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ORIGINAL RESEARCH

Low High-Sensitivity C-Reactive Protein Level in Korean Patients With Chronic Kidney Disease and Its Predictive Significance for Cardiovascular Events, Mortality, and Adverse Kidney Outcomes: Results From KNOW-CKD

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BACKGROUND: Inflammation levels are lower in East Asians than in Western people. We studied the association between high-sensitivity hs-CRP (C-reactive protein) and adverse outcomes in Korean patients with chronic kidney disease.

METHODS AND RESULTS: We included 2018 participants from the KNOW-CKD (Korean Cohort Study for Outcome in Patients With Chronic Kidney Disease) between April 2011 and February 2016. The primary outcome was a composite of extended major cardiovascular events (eMACE) or all-cause mortality. The secondary end points were separate outcomes of eMACE, all-cause death, and adverse kidney outcome. We also evaluated predictive ability of hs-CRP for the primary outcome. The median hs-CRP level was 0.60 mg/L. During the mean follow-up of 3.9 years, there were 125 (6.2%) eMACEs and 80 (4.0%) deaths. In multivariable Cox analysis after adjustment of confounders, there was a graded association of hs-CRP with the primary outcome. The hazard ratios for hs-CRPs of 1.0 to 2.99 and ≥3.0 mg/L were 1.33 (95% CI, 0.87–2.03) and 2.08 (95% CI, 1.30–3.33) compared with the hs-CRP of <1.0 mg/L. In secondary outcomes, this association was consistent for eMACE and all-cause death; however, hs-CRP was not associated with adverse kidney outcomes. Finally, prediction models failed to show improvement of predictive performance of hs-CRP compared with conventional factors.

CONCLUSIONS: In Korean patients with chronic kidney disease, the hs-CRP level was low and significantly associated with higher risks of eMACEs and mortality. However, hs-CRP did not associate with adverse kidney outcome, and the predictive performance of hs-CRP was not strong.

REGISTRATION: URL: http://www.clinicaltrials.gov; Unique identifier: NCT01630486.

Key Words: cardiovascular events ■ chronic kidney disease ■ hs-CRP ■ kidney outcome ■ mortality

Cardiovascular disease (CVD) is the leading cause of death in patients with chronic kidney disease (CKD), and CVD and CKD share common risk factors of smoking, obesity, hypertension, diabetes mellitus, and dyslipidemia. There is an intimate connection between the kidney and the heart. For example, a

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CLINICAL PERSPECTIVE

What Is New?

- Median serum concentration of hs-CRP (high-sensitivity C-reactive protein) was only 0.6 mg/L, and the incidence rate of cardiovascular events was low in Korean patients with chronic kidney disease.
- In these patients with low-grade inflammation, higher hs-CRP levels were associated with increased risk of extended major cardiovascular events and all-cause death compared with those without inflammation.
- However, hs-CRP did not associate with adverse kidney outcome, and the predictive performance of hs-CRP was not strong.

What Are the Clinical Implications?

- Low-grade inflammation level may partly explain the low incidence of cardiovascular events in Korean patients with chronic kidney disease.
- Our findings highlight the importance of hs-CRP as a biomarker but also show its limited value in risk stratification for adverse outcomes in this population.

Nonstandard Abbreviations and Acronyms

CVE	cardiovascular event
eMACE	extended major cardiovascular event
KNOW-CKD	Korean Cohort Study for Outcome in Patients With Chronic Kidney Disease

deteriorating heart can lead to decreased kidney function through multiple mechanisms[1–3] and vice versa.[4,5] Notably, a recent cohort study showed that lower kidney function based on cystatin-C was an independent predictor of heart failure among patients with CKD.[6] In addition, major adverse cardiac and cerebrovascular events occur more frequently in patients with CKD than in those without kidney disease,[7] and people at high risk of cardiovascular events (CVEs) also have increased risk of CKD.[8]

It is well known that inflammation plays a key role in promoting vascular injury and atherosclerosis in patients with CVD.[9–11] In fact, persistently elevated inflammation well predicts future development or recurrence of CVEs and deaths.[12–14] In addition, serum concentrations of inflammatory markers are elevated in patients with CKD compared with those with normal kidney function, and higher levels of these markers have been reported to be associated with worsening kidney function.[15–17] Interestingly, previous studies have shown that levels of serum hs-CRP (high-sensitivity C-reactive protein), a well-known marker of inflammation, is lower in the East Asian population than in the Western population.[14,18–22] Because CKD is generally considered a highly inflamed status, it can be presumed that hs-CRP level is substantially increased even in East Asian patients with CKD. Nevertheless, we previously reported that the median hs-CRP level was only 0.6 mg/L among participants of the KNOW-CKD (Korean Cohort Study for Outcome in Patients With Chronic Kidney Disease).[23] This finding led us to question whether such low-grade inflammation can still serve as a biomarker in our cohort participants. Thus, we studied the associations of hs-CRP level with various adverse clinical outcomes in Korean patients with CKD.

METHODS

Because of ethical issues and data protection regulations, data that support the findings of the present study cannot be made publicly available.

Ethics Approval and Consent to Participate

All procedures performed in the participants were in accordance with the ethical standards of the institutional and national research committees at which the studies were conducted (institutional review board approval number H-1104-089-359) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol was approved by the institutional review board at each participating clinical center. Written informed consent was obtained from all study participants.

Study Population

KNOW-CKD is an ongoing, nationwide, multicenter, prospective cohort study initiated in 2011. The detailed design and methods of the KNOW-CKD study have been previously published (NCT01630486 at http://www.clinicaltrials.gov).[24] Between 2011 and 2016, 2238 patients with CKD stages 1 to 5 who were aged 20 to 75 years before dialysis therapy were recruited for this study. For our current study, we excluded 190 patients who did not have measured hs-CRP level at baseline. An additional 30 patients who undertook baseline examination only but dropped out were also excluded because information on outcome events was not available. Thus, a total of 2018 patients was included in the final analysis (Figure S1).

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Exposure and Outcome Ascertainment

The main predictor of this study was level of hs-CRP. To examine the associations of hs-CRP with adverse outcomes, patients were classified into the following 3 groups according to risk of hs-CRP proposed by the Centers for Disease Control and Prevention and the American Heart Association: <1.0, 1.0 to 2.99, and ≥3.0 mg/L.[25] In addition, we further analyzed this association with hs-CRP as a continuous variable in 1-SD increments.

The primary outcome of interest was a composite of eMACE or all-cause death. eMACE was defined as the first occurrence of cardiac death and nonfatal CVEs including any nonfatal coronary artery event (unstable angina, myocardial infarction, or coronary intervention/surgery), hospitalization for heart failure, ischemic or hemorrhagic stroke, or symptomatic arrhythmia. The secondary end points were individual outcomes of eMACE, all-cause mortality, and CKD progression. CKD progression was defined as a composite CKD outcome ≥50% decline in estimated glomerular filtration rate (eGFR) during follow-up or onset of end-stage kidney disease including initiation of dialysis or kidney transplantation. All patients had been under close observation for occurrence of events, and patients who reached the end points were reported by each center. Regardless of visit schedule, all events and the date of occurrence were thoroughly recorded and reported by each participating center. The study observation closed on March 31, 2018.

