Predictive value of triglyceride/high-density lipoprotein cholesterol for major clinical outcomes in advanced chronic kidney disease: a nationwide population-based study

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ABSTRACT

Background. Dyslipidemia is an essential parameter in the prediction of cardiovascular disease (CVD). We aimed to explore whether lipid profiles could predict major outcomes in patients with advanced chronic kidney disease (CKD).

Methods. We retrospectively reviewed the National Health Insurance Service database for people who received nationwide health screening in 2009. All subjects exposed to a lipid-lowering agent before screening were excluded. The population was divided into control, early [estimated glomerular filtration rate (eGFR) 45–59 mL/min/1.73 m\textsuperscript{2}] and advanced (eGFR < 45 mL/min/1.73 m\textsuperscript{2}) CKD groups. The hazard ratios (HRs) of outcomes were calculated using multivariate Cox regression models.

Results. A total of 3 634 873 participants were included in this study, with 404 298 (11.1\%) and 66 805 (1.8\%) having early and advanced CKD, respectively. For all populations, levels of triglyceride/high-density lipoprotein cholesterol (TG/HDL-C) showed a linear association with major cardiovascular and cerebrovascular events (MACCEs) and all-cause mortality, while
low-density lipoprotein cholesterol (LDL-C) showed a different pattern of association with MACCEs (linear association) from all-cause mortality (U-shaped association). The significance between the levels of LDL-C and outcomes was attenuated in the advanced CKD group. For TG/HDL-C, although the significance was decreased, the linear patterns with both MACCEs and all-cause mortality were maintained in the advanced CKD group.

Conclusions. The pattern and significance of lipid profiles were different according to the grade of kidney function. TG/HDL-C should be additionally considered as a predictive marker for CVD and mortality along with LDL-C in patients with CKD.

Keywords: all-cause mortality, cardiovascular disease, chronic kidney disease, lipid profiles, triglyceride/HDL cholesterol

INTRODUCTION

The risk for cardiovascular disease (CVD) is significantly increased in patients with chronic kidney disease (CKD) and is increasingly apparent as kidney function deteriorates [1, 2]. Guidelines commonly considered patients with advanced CKD to be at high risk for developing atherosclerotic CVD [3, 4] and thus recommended using lipid-lowering agents for patients with nondialysis-dependent CKD Stages 3–5 irrespective of cholesterol level [5]. This recommendation for statin targets lowering the low-density lipoprotein cholesterol (LDL-C) level, which is also one of the most reliable predictive markers for mortality [6]. However, the lipid profiles of patients with CKD show different characteristics from those of the general population and their predictability regarding major clinical outcomes remains elusive.

Dyslipidemia is common in patients with CKD, and the patterns of lipid profiles in CKD patients are different from people with normal kidney function. The levels of triglyceride (TG) and very LDL-C (VLDL-C) are increased, that of high-density lipoprotein cholesterol (HDL-C) is decreased and those of total cholesterol and LDL-C are often within the normal limit or even reduced [7]. In addition, disturbances in lipoprotein metabolism can induce dysfunctional lipoprotein by losing biological activity in renal insufficiency. Therefore the predictability of lipid profiles for CVD in patients with CKD might be decreased [8]. Additionally, the limitation of LDL-C as an outcome predictor due to a discrepancy between its correlation patterns with death (U-shaped) and cardiovascular outcomes (linear) may be more evident in CKD patients in light of issues relating to nutritional deficits. In this regard, we previously demonstrated that LDL-C showed the discrepancy in CKD patients with diabetes despite its predictability of both major adverse cardiac events (MACEs) and all-cause mortality [9].

In this study, using population-based cohort data from >3 million Koreans without diabetes, we aimed to evaluate the pattern of lipid profiles associated with the development of major adverse cardiovascular and cerebrovascular events (MACCEs) and all-cause mortality according to the stages of kidney failure. Furthermore, we aimed to examine the lipid profiles for predicting the risk for MACCEs and all-cause mortality in CKD patients.

