 (12.8)	651	39 (21.5)	–
Revascularization for coronary/peripheral artery disease	652	242 (193.6)	651	223 (173.2)	651	209 (159.0)	–
PCI	652	200 (147.0)	651	195 (142.8)	651	176 (125.4)	–
CABG	652	28 (15.2)	651	15 (8.0)	651	20 (11.0)	–
Peripheral artery disease	652	23 (12.3)	651	24 (12.9)	651	25 (13.8)	–

Values are expressed as number (percentage) unless otherwise indicated. The tertiles of sFlt-1 levels were as follows: tertile 1, ≤94.45; tertile 2, 94.45<, ≤119.69; tertile 3, >119.69 pg/mL. CKD is defined as an eGFR of less than 60 ml/min/1.73 m^2 of body surface area. sFlt-1 indicates soluble fms-like tyrosine kinase1; CKD, chronic kidney disease; SD, standard deviation; eGFR, estimated glomerular filtration rate; IQR, interquartile range; CAD, coronary artery disease; NYHA, New York Heart Association; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; LDL, low-density lipoprotein; HDL, high-density lipoprotein; NT-proBNP, N-terminal pro-brain natriuretic peptide; hs-cTnI, high-sensitivity cardiac troponin I; cTnI, contemporary sensitive cardiac troponin I; hs-CRP, high-sensitivity C-reactive protein; NGAL, neutrophil gelatinase-associated lipocalin; VEGF, vascular endothelial growth factor; PlGF, placental growth factor; UACR, urine albumin to creatinine ratio; RASI, renin angiotensin system inhibitors; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; and MACE, major adverse cardiovascular events.

*The *P* value is for comparison between groups, and is based on the χ^2 test of independence for categorical variables, and the Kruskal-Wallis test for continuous variables.

†Obesity is defined as a body mass index of 25 or more.

‡The Gensini score represents the angiographic severity of coronary artery disease employing a nonlinear points system for degree of luminal narrowing.

§Anemia is defined as a hemoglobin level of less than 13 g/dL in men and less than 12 g/dL in women.

‖Previous cardiovascular events include myocardial infarction, stroke, heart failure hospitalization, and coronary revascularization.

#3-point MACE is defined as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.

**5-point MACE is defined as a composite of 3-point MACE, heart failure hospitalization, and revascularization for coronary/peripheral artery disease.

Table S5. Simple and multiple stepwise regression analyses for the sFlt-1 level* in the entire cohort

Variables	Simple regression			Independent determinants		
	r	SEM	*p*	*β*	SEM	*p*
Age, y	0.004	0.002	0.01			
Male	-0.033	0.038	0.393			
Body mass index, kg/m^2	-0.008	0.004	0.053			
Hypertension	-0.115	0.041	0.005			
Dyslipidemia	-0.234	0.041	<0.001			
Diabetes	0.007	0.036	0.84			
Current smoker	-0.083	0.045	0.068			
Former smoker	0.010	0.035	0.772			
eGFR, ml/min/1.73 m^2	-0.004	0.001	<0.001			
Gensini score*	-0.048	0.012	<0.001			
Previous myocardial infarction	-0.136	0.051	0.008			
Previous stroke	-0.082	0.054	0.129			
Previous heart failure hospitalization	0.488	0.061	<0.001	0.210	0.063	<0.001
Atrial fibrillation	0.583	0.058	<0.001	0.260	0.061	<0.001
Anemia	0.009	0.039	0.81	-0.150	0.040	<0.001
Antihypertensive drug use	0.051	0.046	0.273			
Statin use	-0.248	0.035	<0.001	-0.171	0.034	<0.001
Aspirin use	-0.222	0.035	<0.001			
NT-proBNP, pg/mL*	0.232	0.017	<0.001	0.233	0.022	<0.001
hs-cTnI, pg/mL*	0.145	0.017	<0.001			
hs-CRP, mg/L*	0.082	0.017	<0.001	0.052	0.017	0.003
Cystatin C, mg/L*	0.040	0.018	0.024	-0.142	0.023	<0.001
NGAL, ng/mL*	0.082	0.017	<0.001	0.096	0.021	<0.001
VEGF, pg/mL*	-0.048	0.018	0.006	-0.084	0.017	<0.001
PlGF, pg/mL*	0.033	0.018	0.057			
UACR, mg/g*	0.058	0.029	0.050			

sFlt-1 indicates soluble fms-like tyrosine kinase1; SEM, standard error of the mean; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-brain natriuretic peptide; hs-cTnI, high-sensitivity cardiac troponin I; hs-CRP, high-sensitivity C-reactive protein; NGAL, neutrophil gelatinase-associated lipocalin; VEGF, vascular endothelial growth factor; PlGF, placental growth factor; and UACR, urine albumin to creatinine ratio.

*Natural log-transformed to obtain normal distributions.

Table S6. The tertiles of biomarker levels in the entire cohort, CKD* patients, and non-CKD patients.