Statistical Analysis

Detailed data collection, and statistical analysis methods were described in Data S1. The Cox proportional hazards model was applied to determine the associations between hs-CRP and study outcomes after adjustment for confounding variables. Variables that showed statistical significance in univariable Cox analyses and factors known to have clinical impact on CVEs were selected for the adjustment models. Model 1 represents a hazard ratio (HR) without adjustment. Model 2 was adjusted for age; sex; alcohol intake; smoking status; Charlson comorbidity index; socioeconomic status; educational status; body mass index (BMI); systolic blood pressure; and use of medications, including renin-angiotensin system blockers, β-blockers, diuretics, and statins. Model 3 further included laboratory parameters of eGFR, urine protein-to-creatinine ratio, high-density lipoprotein cholesterol, serum phosphate, and albumin. The results are expressed as HR and 95% CI. To account for time-dependent changes of hs-CRP, we also constructed a time-updated model. In the KNOW-CKD, hs-CRP level was measured at baseline, year 1, and year 3. Thus, in this model, hs-CRP and other time-dependent variables of BMI, systolic blood pressure, high-density lipoprotein cholesterol, serum phosphate, and albumin were treated as time-varying exposures. Proportional hazards assumptions were confirmed using Schoenfeld residuals. For secondary analyses for CKD outcome and eMACE, we used a cause-specific hazard function for a competing risk model. In this analysis, deaths that occurred before CKD events and noncardiac deaths that occurred before eMACE were treated as competing risks and censored. In other words, subjects experiencing a competing risk event are removed from the risk set in a cause-specific hazard model.[26,27] Kaplan–Meier curve analysis for the composite outcome and all-cause death was employed to derive survival rates, and differences between groups were compared by a log-rank test. Cumulative incidence curves for individual renal and cardiovascular outcomes were derived using cumulative incidence functions considering competing risks. The Gray test was used for these 2 outcomes to test statistically significant differences among groups. To prove the findings of primary analysis, sensitivity analysis was performed in tertile and quintile groups of hs-CRP level.

Furthermore, we examined effect modification of hs-CRP for the primary outcome in prespecified subgroups by age (<60 and ≥60 years); sex; BMI (<25 and ≥25 kg/m^2); presence of diabetes mellitus; and previous CVD, baseline GFR (<50 and ≥50 mL/min per 1.73 m^2), serum albumin (<4.0 and ≥4.0 g/dL), and low-density lipoprotein cholesterol levels (<100 and ≥100 mg/dL). To compare predictive ability of hs-CRP, we calculated Harrell c-statistics, area under the receiver-operating characteristics curves, category-free net reclassification improvement, and integrated discrimination improvement for models. The base model included conventional factors of age, sex, alcohol intake, smoking status, Charlson comorbidity index, socioeconomic status, educational status, baseline BMI, systolic blood pressure, high-density lipoprotein cholesterol, total cholesterol, and albumin. The base+hs-CRP model additionally adjusted for hs-CRP in addition to the base model. The renal model additionally adjusted for baseline eGFR and baseline urine protein-to-creatinine ratio in addition to the base model. Finally, the renal+hs-CRP model was constructed after hs-CRP was added to the renal model. Data were analyzed using STATA version 14.2 software (StataCorp, College Station, TX). P<0.05 were considered statistically significant.

RESULTS

Baseline Characteristics

Demographic, clinical, and laboratory details of the patients according to hs-CRP group are presented in Table 1. Among the 2018 participants, the mean

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Table 1. Baseline Characteristics of Patients According to hs-CRP Groups

	hs-CRP Group			Total, N=2018	*P* Value	*P* Value for Trend
	<1.0 mg/L, N=1233	1.0 to 2.99 mg/L, N=508	≥3.0 mg/L, N=277			
Demographic data						
Age, y	54.0 (44.0–63.0)	55.0 (47.0–64.0)	57.0 (46.0–65.0)	55.0 (45.0–63.0)	0.02	<0.01
Sex, male	726 (58.9)	322 (63.4)	175 (63.2)	1223 (60.6)	0.14	0.07
BMI, kg/m^2	24.0±3.1	25.4±3.4	25.6±3.7	24.6±3.4	<0.01	<0.01
SBP, mm Hg	126.7±16.0	129.2±16.6	130.0±16.1	127.8±16.2	<0.01	<0.01
Economic status					0.05	0.06
≥$4905/mo	306 (24.8)	132 (26.0)	64 (23.1)	502 (24.9)		
$1635 to 4905/mo	674 (54.7)	250 (49.2)	137 (49.5)	1061 (52.6)		
<$1635/mo	253 (20.5)	126 (24.8)	76 (27.4)	455 (22.5)		
Education					0.03	0.01
<9 y	275 (22.3)	133 (26.2)	86 (31.0)	494 (24.5)		
9 to 12 y	443 (35.9)	172 (33.9)	90 (32.5)	705 (34.9)		
≥12 y	515 (41.8)	203 (40.0)	101 (36.5)	819 (40.6)		
Smoking status					0.01	0.09
Never	687 (55.7)	263 (51.8)	136 (49.1)	1086 (53.8)		
Current	171 (13.9)	101 (19.9)	49 (17.7)	321 (15.9)		
Former	375 (30.4)	144 (28.3)	92 (33.2)	611 (30.3)		
Alcohol intake					0.65	0.42
Mild, none or <1 g/d	986 (80.0)	391 (77.0)	219 (79.1)	1596 (79.1)		
Moderate, 1 g to 19 g/d	116 (9.4)	52 (10.2)	29 (10.5)	197 (9.8)		
High, ≥20 g/d	131 (10.6)	65 (12.8)	29 (10.5)	225 (11.1)		
Comorbidities						
Hypertension	1171 (95.0)	495 (97.4)	270 (97.5)	1936 (95.9)	0.02	0.01
Diabetes mellitus	380 (30.8)	189 (37.2)	109 (39.4)	678 (33.6)	<0.01	<0.01
COPD	3 (0.2)	3 (0.6)	6 (2.2)	12 (0.6)	<0.01	<0.01
Connective tissue disease	62 (5.0)	36 (7.1)	25 (9.0)	123 (6.1)	0.02	0.01
Liver disease	23 (1.9)	14 (2.8)	9 (3.2)	46 (2.3)	0.27	0.11
Peripheral vascular disease	40 (3.2)	21 (4.1)	14 (5.1)	75 (3.7)	0.30	0.12
Cardiovascular disease	64 (5.2)	33 (6.5)	25 (9.0)	122 (6.0)	0.05	0.02
Congestive heart failure	15 (1.2)	3 (0.6)	13 (4.7)	31 (1.5)	<0.01	<0.01
Charlson comorbidity index	2.2±1.6	2.4±1.6	2.6±1.7	2.3±1.6	<0.01	<0.01
Primary kidney disease					<0.01	0.04
Diabetic nephropathy	292 (23.7)	144 (28.3)	67 (24.2)	503 (24.9)		
Hypertensive	218 (17.7)	102 (20.1)	73 (26.4)	393 (19.5)		
Glomerulonephritis	411 (33.3)	151 (29.7)	73 (26.4)	635 (31.5)		
PKD	228 (18.5)	71 (14.0)	37 (13.4)	336 (16.7)		
Others	84 (6.8)	40 (7.9)	27 (9.7)	151 (7.5)		
Medication						
RAS blockers	963 (78.1)	414 (81.5)	228 (82.3)	1605 (79.5)	0.08	0.20
Statin	649 (52.6)	266 (52.4)	135 (48.7)	1050 (52.0)	0.49	0.31
Laboratory parameters						
eGFR, mL/min per 1.73 m^2	55.7±31.9	51.7±28.9	48.2±29.5	53.6±31.0	<0.01	<0.01
BUN, mg/dL	27.7±15.8	28.1±14.9	30.0±16.4	28.1±15.7	0.08	<0.01
WBC, 10^3/μL	6.3±1.8	6.9±1.9	7.5±2.2	6.6±1.9	<0.01	<0.01
Neutrophil, %	57.5±8.8	58.6±8.8	61.7±9.2	58.3±9.0	<0.01	<0.01

(*Continued*)

