Association Between Serum High-Density Lipoprotein Cholesterol Levels and Progression of Chronic Kidney Disease: Results From the KNOW-CKD

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Background—High-density lipoprotein (HDL) cholesterol (HDL-C) levels are generally decreased in patients with chronic kidney disease (CKD). However, studies on the relationship between HDL-C and CKD progression are scarce.

Methods and Results—We studied the association between serum HDL-C levels and the risk of CKD progression in 2168 participants of the KNOW-CKD (Korean Cohort Study for Outcome in Patients With Chronic Kidney Disease). The primary outcome was the composite of a 50% decline in estimated glomerular filtration rate from baseline or end-stage renal disease. The secondary outcome was the onset of end-stage renal disease. During a median follow-up of 3.1 (interquartile range, 1.6–4.5) years, the primary outcome occurred in 335 patients (15.5%). In a fully adjusted Cox model, the lowest category with HDL-C of <30 mg/dL (hazard ratio, 2.21; 95% CI, 1.30–3.77) and the highest category with HDL-C of ≥60 mg/dL (hazard ratio, 2.05; 95% CI, 1.35–3.10) were associated with a significantly higher risk of the composite renal outcome, compared with the reference category with HDL-C of 50 to 59 mg/dL. This association remained unaltered in a time-varying Cox analysis. In addition, a fully adjusted cubic spline model with HDL-C being treated as a continuous variable yielded similar results. Furthermore, consistent findings were obtained in a secondary outcome analysis for the development of end-stage renal disease.

Conclusions—A U-shaped association was observed between serum HDL-C levels and adverse renal outcomes in this large cohort of patients with CKD. Our findings suggest that both low and high serum HDL-C levels may be detrimental to patients with nondialysis CKD. (J Am Heart Assoc. 2019;8:e011162. DOI: 10.1161/JAHA.118.011162.)

Key Words: chronic kidney disease • high-density lipoprotein • high-density lipoprotein cholesterol • kidney • kidney disease progression

Serum high-density lipoprotein (HDL) has traditionally been considered to be protective against cardiovascular disease in the general population. HDL exerts an anti-atherogenic effect through reverse cholesterol transport, a multiorgan process that removes excess cholesterol from lipid-laden macrophages and peripheral tissue.1 In addition,
HDL-C and CKD Progression

Clinical Perspective

What Is New?

- Compared with a reference category with high-density lipoprotein cholesterol (HDL-C) of 50 to 59 mg/dL, both low (<30 mg/dL) and high (≥60 mg/dL) HDL-C levels were associated with an increased risk of disease progression in patients with chronic kidney disease who were not yet undergoing dialysis.
- The time-varying Cox analysis and cubic spline model further supported these findings, showing that the association between HDL-C and adverse renal outcome follows a nonlinear U-shaped relationship.

What Are the Clinical Implications?

- Both low and high HDL-C levels could be harmful with respect to chronic kidney disease progression.
- Our findings support the result of previous studies showing that HDL-C becomes dysfunctional and even transforms into toxic particles in patients with chronic kidney disease.
- Future research should focus on the role of the composition and function of HDL in the progression of chronic kidney disease rather than its levels alone.

Materials and Methods

Study Design and Participants

The KNOW-CKD (Korean Cohort Study for Outcome in Patients With Chronic Kidney Disease) is a prospective nationwide cohort study investigating various clinical courses and risk factors for the progression of CKD in Korean patients. Patients, aged between 20 and 75 years, with CKD stages from 1 to 5 before dialysis, who voluntarily provided informed consent, were enrolled from 9 tertiary-care general hospitals throughout Korea between June 2011 and February 2016. The study rationale, design, methods, and protocol summary are provided in detail elsewhere (NCT01630486 at http://www.clinicaltrials.gov).

Among 2238 patients in the KNOW-CKD cohort, 70 with missing data of HDL-C levels were excluded. Finally, 2168 patients were included in the present analysis.

The data that support the findings of this study are available from the KNOW-CKD investigators on reasonable request. The request can initially be sent to the corresponding author, then will be distributed to the investigators. The relevant data, analytical methods, and study materials will be open to researchers after a comprehensive discussion.
Data Collection and Measurements

Demographic details, including age, sex, smoking status, alcohol intake, physical activity, medical history, and comorbid diseases, were obtained from the KNOW-CKD database. Smoking status was classified as never, former, or current. Alcohol intake was categorized as none, moderate (<20 g/d), or high (≥20 g/d). The weekly frequency of moderate- or vigorous-intensity physical activity was also investigated. Anthropometric data, including height and weight, were collected at enrollment. Body mass index (BMI) was calculated as initial body weight divided by height squared (kg/m²). Blood pressure was measured in the sitting position after subjects had been in a relaxed state for at least 5 minutes, by using an electronic sphygmomanometer. 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, including lipid profiles, were done at the local laboratory of each participating center. Most laboratory parameters were measured every 6 months in the first year and annually thereafter, including complete blood cell count, fasting glucose, blood urea nitrogen, creatinine, albumin, calcium, and phosphorus. C-reactive protein, iron profiles (including total iron-binding capacity and serum ferritin), and lipid profiles (including triglyceride, HDL-C, and low-density lipoprotein cholesterol) were measured repeatedly after 1 year and biennially thereafter. We used a creatinine method that requires calibration traceable to isotope dilution mass spectrometry, and estimated glomerular filtration rate (eGFR) was calculated using the CKD Epidemiologic Collaboration equation. Along with blood samples, urine samples were also immediately sent to the central laboratory for proteinuria measurement. Urine albumin/creatinine ratio was calculated as the urine albumin concentration divided by the urine creatinine concentration (mg/g).

Exposure and Outcome Ascertainment

The exposures of interest were baseline and time-varying serum HDL-C levels. Given a possible nonlinear relationship with event rates, serum HDL-C levels were treated as a categorical variable and divided into 5 categories with 10-mg/dL increments: <30, 30 to <40, 40 to <50, 50 to <60 (reference), and ≥60 mg/dL. The reference category for each analysis was selected as the fourth group because these groups were the modal categories with the lowest event rates and allowed for the most powerful analyses. We also treated HDL-C level as a continuous variable and modeled a nonlinear effect by using a restricted cubic spline function.