MATERIALS AND METHODS

Study population

All subjects who underwent health screening in 2009 were initially included in the study. We excluded subjects <45 or ≥100 years old; with a history of diabetes; on current lipid-lowering therapy; without creatinine value or lipid profile data; with a history of renal replacement therapy, including dialysis and kidney transplantation; with a history of MACCEs within 3 years before health screening and with a history of malignancy within 3 years before the health screening and inclusion period. Finally, the included subjects were followed up until December 2016.

Data source and acquisition

This study was performed using the extracted data from the Korean National Health Insurance Service (NHIS) and the Health Insurance Review and Assessment Service (HIRA) database. Korea provides health insurance for all citizens living in the country through social health insurance and public assistance. All citizens ≥20 years of age have a right to undergo health screening biannually and the population ≥40 years of age participates in a specific cancer screening program. The baseline characteristics, such as demographic information, anthropometric data and laboratory data, acquired from the health screening data were obtained from the NHIS database [10]. In addition, healthcare utilization information, diagnosis with International Classification of Diseases, Tenth Revision (ICD-10) codes, medical procedures, prescription records and medical costs were obtained from the HIRA database [11].

Collected data

We collated the baseline information, such as age, sex, income status, smoking status, alcohol consumption, and anthropometric data including height, weight, waist and hip circumference and blood pressure, as well as laboratory data such as serum creatinine (sCr), serum glucose and lipid profile, including total cholesterol, LDL-C, HDL-C, TG and TG/HDL-C. LDL-C was calculated using the Friedewald formula [12]. In cases with TG >400 mg/dL, LDL-C was measured by enzymatic assay. We assessed kidney function by the estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) formula based on sCr: 175 × sCr⁻¹.154 × age⁻⁰.203 × 0.742 (if female). To evaluate the comorbidities, we assessed diagnostic information using ICD-10 codes. Any subject with the same diagnostic code at least two times within the study period was identified as a patient with the disease.

Study outcome

We divided subjects into three different groups by eGFR and albuminuria: control, eGFR >60 mL/min/1.73 m²; early CKD, eGFR 45–<60 mL/min/1.73 m² or eGFR >60 mL/min/1.73 m² and urine albumin ≥1+; and advanced CKD, eGFR <45 mL/min/1.73 m². The lipid profiles were divided by decile. The major clinical outcomes were MACCEs and all-cause mortality.

The development of all-cause mortality and MACCEs consisting of acute myocardial infarction, revascularization and acute ischemic stroke was identified during the study period between 2009 and 2016. Acute myocardial infarction was defined using the ICD-10 code I21 or I22 during admission.
Revascularization was defined by a claim history of percutaneous coronary intervention. Acute ischemic stroke was defined using the ICD-10 code I63 during admission.

First, we assessed the relative risk for the development of clinical outcomes according to lipid profile by decile in all study subjects, which revealed the association between the levels of lipid profiles and the risk of clinical outcomes. Second, we performed the same analysis in the subgroups consisting of three different renal functions and compared the relative risk for the clinical outcomes. The major lipid profiles were LDL-C and TG/HDL-C.

**Statistical analysis**

We performed the Wilcoxon rank-sum test and chi-squared test to compare the baseline characteristics. We described the mean with standard deviation (SD) and the number with percent for continuous and categorical variables, respectively. Two-sided P-values were derived by setting the significance level at 0.05. Cox proportional regression analysis was conducted to evaluate the relative risk of clinical outcomes. The risks for outcome were expressed by the adjusted hazard ratio (aHR) with a 95% confidence interval (CI). To secure the cut-off points to predict MACCEs in different stages of CKD, we performed survival receiver operating characteristics (ROC) analysis. We used variables including age, sex, body mass index, smoking habits, systolic blood pressure (SBP), MDRD eGFR, urinary albumin and Charlson comorbidity index. These statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

**Ethical considerations**

This study was approved by the Institutional Review Board of Seoul National University Hospital (E-1801-105-917). The attending government organization approved the use of the NHIS database (no. 2018-1-181). This study was conducted in accordance with the Declaration of Helsinki.