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Table 1. Continued

	hs-CRP Group			Total, N=2018	*P* Value	*P* Value for Trend
	<1.0 mg/L, N=1233	1.0 to 2.99 mg/L, N=508	≥3.0 mg/L, N=277			
Hemoglobin, g/dL	12.8±2.0	13.0±2.0	12.6±2.1	12.8±2.0	0.02	0.19
Hematocrit, %	38.0±5.6	38.5±5.7	37.3±5.7	38.0±5.6	0.02	0.32
Albumin, g/dL	4.2±0.4	4.2±0.4	4.1±0.4	4.2±0.4	0.01	<0.01
hs-CRP, mg/L	0.3 (0.1–0.5)	1.6 (1.2–2.1)	5.8 (3.9–11.0)	0.6 (0.2–1.7)	<0.01	<0.01
Ferritin, ng/mL	90.9 (48.3–168.0)	110.9 (59.0–180.0)	121.0 (64.4–208.0)	98.1 (53.0–175.7)	<0.01	<0.01
Phosphate, mg/dL	3.7±0.7	3.7±0.7	3.7±0.6	3.7±0.7	0.88	0.72
Fasting glucose, mg/dL	108.3±36.8	112.6±38.1	117.1±51.9	110.6±39.6	<0.01	<0.01
Tchol, mg/dL	173.4±38.8	177.0±40.4	172.6±37.0	174.2±39.0	0.17	0.38
HDL-C, mg/dL	51.5±16.1	46.6±13.9	45.4±13.1	49.5±15.4	<0.01	<0.01
TG, mg/dL	125.0 (88.0–177.0)	150.5 (102.5–222.5)	137.0 (87.0–190.0)	132.0 (92.0–192.0)	<0.01	<0.01
LDL-C, mg/dL	96.1±32.3	99.5±32.6	97.9±28.4	97.2±31.9	0.11	0.02
uPCR, g/g	0.5 (0.1–1.4)	0.5 (0.2–1.5)	0.6 (0.2–1.8)	0.5 (0.1–1.5)	0.04	0.01
uACR, mg/g	342.0 (70.5–1030.5)	342.3 (79.3–1074.9)	385.5 (105.9–1273.5)	347.9 (77.5–1049.3)	0.18	0.07

Data are presented as mean±SD, number (%), or as median and interquartile ranges. BMI indicates body mass index; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; SBP, systolic blood pressure; HbA1c, glycated hemoglobin; LDL-C, low-density lipoprotein cholesterol; PKD, polycystic kidney disease; RAS, renin-angiotensin system; Tchol, total cholesterol; TG, triglyceride; uACR, urine albumin-to-creatinine ratio; uPCR, urine protein-to-creatinine ratio; and WBC, white blood cell.

age was 55.0 (IQR 45.0–63.0) years, and 1223 (60.6%) were men. The median hs-CRP level was 0.6 mg/L (IQR 0.2–1.7). The distribution of hs-CRP is presented in Figure S2. Patients with higher hs-CRP level were older, more likely to be men and current smokers, and had more comorbid conditions such as diabetes mellitus and previous CVDs than those with lower hs-CRP level. In addition, these patients had higher blood pressure readings and BMI and lower eGFR.

Association of hs-CRP With the Primary Outcome

We analyzed whether hs-CRP level was associated with adverse clinical outcomes. During a mean follow-up of 3.9±1.7 years, the primary composite outcome occurred in 184 (9.1%) patients, with an incidence rate of 2.32 per 100 person-years. There were 94 (7.6%), 49 (9.7%), and 41 (14.8%) primary outcome events in patients with hs-CRP levels <1.0, 1.0 to 2.99, and ≥3.0 mg/L, respectively. The corresponding incidence rates were 1.93, 2.41, and 4.01 per 100 person-years, respectively (Table S1). In addition, time to primary outcome events was significantly shorter among patients with higher hs-CRP levels (Figure 1A). Multivariable Cox models after sequential adjustments confirmed this association (Table 2). In the fully adjusted model, compared with hs-CRP of <1.0 mg/L, the HRs for hs-CRP of 1.0 to 2.99 and ≥3.0 mg/L were 1.33 (95% CI, 0.87–2.03) and 2.08 (95% CI, 1.30–3.33), respectively (Table 2; model 3). In additional analysis with hs-CRP as a continuous variable, a 1-SD increase in hs-CRP was associated with a 5.4% higher risk of the primary outcome.

A time-updated hs-CRP model also yielded similar findings (Table 2; model 4). The results showed that patients with hs-CRP ≥3.0 mg/L had a 2.7-fold higher risk of the composite outcome (95% CI, 1.55–4.77) than those with hs-CRP <1.0 mg/L. With continuous modeling, there was a 3.9% higher risk of an adverse outcome per 1-SD increase in hs-CRP level.

Secondary Outcome Analysis

We further analyzed the associations of hs-CRP with the prespecified secondary outcomes. eMACE occurred in 125 (6.2%) patients, and the incidence rate for this outcome was significantly higher in patients with higher hs-CRP level (Table S1). In agreement with the results of primary outcome analysis, the multivariable Cox model consistently showed a higher risk of eMACE among patients with higher hs-CRP levels. In the fully adjusted model, the HR for hs-CRP ≥3.0 mg/L was 1.86 (95% CI, 1.04–3.42) compared with hs-CRP <1.0 mg/L (Table 2 and Figure 1B). In the analysis for all-cause mortality, 80 (4.0%) deaths from any cause occurred during follow-up. Patients with hs-CRP ≥3.0 mg/L had a 2.57-fold (95% CI, 1.26–5.22) higher risk of death than those with hs-CRP <1.0 mg/L. There was no significant difference in risk of eMACE or all-cause death between patients with hs-CRP <1.0 mg/L and those with hs-CRP of 1.0 to 2.99 mg/L (Table 2 and Figure 1C). Finally, a total of 544 (27.0%) patients developed the composite

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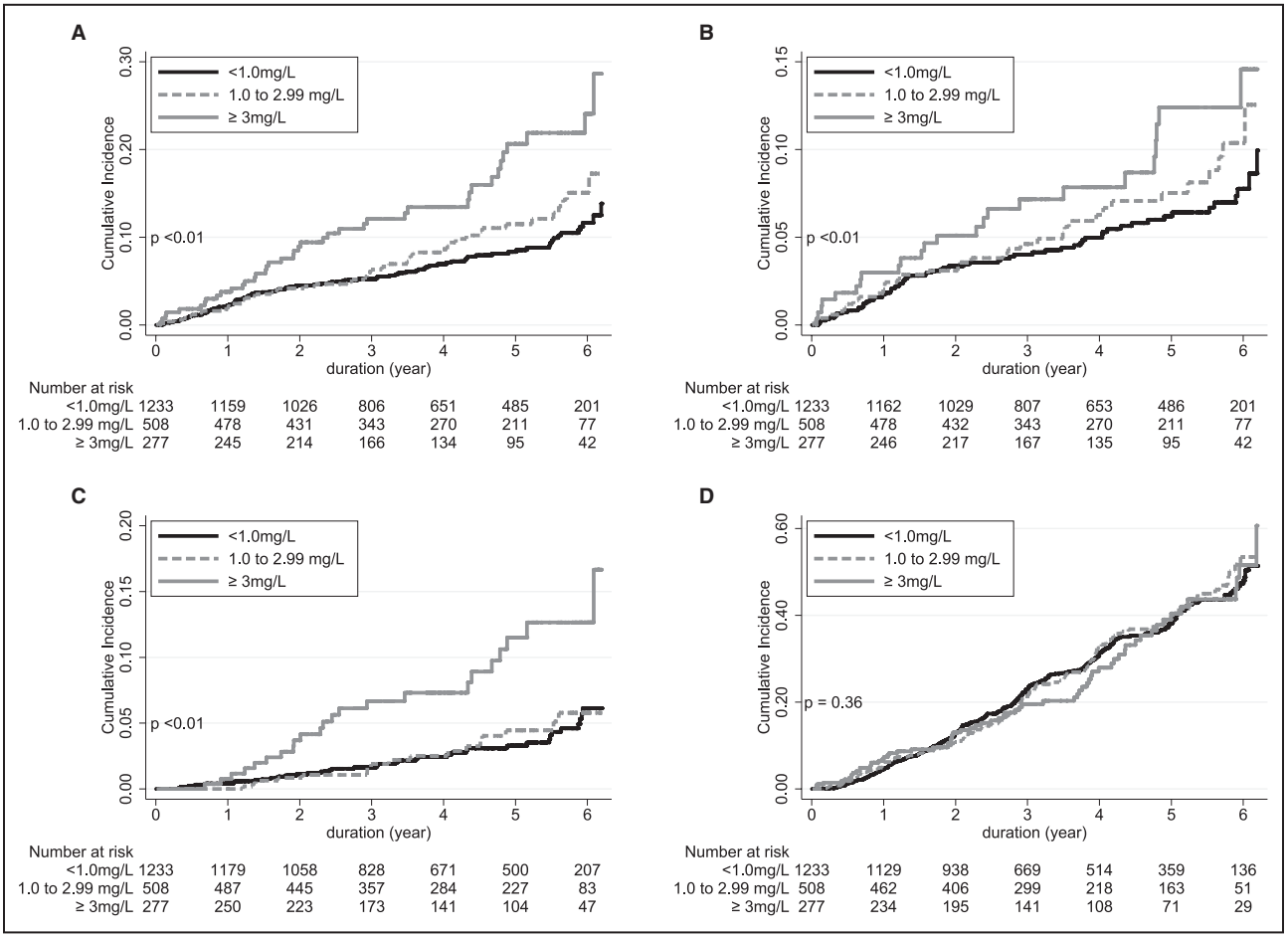