Biomarker levels	Tertile 1		Tertile 2		Tertile 3	
	No.	Value	No.	Value	No.	Value
sFlt-1, pg/mL						
Entire cohort	1086	≤96.59	1084	96.59<, ≤121.17	1085	>121.17
CKD	443	≤100.00	424	100.00<, ≤124.91	434	>124.91
Non-CKD	652	≤94.45	651	94.45<, ≤119.69	651	>119.69
NT-proBNP, pg/mL						
Entire cohort	1094	≤87	1078	87<, ≤352	1083	>352
CKD	435	≤150	432	150<, ≤798	434	>798
Non-CKD	656	≤67	647	67<, ≤221	651	>221
hs-cTnI, pg/mL						
Entire cohort	1089	≤5.2	1082	5.2<, ≤11.8	1084	>11.8
CKD	434	≤6.7	434	6.7<, ≤16.7	433	>16.7
Non-CKD	674	≤4.5	633	4.5<, ≤9.2	647	>9.2
hs-CRP, mg/L						
Entire cohort	1086	≤0.3362	1084	0.3362<, ≤1.1923	1085	>1.1923
CKD	434	≤0.4059	433	0.4059<, ≤1.4484	434	>1.4484
Non-CKD	652	≤0.2991	651	0.2991<, ≤1.0258	651	>1.0258
Cystatin C, mg/L						
Entire cohort	1088	≤0.7200	1082	0.7200<, ≤0.9200	1085	>0.9200
CKD	434	≤0.8794	433	0.8794<, ≤1.1397	434	>1.11397
Non-CKD	652	≤0.6663	651	0.6663<, ≤0.8034	651	>0.8034
NGAL, ng/mL						
Entire cohort	1085	≤78.01	1085	78.01<, ≤121.74	1085	>121.74
CKD	434	≤96.10	433	96.10<, ≤154.46	434	>154.46
Non-CKD	652	≤69.03	651	69.03<, ≤104.00	651	>104.00
VEGF, pg/mL						
Entire cohort	1085	≤221.8	1088	221.8<, ≤400.0	1082	>400.0
CKD	434	≤227.0	433	227.0<, ≤406.1	434	>406.1
Non-CKD	652	≤218.0	652	218.0<, ≤395.9	650	>395.9
PlGF, pg/mL						
Entire cohort	1093	≤12.00	1081	12.00<, ≤15.14	1081	>15.14
CKD	450	≤12.00	417	12.00<, ≤15.50	434	>15.50
Non-CKD	652	≤12.09	656	12.09<, ≤15.00	646	>15.00
sFlt-1/PlGF ratio						
Entire cohort	1085	≤6.6917	1085	6.6917<, ≤9.4339	1085	>9.4339

CKD	434	≤6.7955	433	6.7955<, ≤9.5959	434	>9.5959
Non-CKD	652	≤6.6224	651	6.6224<, ≤9.2593	651	>9.2593
UACR, mg/g						
CKD	360	≤10.500	359	10.500<, ≤45.313	359	>45.313

CKD indicates chronic kidney disease; IQR, interquartile range; NT-proBNP; N-terminal pro-brain natriuretic peptide; hs-cTnI, high-sensitivity cardiac troponin I; hs-CRP, high-sensitivity C-reactive protein; NGAL, neutrophil gelatinase-associated lipocalin; VEGF, vascular endothelial growth factor; PlGF, placental growth factor; and UACR, urine albumin to creatinine ratio.

* CKD is defined as an estimated glomerular filtration rate of less than 60 ml/min/1.73 m^2.

Table S7. Incremental predictive performance of selected biomarkers for all-cause death in the entire cohort, CKD patients, and non-CKD patients.

Subgroups and prediction models	C Statistics	∆C Statistics	Continuous NRI, 95%CI	*P* Value	IDI, 95%CI	*P* Value
Entire cohort						
Base model*	0.799	-	-		-	
Base+sFlt-1†	0.805	0.007	0.319 (0.181-0.457)	<0.001	0.006 (0.001-0.010)	0.024
Base+sFlt-1 (top tertile)†	0.804	0.005	0.342 (0.204-0.480)	<0.001	0.005 (0.001-0.010)	0.023
Base+NT-proBNP†	0.816	0.018	0.365 (0.228-0.502)	<0.001	0.017 (0.008-0.027)	<0.001
Base+hs-cTnI†	0.806	0.007	0.375 (0.237-0.512)	<0.001	0.005 (0.001-0.010)	0.027
Base+hs-CRP†	0.814	0.015	0.412 (0.274-0.549)	<0.001	0.016 (0.008-0.025)	<0.001
CKD						
Base model*	0.774	-	-		-	
Base+sFlt-1†	0.777	0.003	0.266 (0.084-0.448)	0.004	0.006 (0.000-0.012)	0.064
Base+sFlt-1 (top tertile)†	0.776	0.002	0.300 (0.119-0.481)	0.001	0.008 (0.001-0.015)	0.019
Base+NT-proBNP†	0.792	0.018	0.333 (0.152-0.514)	<0.001	0.021 (0.008-0.033)	0.001
Base+hs-cTnI†	0.782	0.008	0.432 (0.251-0.613)	<0.001	0.009 (0.001-0.016)	0.033
Base+hs-CRP†	0.788	0.014	0.291 (0.110-0.472)	0.002	0.014 (0.003-0.024)	0.010
Non-CKD						
Base model*	0.830	-	-		-	
Base+sFlt-1†	0.837	0.007	0.375 (0.161-0.588)	<0.001	0.007 (-0.002-0.017)	0.132
Base+sFlt-1 (top tertile)†	0.836	0.006	0.383 (0.169-0.597)	<0.001	0.005 (-0.002-0.013)	0.133
Base+NT-proBNP†	0.844	0.014	0.333 (0.120-0.547)	0.002	0.009 (-0.004-0.021)	0.167
Base+hs-cTnI†	0.835	0.005	0.321 (0.107-0.536)	0.003	0.002 (-0.003-0.007)	0.397
Base+hs-CRP†	0.843	0.013	0.333 (0.120-0.547)	0.002	0.018 (0.004-0.032)	0.011

Follow-up results are truncated after 3 years. The biomarkers are natural log-transformed and are modeled as continuous variables unless otherwise

indicated. The ΔC statistic, continuous NRI and IDI show the change in model performance from the base model. CI indicates confidence interval; hs-cTnI, high-sensitivity cardiac troponin I; hs-CRP, high-sensitivity C-reactive protein; IDI, integrated discrimination improvement; NRI, net reclassification improvement; NT-proBNP, N-terminal pro-brain natriuretic peptide; and sFlt-1, soluble fms-like tyrosine kinase 1.