The primary outcome was a composite of a 50% decline in eGFR from the baseline value or the onset of end-stage renal disease (ESRD) during the follow-up period. ESRD was defined as the initiation of renal replacement therapy, including dialysis or renal transplantation. The secondary outcome was the development of ESRD. Patients were followed up until December 31, 2016, and were censored at the date of the last study visit, death, or the studied events.

Statistical Analyses

Cox proportional hazard regression models were separately performed to study the associations of serum HDL-C levels with subsequent renal outcomes using 2 approaches: (1) fixed models with baseline values were examined to ascertain the association of long-term exposure with CKD progression, and (2) time-varying models were assessed to account for changes in exposure over time and to ascertain their short-term associations. In time-varying analyses, all laboratory data were incorporated as time-dependent variables. For each analysis, unadjusted and 2 additional models were constructed on the basis of the level of multivariate adjustment: (1) model 1: unadjusted; (2) model 2: demographic and clinical characteristics of age, sex, study center (Seoul National University Hospital, Seoul National University Bundang Hospital, Yonsei University Severance Hospital, Kangbuk Samsung Medical Center, Seoul St Mary’s Hospital, Gil Hospital, Eulji General Hospital, Chonnam National University Hospital, or Pusan Paik Hospital), comorbidities (diabetes mellitus, hypertension, coronary artery disease, congestive heart failure, peripheral arterial occlusive disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, and liver disease), smoking status (former or current versus never), alcohol intake (none versus 1–19 or ≥20 g/d), physical activity (<3 versus ≥3 times/week), and use of lipid-modifying drugs (statin, ezetimibe, fibrates, and others); and (3) model 3 (fully adjusted): model 2 plus anthropometric and laboratory parameters, including BMI, systolic blood pressure, serum low-density lipoprotein cholesterol, triglyceride, white blood cell count, fasting glucose, albumin, calcium, phosphorus, total iron-binding capacity, ferritin, C-reactive protein, eGFR, and random urine albumin/creatinine ratio. In addition, we explored the continuous, potentially nonlinear relationship between HDL-C levels and the studied outcomes by using fully adjusted restricted cubic spline models with 4 knots. For sensitivity analysis, we also repeated analyses using HDL-C categorized into quintiles, where the range of quintiles was <36, 36 to <43, 43 to <50.3, 50.3 to <60, and ≥60 mg/dL for baseline HDL-C and <37, 37 to <44, 44 to <51, 51 to <61, and ≥61 mg/dL for time-varying HDL-C values.

To test the robustness of our findings, we then performed subgroup analyses using baseline HDL-C values, which include age (<60 versus ≥60 years), sex, diabetic CKD, statin...
use, BMI (<25 versus ≥25 kg/m²), systolic blood pressure (<130 versus ≥130 mm Hg), serum albumin concentration (<4.0 versus ≥4.0 g/dL), C-reactive protein levels (<0.6 versus ≥0.6 mg/dL), and eGFR (<15 versus ≥15 mL/min per 1.73 m²) at baseline. All exposure-event associations were expressed as hazard ratios (HRs) and 95% CIs. Data from descriptive analyses were summarized using means±SD, medians (interquartile ranges), or proportions, as appropriate, and were compared using Student t test, ANOVA, Kruskal-Wallis test, and χ² test. Statistical significance was defined as P<0.05. All statistical analyses were performed using Stata, version 14.2 (Stata Corporation, College Station, TX).

Ethics Statement
We performed the study in accordance with the Declaration of Helsinki, and the study protocol was approved by the institutional review board of each participating clinical center (in 2011), as follows: Seoul National University Hospital (1104-089-359), Seoul National University Bundang Hospital (B-1106/129-008), Yonsei University Severance Hospital (4-2011-0163), Kangbuk Samsung Medical Center (2011-01-076), Seoul St Mary’s Hospital (KC11OIMI0441), Gil Hospital (GIRBA2553), Eulji General Hospital (201105-01), Chonnam National University Hospital (CNUH-2011-092), and Pusan Paik Hospital (11-091).

Results

Baseline Characteristics of the Study Population
The demographic, clinical, and laboratory characteristics of the patients, according to HDL-C categories, are presented in Table 1. Among the 2168 participants, 1335 (61.6%) were men. Their mean±SD age was 53.7±12.2 years, and their mean±SD HDL-C level was 49.2±15.4 mg/dL. Low (<40 mg/dL) and high (≥60 mg/dL) HDL-C levels were observed in 614 patients (28.3%) and 460 patients (21.2%), respectively. Patients with a higher HDL-C were younger; were more likely to be women and never smokers; and had fewer comorbid conditions, such as diabetes mellitus, hypertension, coronary artery disease, and cerebrovascular disease. In addition, these patients had a lower blood pressure and were less obese and less inflamed than those with a lower HDL-C. Kidney function was more preserved and the amount of urinary protein excretion was lower in patients with a higher HDL-C.

HDL-C and Risk of CKD Progression
During a median follow-up of 3.1 (interquartile range, 1.6–4.5) years, the primary outcome occurred in 335 patients (15.5%). The composite adverse renal outcome occurred most commonly in patients with diabetic nephropathy than in those with other causes of CKD (Table 2). As expected, more patients with a lower eGFR at baseline reached a ≥50% decline in eGFR, or ESRD (Table 2). We then evaluated renal outcomes among HDL-C categories. The primary outcome occurred in 32 (34.4%), 97 (18.6%), 89 (14.0%), 56 (12.2%), and 61 (13.3%) of patients with baseline HDL-C levels of <30, 30 to 39, 40 to 49, 50 to 59, and ≥60 mg/dL, respectively (P<0.001) (Table 3). The unadjusted HRs in the categories of HDL-C levels of <30 and ≥60 mg/dL were 3.42 (95% CI, 2.21–5.28) and 1.10 (95% CI, 0.77–1.59), respectively, compared with the category of HDL-C level of 50 to <60 mg/dL (model 1). This association was not changed after adjustment for demographic factors, comorbidities, and medications (model 2). However, in a fully adjusted Cox model in which BMI, systolic blood pressure, and laboratory parameters were additionally included, the risk of the composite renal outcome was significantly higher in both the lowest (HR, 2.21; 95% CI, 1.30–3.77) and the highest (HR, 2.05; 95% CI, 1.35–3.10) categories (Table 3, Figure 1). The time-varying analysis consistently showed an increased risk of the composite renal outcome in the groups with HDL-C levels of <30 mg/dL (HR, 2.06; 95% CI, 1.18–3.61) and ≥60 mg/dL (HR, 1.62; 95% CI, 1.05–2.52), compared with the reference category (Table 3, Figure 1). Restricted cubic spline models with HDL-C being treated as a continuous variable yielded a similar result (Figure 2). The association of HDL-C with the composite renal outcome followed a U-shaped trend, indicating an increased risk of CKD progression with low and high HDL-C levels.