Figure 1. Cumulative incidence curve for (A) the primary and individual secondary outcomes of (B) eMACE, (C) all-cause mortality, and (D) composite renal outcome according to hs-CRP group.
eMACE indicates extended major cardiovascular events; and hs-CRP, high-sensitivity C-reactive protein.

kidney outcome in our cohort. However, hs-CRP level was not associated with adverse kidney outcomes, and the HRs for hs-CRP of 1.0 to 2.99 and ≥3.0 mg/L were 1.03 (95% CI, 0.64–1.67) and 0.68 (95% CI, 0.32–1.45), respectively, compared with hs-CRP <1.0 mg/L (Table 2 and Figure 1D).

Sensitivity Analysis

To validate our findings, we then performed sensitivity analysis in tertile groups of hs-CRP levels. In line with the primary analysis, there was a graded association between hs-CRP and the primary outcome. The HRs for the middle and highest tertiles of hs-CRP were 1.23 (95% CI, 0.76–2.00) and 1.92 (95% CI, 1.20–3.06), respectively, compared with the lowest tertile. This association was consistent in additional models by quintile of hs-CRP (Table S2).

Subgroup Analysis

We examined effect modification of hs-CRP in prespecified subgroups. There were no significant interactions among subgroups stratified by sex, age, BMI, CVD history, diabetes mellitus status, baseline kidney function, serum albumin, and low-density lipoprotein cholesterol level, suggesting that the significant association of hs-CRP with adverse outcome existed across the subgroups (Figure 2).

Predictive Ability of hs-CRP for the Primary Outcome

The predictive ability of hs-CRP for the primary outcome was tested by comparing area under the receiver-operating characteristics curves, c-statistics, net reclassification improvement, and integrated discrimination improvement (Table 3 and Figure S3) among the base, base+hs-CRP, renal, and renal+hs-CRP models. The area under the receiver-operating characteristics curve and c-statistic for the base model were 0.764 (0.722–0.806) and 0.776 (0.737–0.816), respectively. Adding eGFR and proteinuria to the base model increased area under the receiver-operating characteristics curve (P=0.02), c-statistic (P=0.01), category-free net reclassification

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Table 2. HRs for the Primary Composite Outcome and Secondary Outcomes According to hs-CRP Groups

hs-CRP Category	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Primary composite outcome*								
<1.0 mg/L	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
1.0–2.99 mg/L	1.28 (0.90–1.81)	0.16	1.31 (0.87–1.99)	0.20	1.33 (0.87–2.03)	0.19	1.76 (1.06–2.95)	0.03
≥3.0 mg/L	2.10 (1.46–3.03)	<0.01	2.24 (1.43–3.51)	<0.01	2.08 (1.30–3.33)	<0.01	2.72 (1.55–4.77)	<0.01
eMACE								
<1.0 mg/L	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
1.0–2.99 mg/L	1.24 (0.82–1.88)	0.30	1.35 (0.83–2.22)	0.23	1.44 (0.87–2.38)	0.15	2.16 (1.09–4.31)	0.03
≥3.0 mg/L	1.71 (1.07–2.73)	0.02	1.84 (1.04–3.28)	0.04	1.86 (1.04–3.42)	0.04	2.51 (1.09–5.79)	0.03
All-cause mortality								
<1.0 mg/L	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
1.0–2.99 mg/L	1.11 (0.64–1.94)	0.71	1.08 (0.54–2.19)	0.82	1.05 (0.51–2.15)	0.90	1.65 (0.82–3.33)	0.16
≥3.0 mg/L	2.82 (1.68–4.72)	<0.01	2.94 (1.51–5.71)	<0.01	2.57 (1.26–5.22)	0.01	2.78 (1.33–5.80)	0.01
Composite renal outcome†								
<1.0 mg/L	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
1.0–2.99 mg/L	1.03 (0.85–1.26)	0.75	1.08 (0.87–1.35)	0.26	1.03 (0.64–1.67)	0.90	0.98 (0.76–1.27)	0.91
≥3.0 mg/L	1.00 (0.77–1.29)	0.97	0.79 (0.58–1.09)	0.15	0.68 (0.32–1.45)	0.32	0.83 (0.59–1.18)	0.30

Model 1: without adjustment. Model 2: adjusted for age, sex, alcohol intake, smoking status, Charlson comorbidity index, socioeconomic status, educational status, body mass index, systolic blood pressure, use of renin-angiotensin system blockers, β-blockers, diuretics, and use of statin. Model 3: adjusted for model 2 plus laboratory parameters such as estimated glomerular filtration rate, urine protein-to-creatinine ratio, high-density lipoprotein cholesterol, serum phosphate, and serum albumin. Model 4: time-varying model adjusted for age, sex, alcohol intake, smoking status, Charlson comorbidity index, socioeconomic status, educational status, use of renin-angiotensin system blockers, β-blockers, diuretics, use of statin, baseline estimated glomerular filtration rate, urine protein-to-creatinine ratio, and time-varying covariates at any given visit such as body mass index, systolic blood pressure, high-density lipoprotein cholesterol, serum phosphate, and serum albumin. eMACE indicates extended major cardiovascular events; HR, hazard ratio; and hs-CRP, high-sensitivity C-reactive protein.

*Primary composite outcome included eMACE, cardiac death, or all-cause death, whichever came first.

†Composite kidney outcome included a ≥50% decline in estimated glomerular filtration rate or the onset of end-stage kidney disease, whichever came first.

improvement (*P*=0.02), and integrated discrimination improvement (*P*=0.04). However, adding hs-CRP to the base or renal model did not improve any of the 4 prediction indexes (Table 3 and Figure S3). These findings suggest that the predictive ability of hs-CRP was not greater than that of conventional factors.

DISCUSSION

In this study, we showed that hs-CRP level was low in Korean patients with CKD, and this low-grade inflammation was associated with significantly higher risk of adverse cardiovascular outcome and mortality. However, hs-CRP was not associated with CKD progression, and the predictive performance of hs-CRP for the primary outcome was not greater than that of conventional factors.

Inflammation plays an important role in atherosclerotic plaque progression, vulnerability, and thrombogenicity[28–30] and has become an established nontraditional risk factor for CVEs.[31,32] Patients with CKD have generally been considered to have high inflammation levels, and many studies have shown that serum concentrations of inflammatory markers are elevated in these patients.[33] However, in our KNOW-CKD cohort subjects, the median hs-CRP level was only 0.6 mg/L, and 61.1% had hs-CRP level <1.0 mg/L. This inflammation level is still lower than the median hs-CRP level of 2.5 mg/L in another CKD cohort of the Western population given the similar kidney function in the 2 CKD cohorts.[34] Our literature review on this issue also indicated that Korean patients and other East Asian cohorts had lower hs-CRP levels than Western populations although we could not directly compare hs-CRP levels among groups (Table S3). Interestingly, our cohort involving patients with CKD alone had lower hs-CRP level than the Western population at high risk of major cardiovascular event but with preserved kidney function. These findings led us to question whether such low-grade inflammation could perform well as a biomarker for Korean patients with CKD.