*The base model is based on age, sex, body mass index, hypertension, dyslipidemia, diabetes, current smoking, estimated glomerular filtration rate, the Gensini score, previous myocardial infarction, previous stroke, previous heart failure hospitalization, atrial fibrillation, anemia, antihypertensive drug use, statin use, and aspirin use.

†The change of model performance was evaluated against the base model.

Table S8. Incremental predictive performance of selected biomarkers for CV death in the entire cohort, CKD patients, and non-CKD patients.

Subgroups and prediction models	C Statistics	ΔC Statistics	Continuous NRI, 95%CI	*P* Value	IDI, 95%CI	*P* Value
Entire cohort						
Base model*	0.776	-	-		-	
Base+sFlt-1†	0.790	0.014	0.344 (0.125-0.563)	0.002	0.008 (0.000-0.015)	0.042
Base+sFlt-1 (top tertile)†	0.789	0.013	0.467 (0.250-0.684)	<0.001	0.006 (0.001-0.011)	0.013
Base+NT-proBNP†	0.813	0.037	0.582 (0.369-0.796)	<0.001	0.034 (0.016-0.052)	<0.001
Base+hs-TnI†	0.802	0.026	0.510 (0.292-0.728)	<0.001	0.014 (0.005-0.023)	0.002
CKD						
Base model*	0.735	-	-		-	
Base+sFlt-1†	0.741	0.006	0.282 (0.000-0.564)	0.050	0.003 (-0.003-0.009)	0.306
Base+sFlt-1 (top tertile)†	0.748	0.013	0.429 (0.148-0.711)	0.003	0.008 (-0.001-0.016)	0.066
Base+NT-proBNP†	0.788	0.053	0.599 (0.325-0.873)	<0.001	0.038 (0.014-0.062)	0.002
Base+hs-TnI†	0.770	0.035	0.631 (0.355-0.907)	<0.001	0.021 (0.007-0.035)	0.003
Non-CKD						
Base model*	0.824	-	-		-	
Base+sFlt-1†	0.849	0.025	0.403 (0.055-0.751)	0.023	0.025 (-0.002-0.053)	0.070
Base+sFlt-1 (top tertile)†	0.839	0.015	0.465 (0.119-0.812)	0.008	0.008 (-0.001-0.018)	0.090
Base+NT-proBNP†	0.856	0.032	0.548 (0.205-0.890)	0.002	0.032 (0.004-0.060)	0.024
Base+hs-TnI†	0.849	0.025	0.433 (0.084-0.782)	0.015	0.009 (-0.007-0.025)	0.274

Follow-up results are truncated after 3 years. The biomarkers are natural log-transformed and are modeled as continuous variables unless otherwise indicated. The ΔC statistic, continuous NRI and IDI show the change in model performance from the base model. CI indicates confidence interval; CV, cardiovascular; hs-cTnI, high-sensitivity cardiac troponin I; IDI, integrated discrimination improvement; NRI, net reclassification improvement; NT-proBNP, N-terminal pro-brain natriuretic peptide; and sFlt-1, soluble fms-like tyrosine kinase 1.

*The base model is based on age, sex, body mass index, hypertension, dyslipidemia, diabetes, current smoking, estimated glomerular filtration rate, the Gensini score, previous myocardial infarction, previous stroke, previous heart failure hospitalization, atrial fibrillation, anemia, antihypertensive drug use, statin use, and aspirin use.

†The change of model performance was evaluated against the base model.

Table S9. Incremental predictive performance of selected biomarkers for 5-point MACE in the entire cohort, CKD patients, and non-CKD patients.

Subgroups and prediction models	C Statistics	ΔC Statistics	Continuous NRI, 95%CI	*P* Value	IDI, 95%CI	*P* Value
Entire cohort						
Base model*	0.730	-	-		-	
Base+NT-proBNP†	0.731	0.000	0.058 (-0.012-0.127)	0.104	0.001 (0.000-0.003)	0.084
Base+hs-TnI†	0.732	0.002	0.069 (0.002-0.137)	0.044	0.003 (0.001-0.005)	0.009
Base+hs-CRP†	0.731	0.001	0.096 (0.029-0.163)	0.005	0.001 (0.000-0.002)	0.079
Base+cystatin C†	0.731	0.001	0.089 (0.020-0.158)	0.011	0.002 (0.001-0.004)	0.011
CKD						
Base model*	0.738	-	-		-	
Base+NT-proBNP†	0.743	0.004	0.159 (0.050-0.267)	0.004	0.007 (0.002-0.011)	0.005
Base+hs-TnI†	0.741	0.003	0.195 (0.089-0.301)	<0.001	0.006 (0.002-0.011)	0.009
Base+hs-CRP†	0.738	0.000	0.196 (0.091-0.301)	<0.001	0.002 (0.000-0.005)	0.081
Base+cystatin C†	0.739	0.001	0.154 (0.046-0.263)	0.005	0.002 (0.000-0.005)	0.089
Non-CKD						
Base model*	0.726	-	-		-	
Base+NT-proBNP†	0.726	0.000	-0.032 (-0.123-0.058)	0.484	0.000 (0.000-0.000)	0.770
Base+hs-TnI†	0.726	0.000	0.047 (-0.041-0.134)	0.297	0.001 (-0.001-0.003)	0.176
Base+hs-CRP†	0.726	0.000	0.032 (-0.055-0.119)	0.473	0.000 (-0.001-0.001)	0.362
Base+cystatin C†	0.727	0.001	0.150 (0.059-0.240)	0.001	0.003 (0.000-0.006)	0.024