**RESULTS**

**Study population**

A total of 10,505,818 subjects who underwent national health screening in 2009 were included in the study. After excluding subjects who were ineligible, 3,163,770 (87%), 404,298 (11.1%) and 66,805 (1.8%) participants were classified into the control, early CKD and advanced CKD groups, respectively (Figure 1).

**Baseline characteristics**

Participants in the advanced CKD group were the oldest and had the lowest incidence of low income and the highest SBP and serum glucose. Although all of the baseline characteristics were significantly different according to the stages of CKD, there was no non-linearity with renal function. The mean levels of all lipid profiles were highest in the early CKD group (P < 0.001) (Table 1).

**Risks of MACCEs and all-cause mortality according to the levels of each lipid profile**

The lipid profiles were divided by decile and the ranges between minimum and maximum are described in Supplementary data, Table S1. LDL-C, TG and TG/HDL-C showed a positive correlation and HDL-C showed an inverse correlation with the risk for MACCEs (Figure 2). In the analysis using deciles of the lipid profiles, higher values of LDL-C, TG and TG/HDL-C and lower values of HDL-C were incrementally associated with a higher risk of MACCEs. When those who were in the fifth decile were used as reference subjects, aHRs of the 10th decile were 1.45 (95% CI 1.42–1.49) for LDL-C, 1.25 (95% CI 1.22–1.28) for TG, 0.88 (95% CI, 0.85–0.90) for HDL-C and 1.30 (95% CI 1.27–1.33) for TG/HDL-C.

Although the predictive power was lower than that of MACCEs, lower values of HDL-C and higher values of TG and TG/HDL-C were incrementally associated with an increased risk of all-cause mortality. LDL-C showed a U-shaped association with all-cause mortality instead of a linear association (Figure 2).

**Risks of MACCEs according to the levels of LDL-C and TG/HDL-C in different stages of CKD**

In all stages of CKD, the pattern for MACCEs with LDL-C and TG/HDL-C exhibited linear correlation in common. The significance was most obvious in the control group and decreased as kidney function declined (Figure 3). Although the linear pattern was similar for LDL-C and TG/HDL-C in advanced CKD, the slope was steeper for TG/HDL-C.

According to the decile of TG, the risk of MACCEs was significantly increased beginning in the fifth decile in the control group, and the significance was decreased in the process of renal dysfunction (Supplementary data, Table S2). In addition, HDL-C showed a negative correlation with the risk of MACCEs, as demonstrated in Figure 2. The significance was not
maintained in the advanced CKD group (Supplementary data, Table S3).

In the survival ROC analysis for the 5-year outcome prediction model, the cut-off point of TG/HDL-C was 1.97 in advanced CKD, and it was the highest value according to the stage of CKD. In addition, the cut-off point of LDL-C was 89–93 mg/dL in LDL-C according to the stage of CKD (Supplementary data, Table S4).

Risks of nonfatal myocardial infarction, revascularization and ischemic stroke according to the levels of LDL-C and TG/HDL-C in different stages of CKD

In the subgroup analysis for a specific disease in the MACCE category, the overall pattern according to renal function was similar, as shown in Figure 3. The increasing levels of TG/HDL and LDL showed a significant association with increased risk of myocardial infarction, revascularization and stroke in the control and early CKD groups. Although the significance of the risk association was decreased in advanced CKD, positive linearity was maintained, except for stroke (Supplementary data, Figure S1).