HDL-C and Risk of ESRD
The findings from analyses of primary outcome remained unaltered in separate analyses of secondary outcome (development of ESRD). ESRD developed in 30 (32.3%), 81 (15.6%), 71 (11.2%), 41 (8.9%), and 51 (11.1%) of patients with HDL-C levels of <30, 30 to 39, 40 to 49, 50 to 59, and ≥60 mg/dL, respectively (P<0.001) (Table 4). Both groups with low (<30 mg/dL; HR, 3.42; 95% CI, 1.87–6.27) and high (≥60 mg/dL; HR, 3.24; 95% CI, 2.00–5.27) baseline levels of HDL-C had a higher risk of ESRD development than the reference group with a baseline HDL-C level of 50 to 59 mg/dL (Table 4, Figure 3). In addition, we observed a similar association between HDL-C levels and the risk of ESRD in the time-varying Cox analysis (Table 4, Figure 3). A U-shaped association between HDL-C level and ESRD development was also found in restricted cubic spline models (Figure 4).

Subgroup Analyses
The results of subgroup analyses are shown in Figure 5. A significant association of low baseline HDL-C (<30 mg/dL)
Table 1. Baseline Characteristics of Patients According to Baseline HDL-C Levels Categorized Into 5 Groups

| Characteristics                      | Total (n=2168) | Baseline Serum HDL-C Concentrations, mg/dL | P Value for Trend |
|--------------------------------------|----------------|--------------------------------------------|-------------------|
|                                      |                | <30 (n=93; 4.3%) | 30–40 (n=521; 24.0%) | 40–50 (n=635; 29.3%) | 50–60 (n=659; 21.2%) | ≥60 (n=640; 21.2%) |
| Age, y                               | 53.7±12.2      | 57.2±10.8       | 55.7±11.6       | 54.1±12.1       | 52.6±12.5       | 51.4±12.6       | <0.001 |
| Sex (men), %                         | 61.6           | 80.6            | 77.4            | 67.2            | 55.1            | 38.5            | <0.001 |
| Cause of CKD, %                      |                |                |                |                |                |                |        |
| Glomerulonephritis                   | 36.2           | 16.1            | 30.9            | 36.7            | 40.1            | 41.5            | <0.001 |
| Diabetic nephropathy                 | 23.2           | 58.1            | 30.9            | 24.9            | 15.0            | 13.3            | <0.001 |
| Hypertension                         | 18.5           | 18.3            | 22.6            | 20.5            | 17.2            | 12.2            | <0.001 |
| Polycystic kidney disease            | 16.1           | 5.4             | 1.0             | 11.0            | 22.7            | 25.9            | <0.001 |
| Others                               | 6.0            | 2.2             | 5.6             | 6.9             | 5.0             | 7.2             | 0.237  |
| Comorbidities, %                     |                |                |                |                |                |                |        |
| DM                                   | 33.9           | 68.8            | 41.1            | 37.0            | 24.6            | 23.5            | <0.001 |
| Hypertension                         | 96.1           | 97.8            | 99.0            | 97.3            | 95.0            | 92.0            | <0.001 |
| Coronary artery disease              | 1.7            | 4.3             | 3.1             | 1.9             | 0.7             | 0.2             | <0.001 |
| CHF                                  | 1.5            | 2.2             | 1.9             | 1.9             | 1.3             | 0.7             | 0.068  |
| PAOD                                 | 3.6            | 4.3             | 4.6             | 3.0             | 4.1             | 2.4             | 0.141  |
| Cerebrovascular disease              | 6.0            | 6.5             | 7.3             | 6.0             | 7.0             | 3.5             | 0.043  |
| Dementia                             | 0.0            | 0.0             | 0.0             | 0.2             | 0.0             | 0.0             | 0.556  |
| COPD                                 | 0.6            | 1.1             | 0.4             | 1.1             | 0.2             | 0.2             | 0.244  |
| Connective tissue disease            | 6.2            | 3.2             | 7.7             | 6.3             | 5.9             | 5.4             | 0.411  |
| Peptic ulcer disease                 | 1.8            | 1.1             | 1.3             | 2.0             | 1.3             | 2.4             | 0.314  |
| Liver disease                        | 2.6            | 2.2             | 3.3             | 3.1             | 1.5             | 2.4             | 0.269  |
| Smoking status, %                    |                |                |                |                |                |                |        |
| Never                                | 53.6           | 40.9            | 38.2            | 52.5            | 59.0            | 69.5            | <0.001 |
| Former                               | 30.6           | 36.6            | 41.8            | 30.4            | 26.1            | 21.4            | <0.001 |
| Current                              | 15.8           | 22.6            | 20.0            | 17.0            | 14.8            | 9.2             | <0.001 |
| Alcohol intake, %                    |                |                |                |                |                |                |        |
| None                                 | 79.5           | 83.2            | 79.4            | 77.4            | 81.3            | 77.3            | 0.167  |
| Moderate (1–19 g/d)                  | 8.7            | 7.5             | 9.8             | 9.8             | 8.7             | 7.3             | 0.681  |
| High (≥20 g/d)                       | 11.8           | 9.3             | 10.9            | 12.8            | 9.9             | 15.4            | 0.035  |
| Physical activity, %                 |                |                |                |                |                |                |        |
| <3 Times/wk                          | 61.8           | 63.0            | 64.1            | 62.4            | 59.3            | 60.0            | 0.179  |
| ≥3 Times/wk                          | 38.2           | 37.0            | 35.9            | 37.6            | 40.7            | 40.0            | 0.179  |
| Body mass index, kg/m²               | 24.6±3.4       | 25.4±2.8        | 25.4±3.2        | 25.0±3.3        | 24.4±3.5        | 23.2±3.4        | <0.001 |
| Blood pressure, mm Hg                |                |                |                |                |                |                |        |
| SBP                                  | 128.6±16.6     | 131.1±19.2      | 129.4±17.0      | 129.0±16.0      | 127.4±16.0      | 127.8±16.8      | 0.017  |
| DBP                                  | 76.8±11.2      | 74.8±13.1       | 76.6±11.1       | 76.8±10.7       | 77.2±10.9       | 76.9±11.8       | 0.197  |
| MAP                                  | 111.3±13.7     | 112.3±16.0      | 111.8±14.0      | 111.6±13.2      | 110.7±13.1      | 110.8±14.3      | 0.118  |