Follow-up results are truncated after 3 years. The biomarkers are natural log-transformed and are modeled as continuous variables unless otherwise indicated. The ΔC statistic, continuous NRI and IDI show the change in model performance from the base model. CI indicates confidence interval; hs-cTnI, high-sensitivity cardiac troponin I; hs-CRP, high-sensitivity C-reactive protein; IDI, integrated discrimination improvement; MACE, major adverse cardiovascular events; NRI, net reclassification improvement; and NT-proBNP, N-terminal pro-brain natriuretic peptide.

*The base model is based on age, sex, body mass index, hypertension, dyslipidemia, diabetes, current smoking, estimated glomerular filtration rate, the Gensini score, previous myocardial infarction, previous stroke, previous heart failure hospitalization, atrial fibrillation, anemia, antihypertensive drug use, statin use, and aspirin use.

†The change of model performance was evaluated against the base model.

Figure S1. Comparison of sFlt-1 levels among patients without CKD and those with CKD stages 3a, 3b, 4, and 5. Serum levels of sFlt-1 are natural log-transformed, and are expressed as mean ± SD. CKD is defined as an estimated glomerular filtration rate (eGFR) of less than 60 ml/min/1.73 m^2 of body surface area. eGFRs of stages 3a, 3b, 4, and 5 are defined as follows: stage 3a, 45–59 ml/min/1.73 m^2; stage 3b, 30–44 ml/min/1.73 m^2; stage 4, 15–29 ml/min/1.73 m^2; stage 5, ≤14 ml/min/1.73 m^2. Differences between groups were assessed by the Kruskal-Wallis test. Ln indicates natural log-transformed; sFlt-1, soluble fms-like tyrosine kinase 1; CKD, chronic kidney disease; and SD, standard deviation.

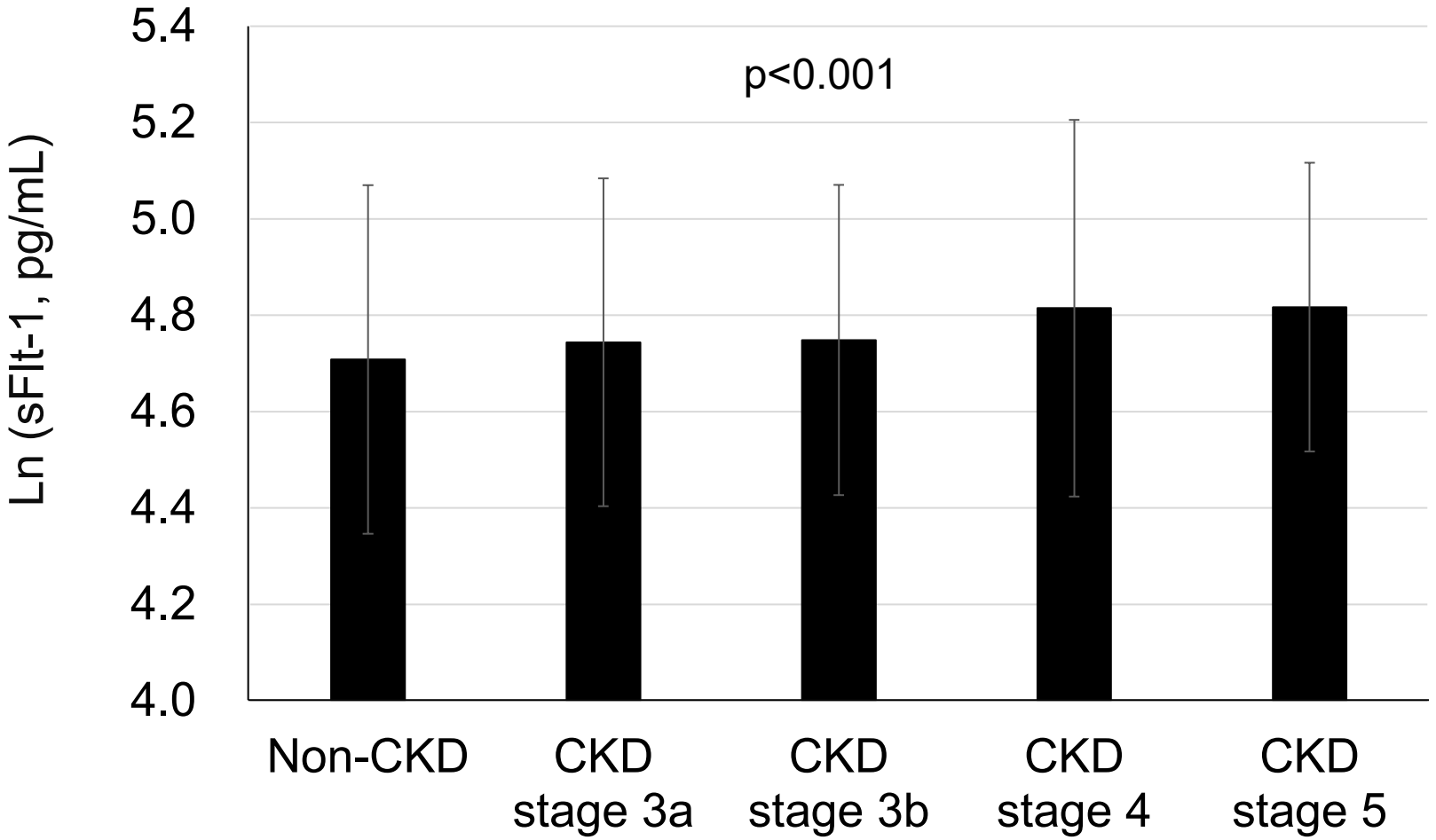
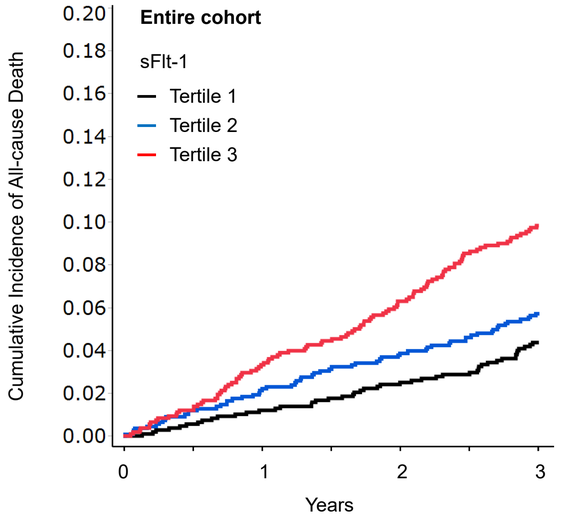