Risks of mortality according to the levels of LDL-C and TG/HDL-C in different stages of CKD

All-cause mortality and LDL-C showed a U-shaped association, and the lowest level of LDL-C showed the highest aHR [1.23 (95% CI 1.20–1.27)] in the control group. On the other hand, the association of TG/HDL-C with all-cause mortality showed a linear association, which exhibited a similar pattern of association with MACCEs. These patterns of associations were maintained in the early CKD group. In advanced CKD, there was no significant pattern in the relationship between all-cause mortality and LDL-C level. Even though there was an outlier pattern in the ninth decile of TG/HDL-C, the linear pattern of association between all-cause mortality and TG/HDL-C was maintained in advanced CKD. When those who were in the fifth decile were used as reference subjects, the aHRs of the lowest and highest deciles were 1.16 (95% CI 1.02–1.32) and 0.94 (95% CI 0.82–1.07), respectively, for LDL-C, while they were 0.99 (95% CI 0.84–1.17) and 1.16 (95% CI 1.02–1.31), respectively, for TG/HDL-C (Table 2).

The cut-off value of TG/HDL-C for predicting mortality was incrementally increased from 1.28 to 1.76 from control to advanced CKD. In contrast, the cut-off value of LDL-C was similar between early and advanced CKD (Supplementary data, Table S5).

### Table 1. Baseline characteristics according to the stage of CKD

| Variables                        | Control (n = 3 163 770) | Early CKD (n = 404 298) | Advanced CKD (n = 66 805) |
|----------------------------------|-------------------------|-------------------------|---------------------------|
| Age (years)                      | 55.6 ± 8.5              | 57.9 ± 10.2             | 58.3 ± 10.7               |
| Male, n (%)                      | 1 609 975 (50.9)        | 1 675 990 (41.5)        | 2 932 737 (43.9)          |
| Smoking, n (%)                   |                         |                         |                           |
| Non-smoker                       | 2 012 162 (63.6)        | 2 086 228 (70.8)        | 45 126 (67.6)             |
| Ex-smoker                        | 486 289 (15.4)          | 54 898 (13.6)           | 10 692 (16.0)             |
| Current smoker                   | 665 319 (21.0)          | 63 172 (15.6)           | 10 987 (16.5)             |
| Alcohol, n (%)                   |                         |                         |                           |
| None                             | 1 856 862 (58.7)        | 2 664 442 (65.9)        | 41 976 (62.8)             |
| Moderate                         | 1 077 615 (34.1)        | 1 169 190 (28.9)        | 21 705 (32.5)             |
| Heavy                            | 229 293 (7.3)           | 20 937 (5.2)            | 3124 (4.7)                |
| Low income, n (%)                | 721 894 (22.8)          | 96 520 (23.8)           | 11 291 (16.9)             |
| Waist circumference, cm          | 80.6 ± 8.2              | 80.9 ± 8.6              | 80.8 ± 8.0                |
| BMI, n (%)                       |                         |                         |                           |
| <18.5                            | 78 404 (2.5)            | 9937 (2.5)              | 1776 (2.7)                |
| 18.5–23                          | 1 236 398 (39.1)        | 1 429 190 (35.4)        | 26 293 (39.4)             |
| 23–25                            | 878 134 (27.8)          | 1 106 071 (27.2)        | 18 660 (27.9)             |
| 25–30                            | 900 209 (28.5)          | 1 290 000 (31.9)        | 18 472 (27.7)             |
| ≥30                              | 70 625 (2.2)            | 12 375 (3.1)            | 1604 (2.4)                |
| Charlson comorbidity index       | 0.7 ± 1.0               | 0.8 ± 1.1               | 0.9 ± 1.2                 |
| eGFR (mL/min/1.73 m²)            | 83.3 ± 18.1             | 59.7 ± 12.5             | 17.7 ± 16.2               |
| SBP (mmHg)                       | 123.9 ± 15.2            | 124.9 ± 15.9            | 125.8 ± 15.5              |
| DBP (mmHg)                       | 77.13 ± 10.1            | 77.6 ± 10.3             | 77.1 ± 10.1               |
| Glucose (mg/dL)                  | 94.0 ± 11.5             | 94.8 ± 11.8             | 95.5 ± 11.5               |
| Total cholesterol (mg/dL)        | 199.3 ± 34.0            | 204.2 ± 35.5            | 200.7 ± 35.1              |
| HDL-C (mg/dL)                    | 54.5 ± 13.0             | 54.5 ± 13.6             | 53.2 ± 13.3               |
| LDL-C (mg/dL)                    | 118.5 ± 32.0            | 122.2 ± 33.3            | 120.5 ± 32.2              |
| TG (mg/dL), median (interquartile range) | 114.1 (114.0-114.1)   | 119.1 (118.9-119.3)     | 117.58 (117.12–118.04)     |
| TG/HDL-C                         | 2.7 ± 2.2               | 2.8 ± 2.3               | 2.8 ± 2.3                 |
| Non-HDL/HDL-C                    | 2.8 ± 1.1               | 3.0 ± 1.2               | 3.0 ± 1.1                 |
| Non-HDL-C                        | 144.8 ± 33.9            | 149.7 ± 35.3            | 147.5 ± 34.6              |