Despite low inflammation levels in East Asians, hs-CRP well predicted adverse cardiovascular outcomes. In a health screening program cohort composed of 268 803 Korean middle-aged people, there was a significant association of hs-CRP level with risk of CVEs and all-cause mortality.[14] Similar findings were also observed in Japanese and Chinese cohort studies.[35,36] Interestingly, our

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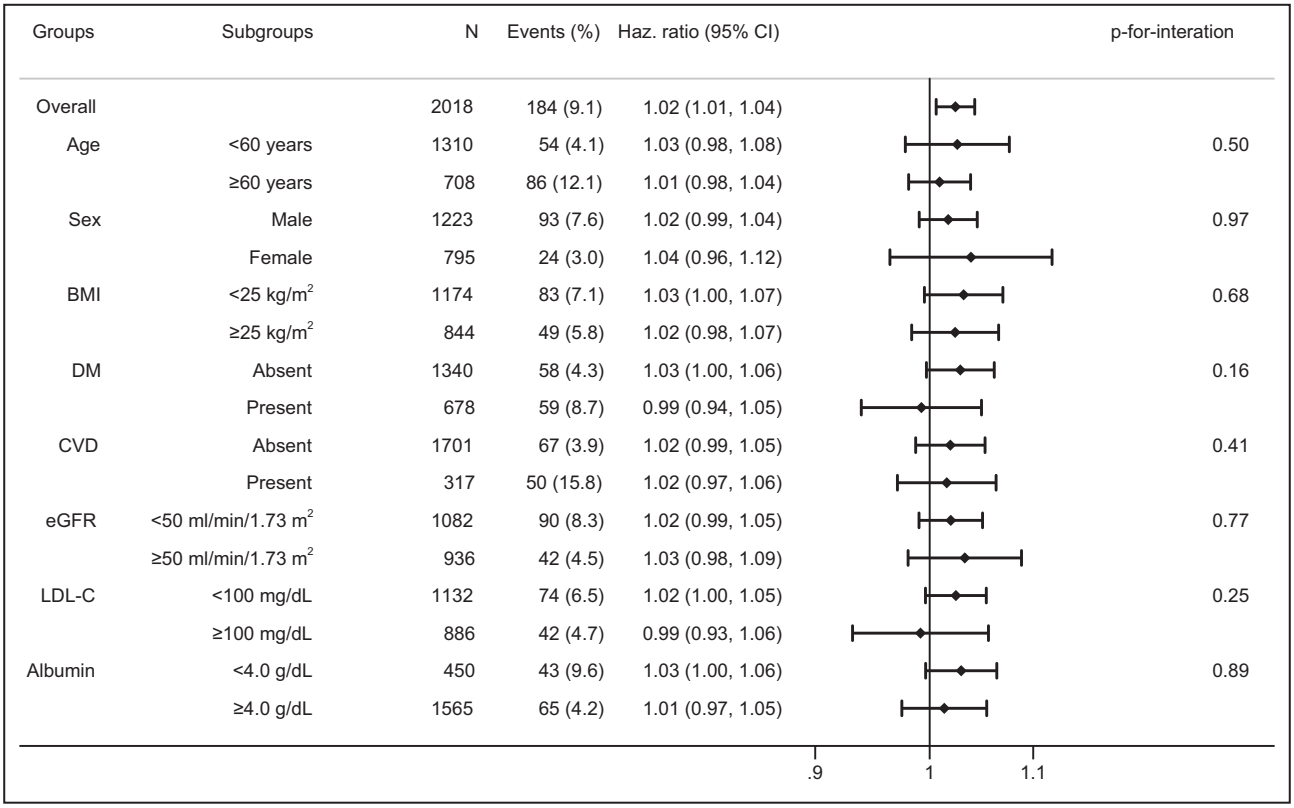

Figure 2. Forest plot for subgroup analysis.
BMI indicates body mass index; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; and LDL-C, low-density lipoprotein cholesterol.

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KNOW-CKD cohort had a low inflammation level, and an elevated hs-CRP level was significantly associated with a higher risk of eMACE and mortality. It is uncertain whether such low-grade inflammation can increase cardiovascular risk in these patients. However, it should be noted that the association of hs-CRP with primary outcome, eMACE, and all-cause death was statistically significant, particularly when hs-CRP was ≥3.0 mg/L; patients with hs-CRP level in this range belong to the high-risk category as suggested by the American Heart Association and Centers for Disease Control and Prevention in 2003.[25] Therefore, it can be presumed that the effect of hs-CRP begins to show when it increases beyond a certain threshold. Given that hs-CRP level varies among different ethnic groups and is relatively low in East Asians, further studies should address this issue on the appropriate cut-off point of hs-CRP to identify patients at high risk of CVD, particularly in East Asians.

This low hs-CRP level might result in lower incidence of CVEs and mortality in our cohort. We noted that the incidence rates of the primary outcome, nonfatal CVEs, and all-cause death in our cohort were 2.32, 1.57, and 0.98 per 100 person-years, respectively. Similar findings were also reported by a Japanese CKD cohort study.[37] Compared with such fewer CVE rates in East Asian cohorts, studies from the US cohorts showed higher incidence rates of all CVE (3.3–3.8 per 100 person-years).[4,38] A schematic figure on different incidence rates of major cardiovascular event among studies is presented in Figure S4. Because inflammation greatly contributes to atherosclerosis and CVE, we surmised that lower CVE rates in our cohort might be partly explained by low inflammation level. Thus, similar hs-CRP levels among different ethnic groups should be interpreted with caution in the context of other cardiovascular risk factors.

Chronic inflammation has also been suggested to be a significant determinant of CKD progression.[34,39] However, there is controversy on the association of hs-CRP level with kidney function decline.[40–42] In our study, hs-CRP was not associated with adverse kidney outcome. In line with our findings, Sarnak et al[40] analyzed the data from the Modification of Diet in Renal Disease Study and found no significant association of hs-CRP level with CKD progression. In addition, in a population-based cohort of 4926 people, a higher hs-CRP level failed to predict the development of CKD.[42]

Table 3. The Predictive Performance of hs-CRP for the Primary Outcome by the c-Statistics, NRI, and IDI

	Base	*P* Value	Base+hs-CRP	*P* Value	Renal	*P* Value	Renal+hs-CRP	*P* Value
Harrell c-statistics (95% CI)	0.776 (0.737 to 0.816)		0.778 (0.739 to 0.818)	0.15	0.786 (0.746 to 0.825)	0.01	0.787 (0.748 to 0.826)	0.28
Category-free NRI, % (95% CI)			−16.18 (−35.01 to 2.65)	0.09	23.19 (4.27 to 42.11)	0.02	−13.44 (−32.36 to 5.47)	0.16
% of events correctly reclassified			−42.37		26.50		−35.04	
% of nonevents correctly reclassified			26.19		−3.31		21.60	
IDI (95% CI)			0.0013 (−0.0030 to 0.0055)	0.56	0.0047 (0.0003 to 0.0091)	0.04	0.0005 (−0.0024 to 0.0034)	0.75
Relative IDI, % (95% CI)			1.30 (−3.03 to 5.63)		4.85 (0.26 to 9.43)		0.47 (−2.40 to 3.35)	

Base model: age, sex, alcohol intake, smoking status, Charlson comorbidity index, socioeconomic status, educational status, baseline body mass index, systolic blood pressure, high-density lipoprotein cholesterol, total cholesterol, and serum albumin. Base+hs-CRP model: base model+hs-CRP, *P* value vs. base model. Renal model: base model+eGFR+urine protein-to-creatinine ratio, *P* value vs. base model. Renal+hs-CRP model: renal model+hs-CRP, *P* value vs. renal model. eGFR indicates estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; IDI, integrated discrimination improvement; and NRI, net reclassification improvement.

Taken together, these findings suggest that many other factors beyond inflammation are involved in CKD progression.