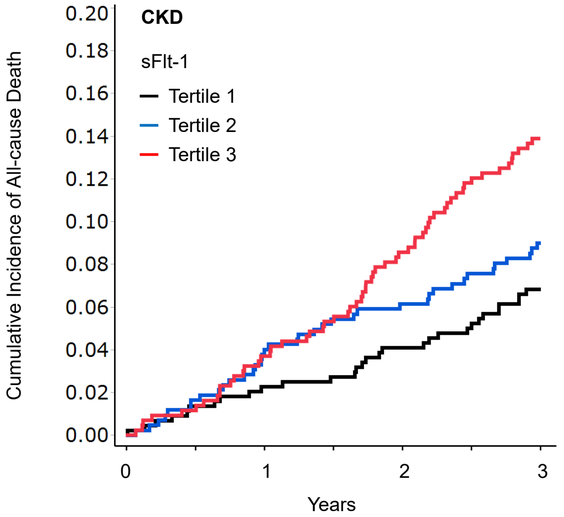
Figure S2. Cumulative incidence of all-cause death in the entire cohort (A), CKD patients (B), and non-CKD patients (C) according to the serum sFlt-1 level at baseline. Follow-up results are truncated after 3 years. The tertiles of sFlt-1 levels were as follows: A) tertile 1, ≤96.59; tertile 2, 96.59<, ≤121.17; tertile 3, >121.17 pg/mL; B) tertile 1, ≤100.00; tertile 2, 100.00<, ≤124.91; tertile 3, >124.91 pg/mL; C) tertile 1, ≤94.45; tertile 2, 94.45<, ≤119.69; tertile 3, >119.69 pg/mL. Abbreviations used in this figure are the same as in Figure S1.

A



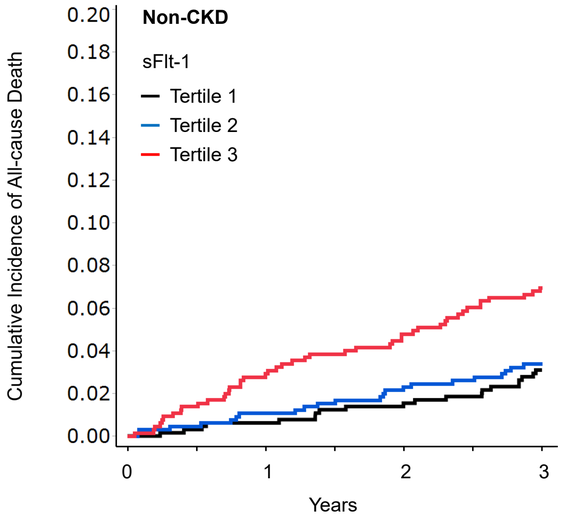
No. at Risk							
Tertile 1	1086	1077	1067	1058	1049	1043	1024
Tertile 2	1084	1070	1060	1049	1041	1031	1011
Tertile 3	1085	1069	1044	1030	1009	985	970

B



No. at Risk							
Tertile 1	443	435	431	426	420	414	403
Tertile 2	424	416	407	400	396	390	381
Tertile 3	434	428	416	409	395	381	372

C



No. at Risk							
Tertile 1	652	649	644	640	637	635	625
Tertile 2	651	648	644	641	636	633	625
Tertile 3	651	640	629	621	615	606	599

Figure S3. Cumulative incidence of CV death in the entire cohort (A), CKD patients (B), and non-CKD patients (C) according to the serum sFlt-1 level at baseline. Follow-up results are truncated after 3 years. The tertiles of sFlt-1 levels are the same as in Figure S2. CV indicates cardiovascular. Other abbreviations used in this figure are the same as in Figure S1.