Values are presented as mean ± SD unless stated otherwise.

DBP, diastolic blood pressure.

aLow income was defined as a total income <20th percentile for the nation.
DISCUSSION

Lipid profiles and the development of MACCEs and/or all-cause mortality have been discussed for several decades. Nevertheless, the difference in risk predictability of each lipid profile according to kidney function has not yet been elucidated. In this study using a nationwide population-based database, we found that TG/HDL-C confers better predictability of major clinical outcomes than LDL-C in patients with advanced CKD. Additionally, TG/HDL-C showed a consistent pattern of its association with mortality and with MACCEs regardless of kidney function, while LDL-C showed different patterns of association with mortality and MACCEs. These results indicate that TG/HDL-C could provide a better predictive marker for major clinical outcomes than LDL-C in patients with CKD.

The development of MACCEs is closely related to all-cause mortality. Atherogenic dyslipidemia, which is characterized by increased LDL-C or TG and decreased HDL-C, is an inevitable risk factor for atherosclerotic CVD [13, 14]. Considering that CVD is a leading cause of death in patients with CKD, it is important to comprehend the physiology and clinical significance of lipid profiles to predict cardiovascular outcome and mortality. Moreover, since the lipid profiles show different patterns in terms of their quantities and function under conditions of kidney dysfunction, physicians should consider their clinical significance differently according to kidney function. High TG and low HDL-C are specific characteristics of dyslipidemia commonly observed in patients with CKD. TG usually increases in the early stages of CKD and is associated with delayed catabolism and decreased activity of hepatic TG lipase and peripheral lipoprotein lipase [7, 15]. HDL-C, which is inversely associated with outcomes, decreases in patients with CKD. In particular, there were alterations not only in the concentration, but also in the composition and functional ability of HDL particles [16]. LDL-C, the most powerful cardiovascular outcome predictor, is also often affected by the oxidative process, and it was not consistently increased in patients with CKD [17–19]. In addition to the quantitative aspect of each lipid profile, changes in the composition, such as decreased TG content in VLDL-C, need to be considered in patients with CKD. These diverse alterations in the characteristics of the lipid profile lead to decreased significance for predicting outcomes in patients with renal insufficiency. However, the latest guidelines for managing dyslipidemia still suggest LDL-C as the main target for screening, diagnosis, and management to prevent CVD [5]. Moreover, CKD patients with eGFR <30 mL/min/1.73 m² were regarded as a very high-risk group and it was recommended that they reduce LDL-C to ≥50% from baseline or <55 mg/dL, irrespective of the baseline cholesterol level.