Several shortcomings of this study should be considered. First, given the observational nature of the study, it is possible that potential confounding factors were not entirely controlled. However, this study included only patients with CKD and analyzed the data using various models after rigorous adjustment of measured covariates. Second, we measured only hs-CRP to assess inflammatory status. There are other inflammatory markers such as tumor necrosis factor α and IL-6. Several studies showed that these markers were more strongly associated with CVEs, mortality, and kidney failure than with hs-CRP.[33,38,41,42] As aforementioned, hs-CRP level was significantly lower in East Asians; to our knowledge, no studies have collectively examined many inflammatory markers.[35,43] Thus, future studies are warranted to find alternative surrogates of inflammation in Korean patients with CKD. Third, hs-CRP level was measured at the local laboratory of each participating center and not at the central laboratory. This may raise concerns about imprecision and bias for measuring hs-CRP. However, all laboratories in our study used the same direct enzymatic assay and measured hs-CRP level within 24 hours of sampling. Furthermore, we thoroughly adjusted for participating centers and other time-varying covariates that could potentially affect outcomes. Fourth, based on our findings, the clinical utility of hs-CRP may be limited because the predictive ability of hs-CRP for adverse cardiovascular outcomes was not superior to that of conventional risk factors. This can be attributed to relatively fewer CVEs and deaths in our cohort, which may not provide statistical power. In addition, adding hs-CRP to the renal model did not improve predictive performance. Notably, the hs-CRP level was higher as eGFR was lower, suggesting higher inflamed status in advanced CKD. Thus, the renal model might reflect this inflammatory condition. This can also explain the failure of hs-CRP for improving predictive performance. Finally, because the hs-CRP level varies according to ethnic group and because we included only Korean patients, our findings may not be generalizable to other populations.

In conclusion, we showed that hs-CRP level was low in Korean patients with CKD. Elevated hs-CRP level was associated with a higher risk of CVD and mortality. However, hs-CRP did not predict adverse kidney outcomes, and the predictive performance of hs-CRP was not superior to that of conventional factors. Our findings add to the existing evidence that inflammation can help to predict adverse outcomes but also raise questions on the clinical utility of hs-CRP in the management of CKD.

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Disclosures

None.

Supplementary Material

Data S1
Tables S1–S3
Figures S1–S4
References 44–53

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SUPPLEMENTAL MATERIAL

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Data S1.

Supplemental Methods

Data collection and survey instruments

Demographic details of age, sex, smoking status, alcohol consumption, medical history, and comorbid diseases were obtained from the KNOW-CKD database. Smoking status was classified as never, former, or current. Anthropometric data, including height and weight, were collected at enrollment. BMI was calculated as initial body weight divided by height squared (kg/m^2). Blood pressure was measured using an electronic sphygmomanometer in the sitting position after subjects had been in a relaxed state for at least 5 minutes. After overnight fasting, blood samples were collected and sent to the central laboratory of KNOW-CKD (Lab Genomics, Seongnam, Korea) for measurements of creatinine. Other biochemical analyses were performed at the local laboratory of each participating center. The following laboratory parameters were measured at baseline and annually thereafter: complete blood cell count, fasting glucose, blood urea nitrogen, creatinine, albumin, calcium, and phosphorus. Lipid profiles for total cholesterol, triglycerides, HDL-C, and LDL-C, iron profiles (including total iron-binding capacity and serum ferritin), and hs-CRP were measured at baseline, year 1, and year 3. Serum hs-CRP level was measured at each center using commercially available enzyme-linked immunosorbent assay kits.

We measured creatinine level using a calibration traceable to isotope dilution mass spectrometry method and calculated the eGFR using the CKD Epidemiologic Collaboration equation.[44] Along with blood samples, urine samples were also immediately sent to the central laboratory for proteinuria measurement. The urine protein-to-creatinine ratio was calculated as urine protein concentration divided by urine creatinine concentration (g/g).

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Statistical analysis

Continuous variables with normal distribution were expressed as mean with SD, and those with skewed distribution were described as median with interquartile range. The Shapiro–Wilk normality test was used for normality testing. Categorical variables are presented as number and percentage. One-way analysis of variance was used for normal distributed data, and the Kruskal–Wallis test was used for skewed data to identify differences and compare clinical characteristics between the groups.

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Table S1. Adverse outcome event rates among groups classified by the hs-CRP groups.

	Total	hs-CRP groups		
		<1.0 mg/L	1.0 to 2.99 mg/L	≥ 3.0 mg/L
No. of participants	2018	1233	508	277
Person-year	7934.9	4882.4	2029.3	1023.1
Primary composite outcome*				
Events, (%)	184 (9.1%)	94 (7.6%)	49 (9.7%)	41 (14.8%)
Events per 100 person-yr	2.32	1.93	2.41	4.01
Secondary outcome				
eMACE				
Events, (%)	125 (6.2%)	67 (5.4%)	34 (6.7%)	24 (8.7%)
Events per 100 person-yr	1.57	1.37	1.68	2.33
All-cause mortality				
Events, (%)	80 (4.0%)	39 (3.2%)	18 (3.5%)	23 (8.3%)
Events per 100 person-yr	0.98	0.78	0.86	2.16
Composite kidney outcome†				
Events, (%)	544 (27.0%)	330 (26.8%)	145 (28.5%)	69 (24.9%)
Events per 100 person-yr	7.63	7.56	7.85	7.50

*Primary composite outcome included eMACE, cardiac death or all-cause death, whichever came first.

†Composite kidney outcome included a ≥50% decline in eGFR or the onset of ESKD, whichever came first.

hs-CRP, high-sensitivity C-reactive protein; eMACE, extended major cardiovascular events; ESKD, end-stage kidney disease.

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Table S2. Hazard ratios for the primary composite outcome according to hs-CRP tertile and quintile groups.

	Model 1		Model 2		Model 3		Model 4	
hs-CRP category	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*
Tertile group								
<0.38 mg/L	1.00 [Reference]		1.00 [Reference]		1.00 [Reference]		1.00 [Reference]	
0.38 to 1.20 mg/L	1.17 [0.79-1.73]	0.43	1.15 [0.72-1.85]	0.56	1.23 [0.76-2.00]	0.40	1.01 [0.52-2.00]	0.76
≥1.21 mg/L	1.90 [1.33-2.72]	<0.01	1.94 [1.24-3.03]	<0.01	1.92 [1.20-3.06]	<0.01	2.24 [1.24-4.06]	<0.01
Quintile group								
<0.20 mg/L	1.00 [Reference]		1.00 [Reference]		1.00 [Reference]		1.00 [Reference]	
0.20 to 0.43 mg/L	1.63 [1.01-2.61]	0.04	1.77 [0.95-3.31]	0.07	1.87 [0.99-3.53]	0.06	1.16 [0.56-2.37]	0.69
0.44 to 0.90 mg/L	1.49 [0.92-2.43]	0.11	1.32 [0.72-2.42]	0.37	1.38 [0.74-2.56]	0.31	1.03 [0.37-2.85]	0.95
0.91 to 2.10 mg/L	1.71 [1.03-2.84]	0.04	1.83 [1.03-3.25]	0.04	1.83 [1.02-3.30]	0.04	1.60 [0.75-3.42]	0.22
≥2.11 mg/L	2.44 [1.56-3.82]	<0.01	2.37 [1.35-4.18]	<0.01	2.33 [1.30-4.20]	<0.01	2.66 [1.08-6.55]	<0.01

Note: Model 1: without adjustment

Model 2: adjusted for age, sex, alcohol intake, smoking status, Charlson comorbidity index, socioeconomic status, educational status, BMI, SBP, use of renin-angiotensin system blockers, beta blockers, diuretics, and use of statin

Model 3: adjusted for Model 2 plus laboratory parameters such as eGFR, urine protein-to-creatinine ratio, HDL-C, serum phosphate, and serum albumin

Model 4: Time-varying model adjusted for age, sex, alcohol intake, smoking status, Charlson comorbidity index, socioeconomic status, educational status, use of renin-angiotensin system blockers, beta blockers, diuretics, use of statin, baseline eGFR, urine protein-to-creatinine ratio, and time-varying covariates at any given visit such as BMI, SBP, HDL-C, serum phosphate, and serum albumin

BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein-cholesterol; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; SBP, systolic blood pressure.

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Table S3. hs-CRP levels among different ethnic groups.