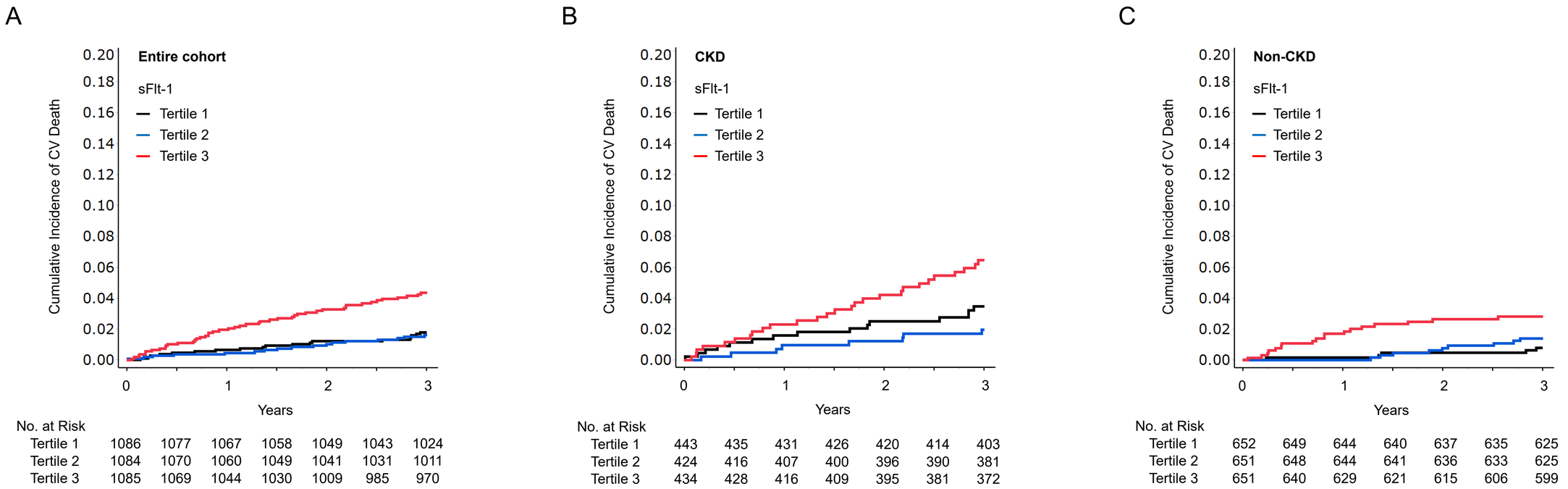
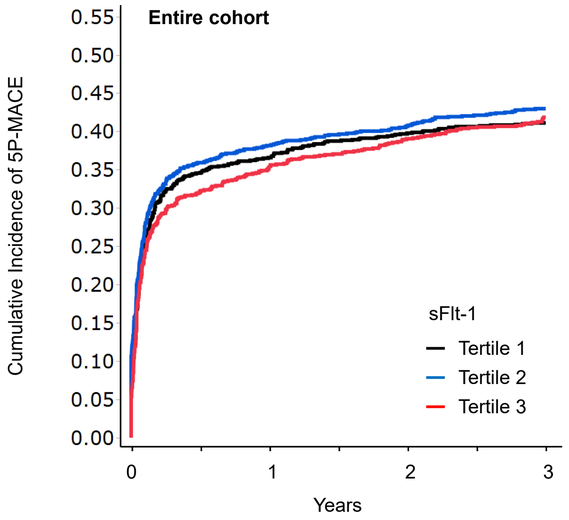


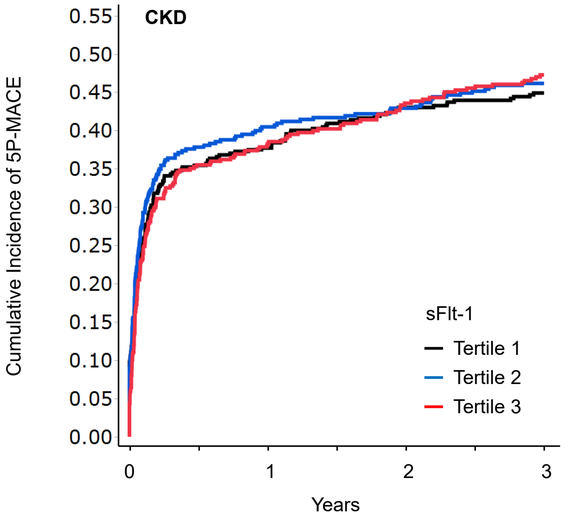
Figure S4. Cumulative incidence of 5P-MACE in the entire cohort (A), CKD patients (B), and non-CKD patients (C) according to the serum sFlt-1 level at baseline. Follow-up results are truncated after 3 years. 5P-MACE is defined as a composite of CV death, nonfatal myocardial infarction, nonfatal stroke, heart failure hospitalization, and coronary/peripheral artery revascularization. The tertiles of sFlt-1 levels are the same as in Figure S2. 5P-MACE indicates 5-point major adverse cardiovascular events. Abbreviations used in this figure are the same as in Figures S1 and S3.