Continued
with CKD progression was evident particularly in men; in those with a lower BMI (<25 kg/m²) and systolic blood pressure (<130 mm Hg); and in those with higher albumin (≥4.0 g/dL) and C-reactive protein (≥0.6 mg/dL) levels (Figure 5A). On the other hand, there was a consistent trend of the impact of baseline high HDL-C with respect to CKD progression in most of the stratified groups (Figure 5B).

### Sensitivity Analyses

To test the robustness and consistency of our findings, we conducted a sensitivity analysis in which participants were recategorized according to quintiles of HDL-C. The risk of the composite renal outcome was significantly higher in both the first (HR, 1.56; 95% CI, 1.01–2.39) and fifth (HR, 2.11; 95% CI, 1.38–3.24) quintiles compared with the fourth quintile of
The time-varying Cox analysis showed that the fifth quintile of HDL-C (HR, 1.61; 95% CI, 1.02–2.52) had a higher risk of the composite renal outcome than the fourth quintile, whereas the risk of the composite renal outcome was not significantly different in the first quintile of HDL-C (HR, 1.32; 95% CI, 0.85–2.06). Similar results were obtained in the secondary outcome analyses for the development of ESRD (Table S2, Figure S2). The risk of ESRD was higher in both the first (HR, 2.05; 95% CI, 1.24–3.41) and fifth (HR, 3.52; 95% CI, 2.13–5.82) quintiles of HDL-C than the fourth quintile of baseline HDL-C. This association remained unaltered in a time-varying Cox analysis.

Discussion

In this large, prospective, cohort study, we showed that, compared with a reference category with HDL-C of 50 to 59 mg/dL, both low (<30 mg/dL) and high (≥60 mg/dL) HDL-C levels were associated with an increased risk of disease progression in patients with CKD who were not yet undergoing dialysis. The time-varying Cox analysis and cubic spline model further supported these findings, showing that the association between HDL-C and adverse renal outcome follows a nonlinear U-shaped relationship. Our findings suggest that both low and high HDL-C levels may contribute to the progression of CKD in patients not yet undergoing dialysis.

Low HDL-C is a traditional risk factor for future cardiovascular events.7 In line with this, several epidemiologic studies have suggested an association between low HDL-C and poor renal function in the general population.16–20 Low HDL-C predicted an increased risk of renal dysfunction in 12 728 participants from the ARIC (Atherosclerosis Risk in Communities) cohort study with baseline serum creatinine of <2.0 mg/dL in men and <1.8 mg/dL in women.16 More recently, Bowe et al also showed a significant relationship between low levels of HDL-C and an increased risk of incident CKD and its progression in a cohort of almost 2 million male veterans over a median follow-up of 9 years.19 Notably, there was a U-shaped relationship between HDL-C level and the future development of CKD in this study, and high HDL-C level was also associated with adverse renal outcomes. However, it is unclear whether these findings can be extrapolated to the whole CKD population because this study included only white elderly veteran men who had normal kidney function (eGFR, >60 mL/min per 1.73 m²) at study initiation.

To date, studies on the relationship between HDL-C levels and adverse renal outcome in nondialysis patients with CKD are scarce and have shown conflicting results.21–24 Baragetti et al showed that low HDL-C levels were associated with earlier entry to a dialysis program or doubling of the plasma creatinine levels in 176 patients with CKD.23 In addition, the MDRD (Modification of Diet in Renal Disease) Study revealed that lower HDL-C independently predicted a faster decline in kidney function in 840 patients with diverse renal diseases.22 In contrast, a recent publication by the CRIC (Chronic Renal Insufficiency Cohort) study investigators showed that HDL-C

Table 2. Clinical Outcomes According to Cause of CKD or eGFR Categories

| Outcomes               | Patients | Renal Outcomes | ≥50% Decline in eGFR | ESRD |
|------------------------|----------|----------------|----------------------|------|
|                        | No. %    | No. %          | No. %                | No. %|
| Overall outcome        | 2168 100.0 | 335 15.5       | 170 7.8              | 274 12.6|
| Cause of CKD           |          |                |                      |      |
| Glomerulonephritis     | 784 36.2 | 87 11.1        | 46 5.9               | 67 8.6|
| Diabetic nephropathy   | 503 23.2 | 147 29.2       | 62 12.3              | 128 25.5|
| Hypertension           | 400 18.5 | 42 10.5        | 24 6.0               | 37 9.3|
| Polycystic kidney disease | 350 16.1 | 47 13.4        | 30 8.6               | 33 9.4|
| Others                 | 131 6.0  | 12 9.2         | 8 6.1                | 9 6.9|
| eGFR categories at T0, mL/min per 1.73 m² | | | | |
| ≥90                    | 260 12.0 | 3 1.2          | 2 0.8                | 1 0.4|
| <90–≥60                | 401 18.5 | 6 1.5          | 6 1.5                | 3 0.8|
| <60–≥45                | 392 18.1 | 19 4.9         | 16 4.1               | 8 2.0|
| <45–≥30                | 473 21.8 | 50 10.6        | 44 9.3               | 32 6.8|
| <30–≥15                | 502 23.2 | 162 32.3       | 85 16.9              | 137 27.3|
| <15                    | 140 6.5  | 95 67.9        | 17 12.1              | 93 66.3|

CKD indicates chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; T0, at baseline.
was not independently associated with the composite end point of ESRD or a 50% reduction in eGFR in 3939 adults with CKD.24 However, HR was determined per 1-SD increase of HDL-C; thus, the insignificant results of the study might be attributable to an inability to distinguish the nonlinear associations among HDL-C categories. Moreover, all the previous studies were limited by analyzing only the baseline HDL-C levels. Our study sought to overcome the limitations of previous studies by analyzing both the baseline HDL-C measurements and the HDL-C changes during the follow-up.