Although the statistical significance decreased in advanced CKD, TG/HDL-C and LDL-C showed a significant pattern for predicting cardiovascular outcome and all-cause mortality. However, LDL-C showed a discrepant association between CVD

![Figure 2: aHR according to the decile range of (A) LDL-C, (B) TG, (C) HDL-C and (D) TG/HDL-C for MACCEs and all-cause mortality. The horizontal axis represents the decile of the lipid profile and the vertical axis shows the aHR. The blue line shows mortality and the orange line shows MACCEs.](https://academic.oup.com/ckj/advance-article/doi/10.1093/ckj/sfaa252/6048391)
FIGURE 3: The aHR for MACCEs in (A and B) control, (C and D) early CKD and (E and F) advanced CKD according to the decile range of LDL-C and TG/HDL-C. The horizontal axis represents the decile of the lipid profile and the vertical axis shows the aHR.

Table 2. Risks of all-cause mortality according to the levels of LDL-C and TG/HDL-C in different stages of CKD

| Stage      | Number | Events | IR (per 1000 Person-years) | HR (95% CI) | Number | Events | IR (per 1000 Person-years) | HR (95% CI) |
|------------|--------|--------|---------------------------|-------------|--------|--------|---------------------------|-------------|
| Control    |        |        |                           |             |        |        |                           |             |
| D1         | 322085 | 17382 | 2.332.124                 | 7.45        | 321087 | 8490  | 2.347.517                 | 3.62        |
| D2         | 319412 | 12573 | 2.327.132                 | 5.40        | 319893 | 9622  | 2.337.736                 | 4.12        |
| D3         | 309183 | 10751 | 2.256.841                 | 4.76        | 318720 | 10428 | 2.327.971                 | 4.48        |
| D4         | 348861 | 11293 | 2.549.719                 | 4.43        | 317636 | 11063 | 2.318.590                 | 4.77        |
| D5         | 287465 | 8750  | 2.102.648                 | 4.16        | 316835 | 11036 | 2.314.197                 | 4.77        |
| D6         | 321691 | 9266  | 2.354.673                 | 3.94        | 315470 | 11193 | 2.311.941                 | 4.84        |
| D7         | 329090 | 9405  | 2.409.760                 | 3.90        | 315154 | 11012 | 2.302.751                 | 4.78        |
| D8         | 302816 | 8293  | 2.218.567                 | 3.74        | 314177 | 11000 | 2.294.888                 | 4.79        |
| D9         | 315776 | 8570  | 2.312.557                 | 3.71        | 312574 | 10632 | 2.283.427                 | 4.66        |
| D10        | 307391 | 8670  | 2.247.304                 | 3.86        | 311159 | 10477 | 2.272.307                 | 4.61        |
| Early CKD  |        |        |                           |             |        |        |                           |             |
| D1         | 36077  | 3092  | 2.257.772                 | 12.00       | 36458 | 1221  | 2.265.780                 | 4.59        |
| D2         | 36055  | 2350  | 2.260.137                 | 9.03        | 37417 | 1647  | 2.271.746                 | 6.06        |
| D3         | 35416  | 2154  | 2.256.091                 | 8.41        | 38791 | 1967  | 2.281.304                 | 6.99        |
| D4         | 41841  | 2297  | 3.032.737                 | 7.57        | 39205 | 2151  | 2.283.995                 | 7.57        |
| D5         | 34944  | 1794  | 2.253.612                 | 7.07        | 40426 | 2391  | 2.292.303                 | 8.18        |
| D6         | 40645  | 1996  | 2.295.290                 | 6.76        | 40498 | 2342  | 2.293.049                 | 7.99        |
| D7         | 43042  | 1837  | 3.132.206                 | 6.34        | 41923 | 2428  | 2.298.898                 | 8.12        |
| D8         | 41094  | 1835  | 2.299.341                 | 6.13        | 42228 | 2578  | 3.050.610                 | 8.44        |
| D9         | 45044  | 1966  | 3.272.665                 | 6.00        | 43322 | 2528  | 3.135.916                 | 8.05        |
| D10        | 50140  | 2299  | 3.636.846                 | 6.32        | 44660 | 2517  | 3.232.652                 | 7.78        |
| Advanced CKD |       |        |                           |             |        |        |                           |             |
| D1         | 6095   | 649   | 4.343.49                  | 14.97       | 5966  | 234   | 4.352.55                  | 5.38        |
| D2         | 6360   | 522   | 4.458.61                  | 11.43       | 6068  | 276   | 4.418.60                  | 6.25        |
| D3         | 6298   | 443   | 4.525.92                  | 9.73        | 6350  | 359   | 4.613.36                  | 7.78        |
| D4         | 7202   | 493   | 5.215.32                  | 9.45        | 6332  | 403   | 4.593.53                  | 7.77        |
| D5         | 6055   | 407   | 4.388.11                  | 9.28        | 6370  | 454   | 4.597.54                  | 9.88        |
| D6         | 6716   | 418   | 4.872.13                  | 8.58        | 6651  | 495   | 4.801.01                  | 10.31       |
| D7         | 7046   | 403   | 5.125.48                  | 7.86        | 6825  | 536   | 4.975.79                  | 10.88       |
| D8         | 6661   | 384   | 4.845.71                  | 7.92        | 7114  | 606   | 5.125.19                  | 11.82       |
| D9         | 7074   | 405   | 5.138.76                  | 7.86        | 7501  | 566   | 5.214.21                  | 10.44       |
| D10        | 7298   | 500   | 5.278.62                  | 9.47        | 7628  | 695   | 5.483.72                  | 12.67       |