A



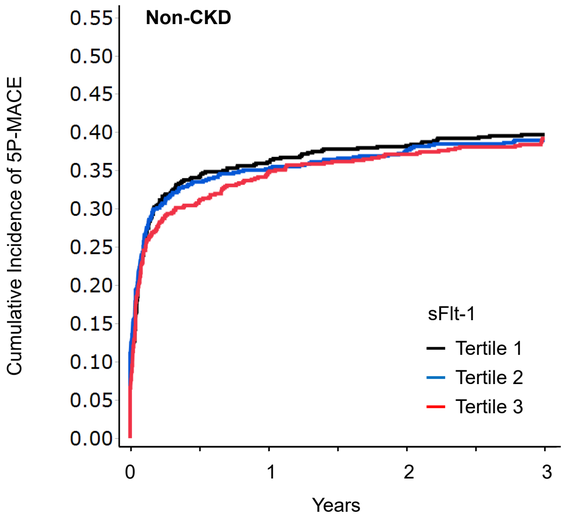
No. at Risk							
Tertile 1	1086	707	679	653	637	624	614
Tertile 2	1084	691	662	641	626	608	589
Tertile 3	1085	733	689	666	639	613	598

B



No. at Risk							
Tertile 1	443	284	273	257	245	239	233
Tertile 2	424	261	246	237	231	219	210
Tertile 3	434	279	264	251	233	221	213

C



No. at Risk							
Tertile 1	652	428	411	399	394	386	378
Tertile 2	651	432	418	409	400	393	387
Tertile 3	651	447	418	407	399	387	380

Figure S5. Adjusted hazard ratios of the biomarker levels for all-cause death in the entire cohort, CKD patients, and non-CKD patients. The data were adjusted for age, sex, body mass index, hypertension, dyslipidemia, diabetes, and current smoking, eGFR, the Gensini score, previous myocardial infarction, previous stroke, previous heart failure hospitalization, atrial fibrillation, anemia, antihypertensive drug use, and statin use. The biomarkers are modeled as 1) continuous variables, 2) tertiles, and 3) the top tertile [i.e., tertile 3 vs tertiles 1 and 2], and are natural log-transformed for use as continuous variables. The tertiles of sFlt-1 levels are the same in Figure S2. CI indicates confidence interval; SD, standard deviation; NT-proBNP, N-terminal pro-brain natriuretic peptide; hs-cTnI, high-sensitivity cardiac troponin I; hs-CRP, high-sensitivity C-reactive protein; NGAL, neutrophil gelatinase-associated lipocalin; VEGF, vascular endothelial growth factor; PlGF, placental growth factor; and UACR: urine albumin to creatinine ratio. Other abbreviations used in this figure are the same as in Figures S1 and S3.