### Table 3. Association of HDL-C Levels With Composite Renal Outcome in the Baseline and Time-Varying Cox Analysis

| HDL-C Level | Patient Event Model 1 | Event Model 2 | Event Model 3 |
|-------------|----------------------|--------------|--------------|
|            | No.       | %     | No. | %     | HR (95% CI) | P Value | HR (95% CI) | P Value | HR (95% CI) | P Value |
| Baseline HDL-C, mg/dL | 2168 | 100.0 | 335 | 15.5 | ... | ... | ... | ... | ... | ... |
| <30 | 93 | 4.3 | 32 | 34.4 | 3.42 (2.21–5.28) | <0.001 | 2.46 (1.56–3.88) | <0.001 | 2.21 (1.30–3.77) | 0.003 |
| 30–<40 | 521 | 24.0 | 97 | 18.6 | 1.64 (1.18–2.27) | 0.003 | 1.45 (1.03–2.04) | 0.032 | 1.28 (0.85–1.91) | 0.233 |
| 40–<50 | 635 | 29.3 | 89 | 14.0 | 1.21 (0.87–1.69) | 0.261 | 1.10 (0.78–1.55) | 0.585 | 1.26 (0.86–1.84) | 0.242 |
| 50–<60 | 459 | 21.2 | 56 | 12.2 | 1.00 (Reference) | ... | 1.00 (Reference) | ... | 1.00 (Reference) | ... |
| ≥60 | 460 | 21.2 | 61 | 13.3 | 1.10 (0.77–1.59) | 0.597 | 1.22 (0.84–1.76) | 0.298 | 2.05 (1.35–3.10) | 0.001 |

| Time-varying HDL-C, mg/dL | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... |
| <30 | ... | ... | ... | ... | 4.57 (2.95–7.09) | <0.001 | 3.50 (2.22–5.56) | <0.001 | 2.06 (1.18–3.61) | 0.011 |
| 30–<40 | ... | ... | ... | ... | 1.92 (1.35–2.72) | <0.001 | 1.58 (1.09–2.29) | 0.016 | 1.15 (0.75–1.77) | 0.533 |
| 40–<50 | ... | ... | ... | ... | 1.61 (1.14–2.28) | 0.007 | 1.40 (0.98–2.02) | 0.068 | 1.51 (1.01–2.26) | 0.045 |
| 50–<60 | ... | ... | ... | ... | 1.00 (Reference) | ... | 1.00 (Reference) | ... | 1.00 (Reference) | ... |
| ≥60 | ... | ... | ... | ... | 1.30 (0.89–1.90) | 0.170 | 1.28 (0.86–1.90) | 0.217 | 1.62 (1.05–2.52) | 0.031 |

Model 1: unadjusted; model 2: adjusted for age, sex, study center, comorbidities (diabetes mellitus, hypertension, coronary artery disease, congestive heart failure, peripheral arterial occlusive disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, and liver disease), smoking status (former or current vs never), alcohol intake (none vs 1–19 or ≥20 g/d), physical activity (<3 vs ≥3 times/week), and lipid-modifying drugs (statin, ezetimibe, fibrates, and others); model 3: adjusted for model 2 plus body mass index, systolic blood pressure, and laboratory findings (white blood cell count, fasting glucose, albumin, calcium, phosphorus, total iron-binding capacity, ferritin, C-reactive protein, low-density lipoprotein cholesterol, triglyceride, estimated glomerular filtration rate, and urine albumin/creatinine ratio). HDL-C indicates high-density lipoprotein cholesterol; HR, hazard ratio.

**Figure 1.** Associations of baseline (A) and time-varying (B) serum high-density lipoprotein cholesterol (HDL-C) levels with composite renal outcomes (hazard ratios and 95% CI error bars). Adjustments in model 1: unadjusted; model 2: age, sex, study center, comorbidities, smoking status, alcohol intake, physical activity, and use of lipid-modifying drugs; and model 3: model 2 plus body mass index, systolic blood pressure, serum low-density lipoprotein cholesterol, triglyceride, white blood cell count, fasting glucose, albumin, calcium, phosphorus, total iron-binding capacity, ferritin, C-reactive protein level, estimated glomerular filtration rate, and random urine albumin/creatinine ratio.

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period in a large cohort of patients with CKD. In this regard, our findings provide robust evidence that both low and high HDL-C levels were associated with an increased risk of CKD progression in patients with nondialysis CKD.