Studies	Population	Ethnicity	Group	Number	eGFR (mL/min/1.73 m^2)	hs-CRP (mg/L)
MESA [21]	General	Caucasians	Men	1253	N/A	1.3 (0.2-2.4)
			Women	1349	N/A	2.5 (0.4-4.5)
		Chinese	Men	388	N/A	0.8 (0.3-1.4)
			Women	413	N/A	1.0 (0.3-1.4)
		African Americans	Men	836	N/A	1.8 (0.4-3.2)
			Women	1035	N/A	3.4 (0.4-6.5)
		Hispanics	Men	716	N/A	1.9 (0.5-3.4)
			Women	681	N/A	3.0 (0.5-5.5)
MESA [45]	General	Multi-ethnic	All	6437	77.7±16.2	N/A
JUPITER [46]	General	Multi-ethnic	Rosuvasatatin	8901	73.3 (64.6-83.7)	4.2 (2.8-7.1)
			Placebo	8901	73.6 (64.6-84.1)	4.3 (2.8-7.1)
CRIC [47]	CKD	Multi-ethnic	All	2399	44.1±13.9	2.5 (1.0-6.0)
CRIC [48]	CKD	Non-Hispanic white	All	1638	47.7±17.1	2.2 (0.9-5.2)

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		Non-Hispanic black	All	1650	43.5±16.3	3.3 (1.3-8.2)
		Hispanic	All	497	39.0±15.2	2.5 (1.0-5.7)
ADVANCE [49]	DM	Multi-ethnic	All	3865	71.48±16.86	1.8 (0.9-4.1)
CANTOS [50]	MI	Multi-ethnic	Placebo	1597	79.0 (65.0-93.0)	4.1 (2.8-6.9)
			Canakinumab	1619	78.5 (64.0-93.0)	4.2 (2.8-7.1)
JNIC [43]	General	Japanese	Men	5213	N/A	0.6 (0.3-1.3)
		Japanese	Women	7071	N/A	0.5 (0.2-0.9)
DDCRT 6 [51]	DM	Japanese	All	3573	N/A	0.8 (0.1-1.7)
CKD-JAC [37,52]	CKD	Japanese	All	2966	28.9 ±12.2	1.0 (0.4-2.0)
Liu et al. [35]	General	Chinese	All	90517	N/A	0.7 (0.3-1.9)
Sung et al. [14]	General	Korean	Men	151962	N/A	0.6 (0.3-1.3)
			Women	116841	N/A	0.4 (0.1-1.1)
CALLISTO [53]	DM/CVD	Korean	All	1561	N/A	0.3 (0.01-7.5)
KNOW-CKD	CKD	Korean	All	2018	46.6 (28.7-73.8)	0.6 (0.2-1.7)

Note: Data are presented as mean ± standard deviation, or as median and interquartile ranges.

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ADVANCE, Action in Diabetes and Vascular Disease; CALLISTO, Correlation of plasma hsCRP concentrations and cardiovascular risk in Korean population: Preterax and Diamicron Modified Release Controlled Evaluation; CANTOS, Canakinumab Anti-Inflammatory Thrombosis Outcomes Study; CKD-JAC, Chronic Kidney Disease Japan Cohort; CRIC, Chronic Renal Insufficiency Cohort;DDCRT, Diabetes Distress and Care Registry at Tenri; eGFR, estimated glomerular filtration rate; JUPITER, The Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin; JNIC, The Japan NCVC-Collaborative Inflammation Cohort; KNOW-CKD, KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease; MESA, multiethnic study of atherosclerosis; N/A, not applicable.

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Figure S1. Flow diagram of study cohort.

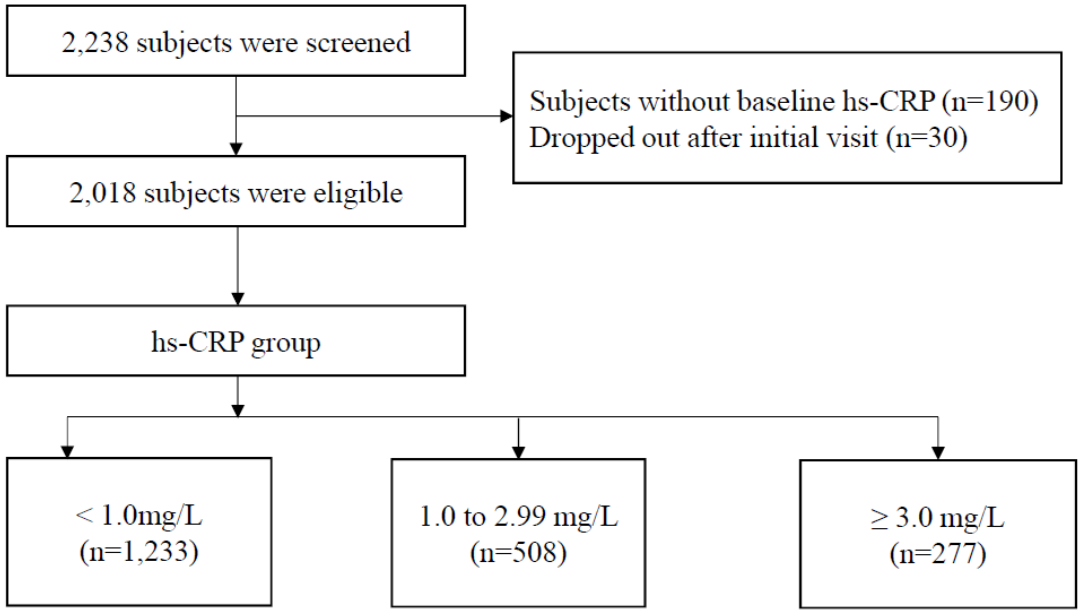

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Figure S2. Distribution of hs-CRP with histogram and kernel density plot.