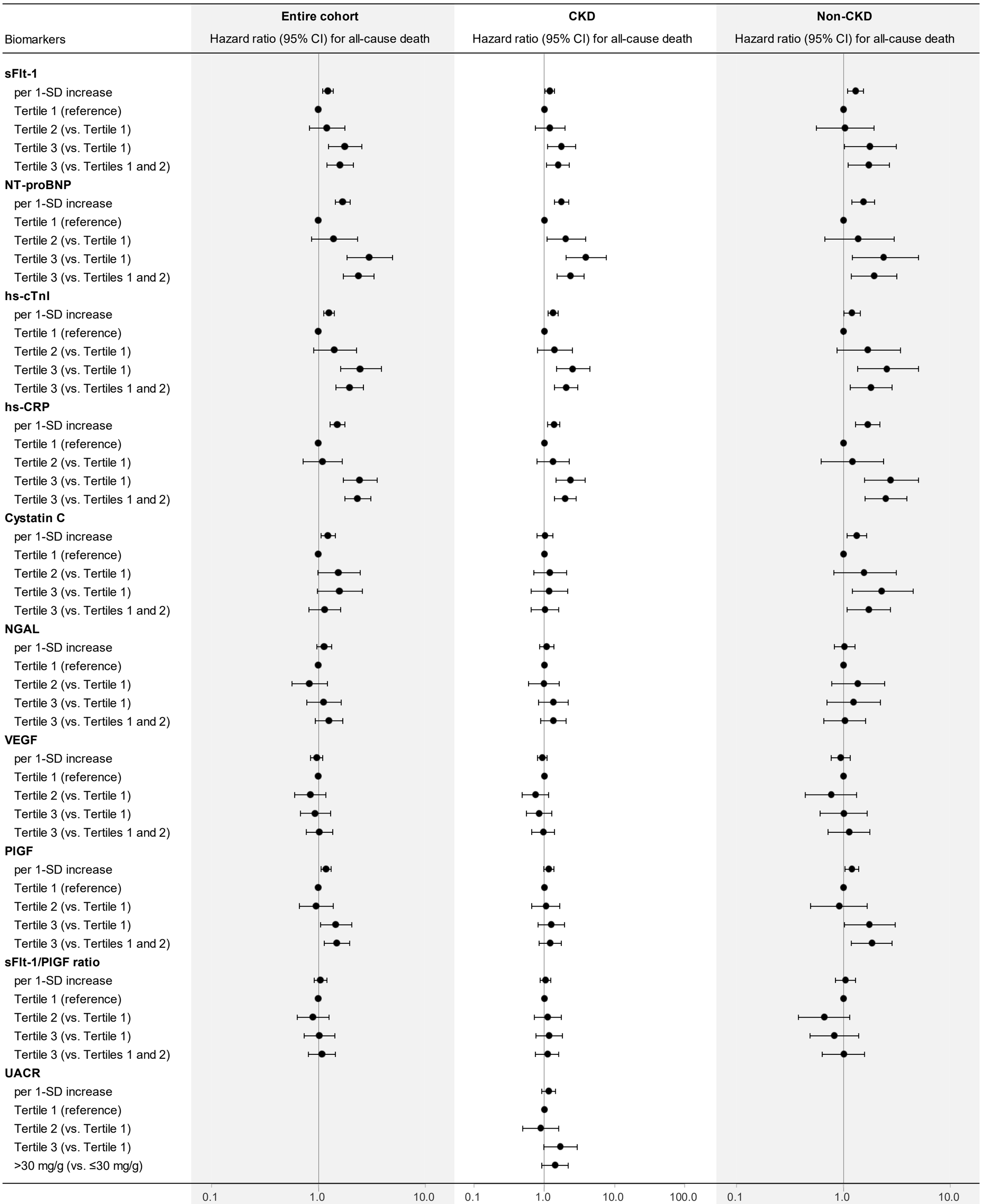


Figure S6. Adjusted hazard ratios of the biomarker levels for CV death in the entire cohort, CKD patients, and non-CKD patients. The data were adjusted and the biomarkers are modeled in the same manner as in Figure S5. Abbreviations used in this figure are the same as in Figures S1, S3, and S5.

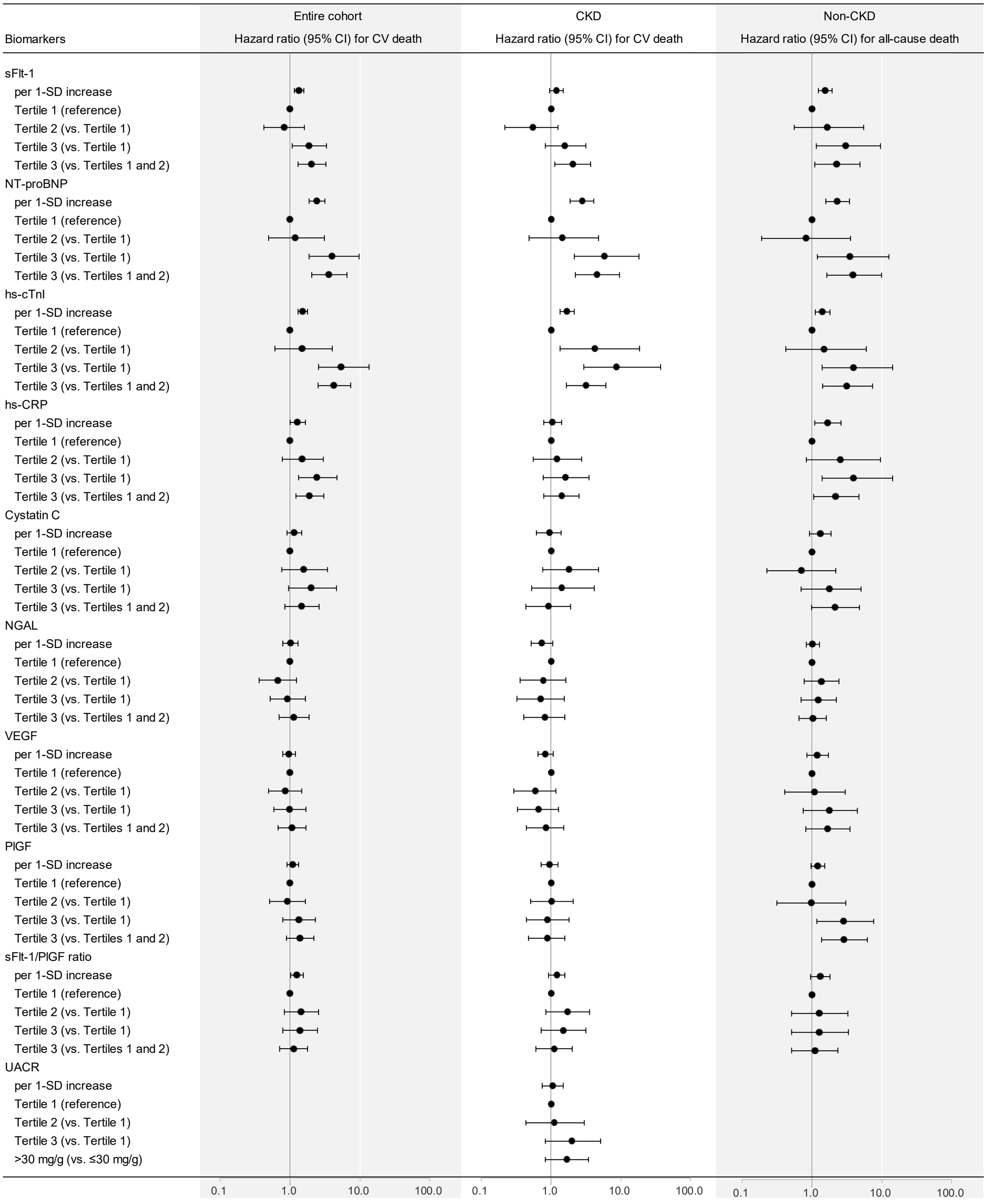


Figure S7. Adjusted hazard ratios of the biomarker levels for 5P-MACE death in the entire cohort, CKD patients, and non-CKD patients. The data were adjusted and the biomarkers are modeled in the same manner as in Figure S5. Abbreviations used in this figure are the same as in Figures S1, and S3–S5.