CKD has an impact on serum HDL-C levels that is determined by the rate of HDL-mediated reverse cholesterol uptake from peripheral tissues and unloading of its cholesterol cargo in the liver. HDL-mediated reverse cholesterol uptake is significantly impaired in chronic inflammatory and oxidative stress conditions, such as CKD. Reduced production and increased catabolism of apolipoprotein A1, downregulation of lecithin-cholesterol acyltransferase, and upregulation of acyl–coenzyme A cholesterol acyltransferase-1 can contribute to the defective HDL-}

Table 4. Association of HDL-C Levels With Development of ESRD in the Baseline and Time-Varying Cox Analysis

| HDL-C Level | Patient | Event | Model 1 | Model 2 | Model 3 |
|-------------|---------|-------|---------|---------|---------|
|             | No.     | %     | No.     | %       | HR (95% CI) | P Value | HR (95% CI) | P Value | HR (95% CI) | P Value | |
| Baseline HDL-C, mg/dL | 2168 | 100.0 | 274 | 12.6 | ... | ... | ... | ... | ... | ... | |
| <30 | 93 | 4.3 | 30 | 32.3 | 4.34 (2.71–6.96) | <0.001 | 2.98 (1.82–4.89) | <0.001 | 3.42 (1.87–6.27) | <0.001 | |
| 30–<40 | 521 | 24.0 | 81 | 15.6 | 1.87 (1.28–2.72) | 0.001 | 1.62 (1.10–2.38) | 0.015 | 1.69 (1.06–2.71) | 0.029 | |
| 40–<50 | 635 | 29.3 | 71 | 11.2 | 1.32 (0.90–1.94) | 0.157 | 1.21 (0.81–1.79) | 0.353 | 1.54 (0.98–2.43) | 0.062 | |
| 50–<60 | 459 | 21.2 | 41 | 8.9 | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) | |
| ≥60 | 460 | 21.2 | 51 | 11.1 | 1.26 (0.83–1.89) | 0.278 | 1.47 (0.96–2.24) | 0.074 | 3.24 (2.00–5.27) | <0.001 | |
| Time-varying HDL-C, mg/dL | | | | | | | | | | |
| <30 | ... | ... | ... | ... | 5.89 (3.61–9.61) | <0.001 | 4.42 (2.61–7.51) | <0.001 | 3.28 (1.71–6.30) | 0.001 | |
| 30–<40 | ... | ... | ... | ... | 2.43 (1.61–3.66) | <0.001 | 1.97 (1.26–3.06) | 0.003 | 1.78 (1.05–3.01) | 0.033 | |
| 40–<50 | ... | ... | ... | ... | 1.88 (1.24–2.83) | 0.003 | 1.64 (1.06–2.54) | 0.027 | 2.06 (1.24–3.43) | 0.005 | |
| 50–<60 | ... | ... | ... | ... | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) | |
| ≥60 | ... | ... | ... | ... | 1.57 (1.01–2.45) | 0.044 | 1.64 (1.03–2.62) | 0.039 | 2.64 (1.55–4.48) | <0.001 | |

Model 1: unadjusted; model 2: adjusted for age, sex, study center, comorbidities (diabetes mellitus, hypertension, coronary artery disease, congestive heart failure, peripheral arterial occlusive disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, and liver disease), smoking status (former or current vs never), alcohol intake (none vs 1–19 or ≥20 g/d), physical activity (<3 vs ≥3 times/week), and lipid-modifying drugs (statin, ezetimibe, fibrates, and others); model 3: adjusted for model 2 plus body mass index, systolic blood pressure, and laboratory findings (white blood cell count, fasting glucose, albumin, calcium, phosphorus, total iron-binding capacity, ferritin, C-reactive protein, low-density lipoprotein cholesterol, triglyceride, estimated glomerular filtration rate, and urine albumin/creatinine ratio). ESRD indicates end-stage renal disease; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio.

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mediated cholesterol uptake in CKD.\textsuperscript{31} In addition, modification of apolipoprotein A1 by reactive oxygen species (oxidation), elevated urea level (carbamylation), and systemic inflammation (myeloperoxidase modification) impairs the ability of HDL to bind to the machinery mediating cholesterol efflux via ATP-binding cassette transporter A1 and G1.\textsuperscript{32} Furthermore, the unloading of HDL-C cargo is also impaired in CKD. The aforementioned modifications may limit the binding of HDL to scavenger receptor-B1, leading to defective disposal of HDL-C cargo in the liver.\textsuperscript{33} Advanced oxidation products, which are carried by oxidized plasma protein and accumulate in renal disease,\textsuperscript{34} also bind to scavenger receptor-B1 with high affinity and further prevent cholesterol influx.\textsuperscript{25} Taken together, reverse cholesterol transport properties are defective in the patients with CKD because both HDL-mediated reverse cholesterol uptake and unloading capacity of its cholesterol cargo are impaired. However, their effects on HDL-C levels are opposite: impaired cholesterol uptake from peripheral tissues leads to HDL-C deficiency, whereas compromised HDL-C unloading capacity increases

Figure 3. Associations of baseline (A) and time-varying (B) serum high-density lipoprotein cholesterol (HDL-C) levels with end-stage renal disease (ESRD; hazard ratios and 95% CI error bars). Adjustments in model 1: unadjusted; model 2: age, sex, study center, comorbidities, smoking status, alcohol intake, physical activity, and use of lipid-modifying drugs; and model 3: model 2 plus body mass index, systolic blood pressure, serum low-density lipoprotein cholesterol, triglyceride, white blood cell count, fasting glucose, albumin, calcium, phosphorus, total iron-binding capacity, ferritin, C-reactive protein level, estimated glomerular filtration rate, and random urine albumin/creatinine ratio.

Figure 4. Adjusted hazard ratios of end-stage renal disease (ESRD) associated with baseline (A) and time-varying (B) serum high-density lipoprotein cholesterol (HDL-C) concentrations in a Cox model using restricted cubic spines. All models were adjusted for age, sex, study center, comorbidities, smoking status, alcohol intake, physical activity, use of lipid-modifying drugs, body mass index, systolic blood pressure, serum low-density lipoprotein cholesterol, triglyceride, white blood cell count, fasting glucose, albumin, calcium, phosphorus, total iron-binding capacity, ferritin, C-reactive protein level, estimated glomerular filtration rate, and random urine albumin/creatinine ratio.
HDL-C levels. In this regard, high HDL-C in CKD might, in part, indicate defective reverse cholesterol transport, rather than improved HDL function.