LDL-C, TG/HDL-C, D, decile; IR, incidence rate; Ref., reference.
and all-cause mortality. High LDL-C was a significant risk factor for CVD and all-cause mortality, but low LDL-C was also a risk factor for all-cause mortality with a U-shaped pattern. Moreover, this U-shaped pattern was markedly attenuated in advanced CKD. Unlike LDL-C, TG/HDL-C showed an identical pattern for two major outcomes. Additionally, these patterns were maintained in the early and advanced CKD groups. Considering that CVD is closely related to death, it is important to identify the lipid profile that predicts both outcomes. This study primarily showed these ambivalent relationships for the two major outcomes in CKD patients according to the stage. In addition, we assessed the association between each lipid profile and two major outcomes together and independently to secure a more sensible lipid profile. Consequently, TG/HDL-C has unique strength as a good predictor for major clinical outcomes, especially in a population with early and advanced CKD.

Elevated TG is a well-known risk factor for CVD, and lowering TG might improve the cardiovascular outcome [20–22]. The association between TG and CVD was revealed using Mendelian randomization studies, and the causal variants were related to all lipid profiles [23, 24]. Moreover, it could be a good predictor of long-term mortality in the high-risk group for CVD [25]. According to the results of our study, this good predictability for CVD and all-cause mortality was maintained in CKD patients. Although the quantity and quality of each lipid profile were changed in CKD, the worth could be maintained through reinforcement using a significant profile of a combination of TG and HDL-C.

This study is the first report using >3 million population-based cohorts composing a lipid-lowering agent-naïve population with diverse stages of renal function in nondiabetic patients. Moreover, it showed the association between each lipid profile and two major outcomes simultaneously. However, there are several limitations to be discussed. First, there were a small number of outcomes for the advanced CKD group, which showed a greater CI with weak statistical power. Second, it was a retrospective study with a single national population. Third, we used a single measured lipid profile in the analysis. Also, the laboratory test was not performed in a central lab and the equipment was different in each center. Last, we could not adjust for new statin use during the follow-up period, which could lead to the attenuation of significance between the levels of LDL-C and the outcomes in patients with advanced CKD. Also, the correlation between lipid profile with the risk of MACCEs in advanced CKD patients might be attenuated due to excluding potentially high-risk subjects who had been prescribed lipid-lowering agents previously.