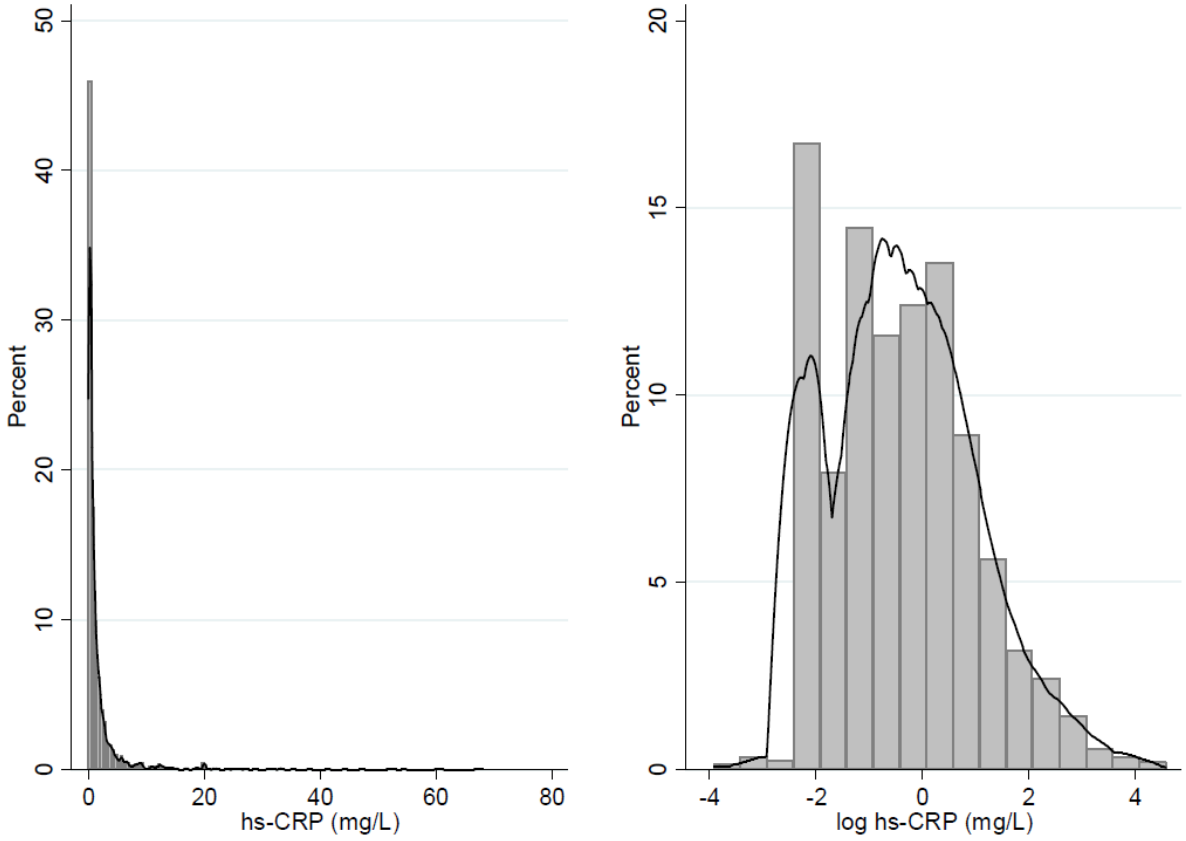

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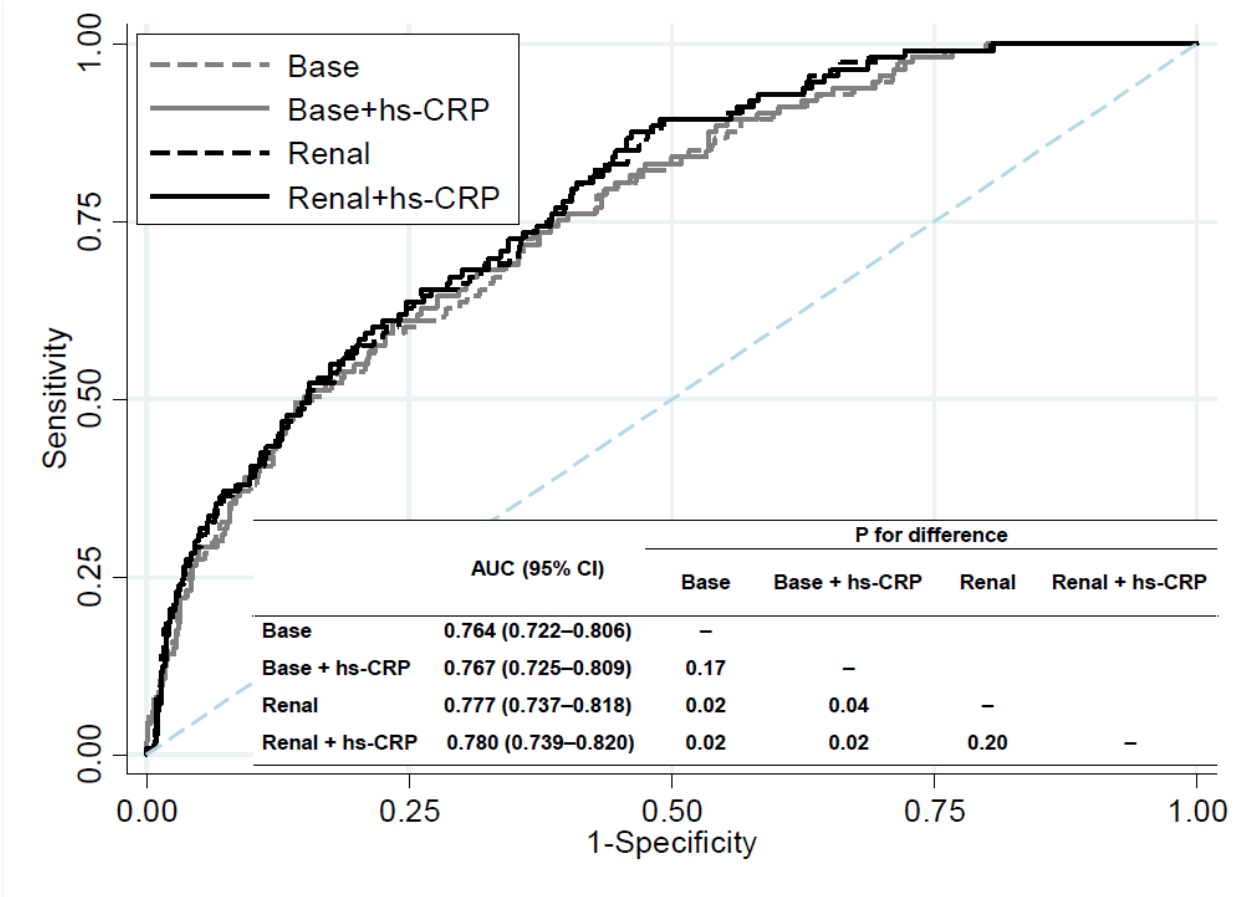
Figure S3. Receiver operating characteristics curve for eMACE among 4 models.



	AUC (95% CI)	P for difference			
		Base	Base + hs-CRP	Renal	Renal + hs-CRP
Base	0.764 (0.722–0.806)	–			
Base + hs-CRP	0.767 (0.725–0.809)	0.17	–		
Renal	0.777 (0.737–0.818)	0.02	0.04	–	
Renal + hs-CRP	0.780 (0.739–0.820)	0.02	0.02	0.20	–

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Base model: age, sex, alcohol intake, smoking status, Charlson comorbidity index, socioeconomic status, educational status, baseline BMI, SBP, HDL-C, total cholesterol, and serum albumin

Base + hs-CRP model: base model + hs-CRP

Renal model: base model + estimated glomerular filtration rate, urine protein-to-creatinine ratio

Renal + hs-CRP model: renal model + hs-CRP

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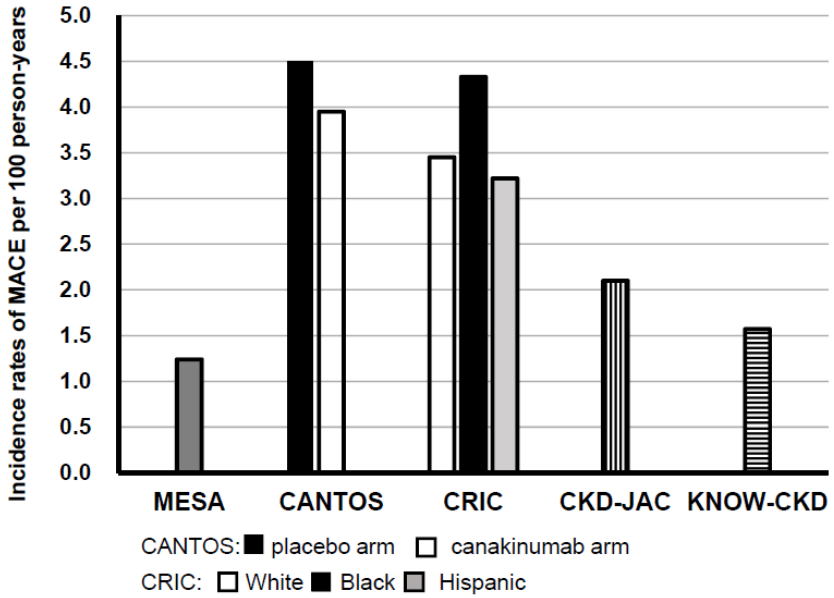
Figure S4. Different incidence rates of MACE among studies.



Note: definitions of MACE among studies

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CANTOS [50]: nonfatal myocardial infarction, any nonfatal stroke, or cardiovascular death

CRIC [48]: composite atherosclerotic events (myocardial infarction, stroke, or peripheral arterial disease) or death outcome

MESA [45]: coronary heart disease events (myocardial infarction, CHD deaths, definite angina, and probable angina if followed by coronary revascularization), stroke, stroke death, and other atherosclerotic deaths coronary heart disease events

CKD-JAC [37]: cardiovascular events (fatal and nonfatal myocardial infarction, angina pectoris, sudden death, congestive heart failure, arrhythmias, cerebrovascular disorder, chronic arteriosclerosis obliterans, and aortic dissection) and all-cause death

KNOW-CKD: composite of eMACE (unstable angina, myocardial infarction, or coronary intervention/surgery, hospitalization for heart failure, or ischemic or hemorrhagic stroke or symptomatic arrhythmia), cardiac deaths, or all-cause deaths

CANTOS, Canakinumab Anti-Inflammatory Thrombosis Outcomes Study; CHD, coronary heart disease; CKD-JAC, Chronic Kidney Disease Japan Cohort; CRIC, Chronic Renal Insufficiency Cohort; eMACE, non-fatal CVEs, or cardiac deaths; KNOW-CKD, KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease; MESA, multiethnic study of atherosclerosis.

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