Although HDL-C levels are affected by CKD itself, our study showed that both low and high HDL-C levels could be harmful with respect to CKD progression, suggesting a bidirectional association between 2 factors. Nevertheless, it is still unclear whether low HDL-C is causally linked to the progression of CKD. In addition to the altered HDL metabolism in CKD, low HDL-C levels might be attributed to poor overall metabolic health, which can contribute to the decline in kidney function.35 In fact, some genetic studies and randomized clinical trials suggested that low HDL-C might simply be a marker reflecting residual risk rather than an independent driver of adverse outcomes.8–10,36 For instance, Coassim et al revealed that the genetic variants having the strongest associations with HDL-C levels were not related to kidney function.34 In addition, pharmacologic agents that increase serum HDL-C, such as niacin and cholesterol ester transfer protein inhibitors, had no effect on cardiovascular events and renal function in randomized clinical trials.8–10 However, we clearly showed an independent association of low HDL-C with CKD progression, even after a rigorous adjustment for multiple confounding factors. Our findings are supported by experimental studies demonstrating that HDL-C deficiency or dysfunction induced renal vascular atherosclerosis and glomerular and tubulointerstitial injury.37–39 Furthermore, a recent mendelian randomization study suggested a small, but robust, causal association between HDL-C concentration and eGFR in the general population.32 These findings together raise the possibility of a causal association between low HDL-C and renal dysfunction.

The association between HDL-C and the risk of adverse renal outcome follows a U-shaped curve, suggesting that high HDL-C could also be harmful with respect to CKD progression. Several studies can explain the possible mechanisms responsible for this phenomenon. An experimental study by Huang et al showed that moderate to high concentrations of HDL in healthy subjects paradoxically impaired endothelial progenitor cells and angiogenesis in the absence of oxidized low-density lipoprotein, suggesting the biphasic effects of HDL.40 In addition, accumulating evidence shows that inflammation and oxidative stress can impair reverse cholesterol transport and reduce the anti-inflammatory and

Figure 5. Adjusted hazard ratios (and 95% CI error bars) of composite renal outcomes for the low (<30 mg/dL; A) and high (≥60 mg/dL; B) high-density lipoprotein cholesterol (HDL-C) categories vs the reference group (30–<60 mg/dL) of baseline HDL-C levels in various subgroups. All models were adjusted for age, sex, study center, comorbidities, smoking status, alcohol intake, physical activity, use of lipid-modifying drugs, body mass index (BMI), systolic blood pressure (SBP), serum low-density lipoprotein cholesterol, triglyceride, white blood cell count, fasting glucose, albumin, calcium, phosphorus, total iron-binding capacity, ferritin, C-reactive protein (CRP) level, estimated glomerular filtration rate (eGFR), and urine albumin/creatinine ratio. CKD indicates chronic kidney disease.
antioxidant properties of HDL. Interestingly, CKD involves a high level of inflammation accompanied by a high burden of oxidative stress, and the antioxidant and anti-inflammatory activity of HDL is diminished in patients with CKD. A reduced activity of HDL-associated antioxidant enzymes, such as paraoxonase-1, glutathione peroxidase, and lecithin-cholesterol acyltransferase, can contribute to these findings in CKD. Furthermore, HDL can transform into the opposite pro-oxidant and proinflammatory directions in CKD. This was demonstrated by Speer et al, who showed that HDL in patients with CKD reduced endothelial NO availability via toll-like receptor-2, leading to impaired endothelial repair, increased proinflammatory activation, and increased blood pressure. This transformation can be facilitated by the oxidative modification of apolipoprotein A1 and other components of HDL and the accumulation of proinflammatory proteins, such as serum amyloid-A, which promote cytokine production and increase the endothelial production of reactive oxygen species. In accordance with these findings, several observational studies showed paradoxical associations between elevated HDL-C levels and cardiovascular events or mortality in certain conditions with chronic inflammation, particularly in patients undergoing hemodialysis. Therefore, it can be presumed that high levels of toxic HDL particles in CKD might contribute to adverse outcomes, including deterioration of kidney function.

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 a large number of participants and analyzed the data by using various multivariable Cox models after a rigorous adjustment for measured covariates. Second, most of the patients in our study had relatively preserved kidney function; thus, the association between HDL-C and CKD progression needs to be verified in patients with advanced CKD. However, the results of subgroup analysis by baseline eGFR were consistent with the main findings, and a significant association was also seen in patients with advanced CKD. Third, HDL-C levels were measured at the local laboratory of each participating center, not the central laboratory. This could raise a concern about imprecision and bias among various methods for measuring HDL-C. However, all laboratories in our study used the same direct enzymatic assay for the measurement. In addition, to mitigate bias associated with the center effect, this was adjusted in the multivariable model and the results were consistent. Fourth, we did not conduct a qualitative assessment of HDL-C composition and function, or HDL-C subclasses. As aforementioned, some researchers have suggested the importance of alterations in the composition and function of HDL-C, rather than the quantity of HDL-C. Nevertheless, we clearly showed the biphasic association of HDL-C with adverse renal outcome by using various statistical models and suggested that quantitative assessment can also explain the complex role of HDL-C in patients with CKD. Finally, as the event rates for cardiovascular disease or mortality were low because of the relatively short duration of follow-up, we did not investigate the relationship between HDL-C and cardiovascular events or mortality. Future reports from the KNOW-CKD will focus on these issues.

In conclusion, both low and high HDL-C levels were associated with an increased risk of disease progression in patients with nondialysis CKD, showing a nonlinear U-shaped relationship. Our findings support the results of previous studies showing that HDL-C becomes dysfunctional and even transforms into toxic particles in patients with CKD. Future research should focus on the role of the composition and function of HDL in the progression of CKD, rather than its levels alone.

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Disclosures

None.

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Supplemental Material
**Appendix**

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Table S1. Association of quintiles of high-density cholesterol levels with composite renal outcome in the baseline and time-varying Cox analyses.

|                        | Patient No | Event No | Model 1 HR (95% CI) | Model 2 HR (95% CI) | Model 3 HR (95% CI) |
|------------------------|------------|----------|---------------------|---------------------|---------------------|
| **Baseline HDL-C (mg/dL)** | 2,168      | 335      |                     |                     |                     |
| Quintile 1             | 369        | 92       | 2.23 (1.58-3.14)    | 1.81 (1.26-2.59)    | 1.56 (1.01-2.39)    |
| Quintile 2             | 449        | 69       | 1.34 (0.93-1.92)    | 1.24 (0.85-1.79)    | 1.31 (0.86-1.98)    |
| Quintile 3             | 483        | 62       | 1.06 (0.73-1.54)    | 0.97 (0.67-1.42)    | 1.24 (0.81-1.90)    |
| Quintile 4             | 407        | 51       | 1.00 (Reference)    | 1.00 (Reference)    | 1.00 (Reference)    |
| Quintile 5             | 460        | 61       | 1.08 (0.75-1.57)    | 1.19 (0.82-1.74)    | 2.11 (1.38-3.24)    |
| **Time-varying HDL-C (mg/dL)** |           |          |                     |                     |                     |
| Quintile 1             | -          | -        | 2.50 (1.76-3.55)    | 2.04 (1.40-2.98)    | 1.32 (0.85-2.06)    |
| Quintile 2             | -          | -        | 1.57 (1.08-2.28)    | 1.35 (0.91-2.01)    | 1.15 (0.74-1.80)    |
| Quintile 3             | -          | -        | 1.41 (0.96-2.08)    | 1.32 (0.88-1.97)    | 1.54 (0.98-2.41)    |
| Quintile 4             | -          | -        | 1.00 (Reference)    | 1.00 (Reference)    | 1.00 (Reference)    |
| Quintile 5             | -          | -        | 1.27 (0.86-1.87)    | 1.28 (0.86-1.93)    | 1.61 (1.02-2.52)    |

HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; CI, confidence interval
Model 1: unadjusted; Model 2: adjusted for age, sex, study center, comorbidities (diabetes mellitus, hypertension, coronary artery disease, congestive heart failure, peripheral arterial occlusive disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease), smoking status (former or current vs never), alcohol intake (none vs 1–19 g/d or ≥20 g/d), physical activity (<3 times/wk vs ≥3 times/wk), and lipid modifying drugs (statin, ezetimibe, fibrates, and others); Model 3: adjusted for model 2 + body mass index, systolic blood pressure, and laboratory findings (white blood cell, fasting glucose, albumin, calcium, phosphorus, total iron binding capacity, ferritin, C-reactive protein, low-density lipoprotein cholesterol, triglyceride, estimated glomerular filtration rate, and urine albumin-to-creatinine ratio)
Table S2. Association of quintiles of high-density cholesterol levels with development of ESRD in the baseline and time-varying Cox analyses.

|                          | Patient No | Event No | Model 1 | Model 2 | Model 3 |
|--------------------------|------------|----------|---------|---------|---------|
|                          | %          | %        | HR (95% CI) | P       | HR (95% CI) | P       |
| Baseline HDL-C (mg/dL)   |            |          |         |         |         |
| Quintile 1               | 369        | 78       | 2.58 (1.75-3.82) | <0.001 | 2.00 (1.32-3.02) | 0.001 |
|                          | 17.0       | 21.1     |         |         | 2.05 (1.24-3.41) | 0.005 |
| Quintile 2               | 449        | 59       | 1.60 (1.06-2.41) | 0.026 | 1.48 (0.97-2.26) | 0.067 |
|                          | 20.7       | 13.1     |         |         | 1.78 (1.09-2.92) | 0.021 |
| Quintile 3               | 483        | 49       | 1.16 (0.76-1.77) | 0.503 | 1.07 (0.69-1.66) | 0.775 |
|                          | 22.3       | 10.1     |         |         | 1.66 (0.99-2.76) | 0.054 |
| Quintile 4               | 407        | 37       | 1.00 (Reference) |       | 1.00 (Reference) |       |
|                          | 18.8       | 9.1      |         |         | 1.00 (Reference) |       |
| Quintile 5               | 460        | 51       | 1.24 (0.81-1.90) | 0.314 | 1.46 (0.95-2.26) | 0.088 |
|                          | 21.2       | 11.1     |         |         | 3.52 (2.13-5.82) | <0.001 |

| Time-varying HDL-C (mg/dL) |          |          |         |         |         |         |
|----------------------------|----------|----------|---------|---------|---------|---------|
| Quintile 1                 | -        | -        | 2.86 (1.92-4.28) | <0.001 | 2.19 (1.41-3.39) | <0.001 |
|                           |          |          |         |         | 1.74 (1.02-2.96) | 0.041 |
| Quintile 2                 | -        | -        | 1.87 (1.22-2.86) | 0.004 | 1.60 (1.01-2.51) | 0.043 |
|                           |          |          |         |         | 1.67 (0.99-2.83) | 0.055 |
| Quintile 3                 | -        | -        | 1.48 (0.94-2.32) | 0.089 | 1.33 (0.82-2.14) | 0.244 |
|                           |          |          |         |         | 1.92 (1.10-3.33) | 0.021 |
| Quintile 4                 | -        | -        | 1.00 (Reference) |       | 1.00 (Reference) |       |
|                           |          |          |         |         | 1.00 (Reference) |       |
| Quintile 5                 | -        | -        | 1.42 (0.91-2.21) | 0.121 | 1.44 (0.90-2.31) | 0.126 |
|                           |          |          |         |         | 2.28 (1.39-4.06) | 0.001 |

ESRD, end-stage renal disease; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; CI, confidence interval

Model 1: unadjusted; Model 2: adjusted for age, sex, study center, comorbidities (diabetes mellitus, hypertension, coronary artery disease, congestive heart failure, peripheral arterial occlusive disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, and liver disease), smoking status (former or current vs never), alcohol intake (none vs 1–19 g/d or ≥20 g/d), physical activity (<3 times/wk vs ≥3 times/wk), and lipid modifying drugs (statin, ezetimibe, fibrates, and others); Model 3: adjusted for model 2 + body mass index, systolic blood pressure, and laboratory findings (white blood cell, fasting glucose, albumin, calcium, phosphorus, total iron binding capacity, ferritin, C-reactive protein
Figure S1. Association of quintiles of high-density cholesterol levels with composite renal outcome in the (A) baseline and (B) time-varying Cox analyses (hazard ratios and 95% confidence interval error bars).
Figure S2. Association of quintiles of high-density cholesterol levels with end-stage renal disease in the (A) baseline and (B) time-varying Cox analyses (hazard ratios and 95% confidence interval error bars).