Dyslipidemia is an inevitable risk factor for CVD and all-cause mortality in control, early and advanced CKD. Although the significance for predicting outcomes was decreased in the progression of renal dysfunction, TG/HDL-C and LDL-C were well correlated with CVD and all-cause mortality. Unlike LDL-C, which showed different patterns in predicting two major outcomes, TG/HDL-C could be considered to have a better available profile by showing identical patterns.

SUPPLEMENTARY DATA
Supplementary data are available at ckj online.

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AUTHORS’ CONTRIBUTIONS
Y.K. and D.K.K. contributed to the conception and design of the study. S.L., Y.L., M.W.K., S.P., J.H.P. and W.Y.P. contributed to the acquisition of data. S.P. and K.H. contributed to the analysis and interpretation of data. Y.K. drafted the article. K.J., S.H., S.S.H., H.L., J.P.L., K.W.J., C.S.L. and Y.S.K. revised the article for important intellectual content. D.K.K. was the principal investigator.

CONFLICT OF INTEREST STATEMENT
The authors have no conflicts of interest to declare.

REFERENCES
1. Go AS, Chertow GM, Fan D et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004; 351: 1296–1305
2. Hemmelgarn BR, Manns BJ, Lloyd A et al. Relation between kidney function, proteinuria, and adverse outcomes. JAMA 2010; 303: 423–429
3. Arnett DK, Blumenthal RS, Albert MA et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019; 74: e177–e232
4. Tonelli M, Wanner C. Lipid management in chronic kidney disease: synopsis of the Kidney Disease: Improving Global Outcomes 2013 clinical practice guideline. Ann Intern Med 2014; 160: 182–189
5. Mach F, Bairent C, Capatano AL et al. 2019 ESC/EAS guidelines for the management of dyslipidaeams: lipid modification to reduce cardiovascular risk. Eur Heart J 2020; 41: 111–188
6. Navarese EP, Robinson JG, Kowalewski M et al. Association between baseline LDL-C level and total and cardiovascular mortality after LDL-C lowering: a systematic review and meta-analysis. JAMA 2018; 319: 1566–1579
7. Vaziri ND. Dyslipidemia of chronic renal failure: the nature, mechanisms, and potential consequences. Am J Physiol Renal Physiol 2006; 290: F262–F272
8. Rysz-Góźniska M, Banach M. Subfractions of high-density lipoprotein (HDL) and dysfunctional HDL in chronic kidney disease patients. Arch Med Sci 2016; 4: 844–849
9. Lee Y, Park S, Lee S et al. Lipid profiles and risk of major adverse cardiovascular events in CKD and diabetes: a nationwide population-based study. PLoS One 2020; 15: e0231328
10. Seong SC, Kim YY, Park SK et al. Cohort profile: the National Health Insurance Service–National Health Screening Cohort (NHIS–HEALS) in Korea. BMJ Open 2017; 7: e016640
11. Cheol Seong S, Kim YY, Khang YH et al. Data resource profile: the National Health Information Database of the National Health Insurance Service in South Korea. Int J Epidemiol 2017; 46: 799–800
12. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in
plasma, without use of the preparative ultracentrifuge. Clin Chem 1972; 18: 499–502
13. Lindner A, Charra B, Sherrard DJ et al. Accelerated atherosclerosis in prolonged maintenance hemodialysis. N Engl J Med 1974; 290: 697–701
14. Bennett WM, Kloster F, Rosch J et al. Natural history of asymptomatic coronary arteriographic lesions in diabetic patients with end-stage renal disease. Am J Med 1978; 65: 779–784
15. Sonmez A, Yilmaz MI, Saglam M et al. The role of plasma triglyceride/high-density lipoprotein cholesterol ratio to predict cardiovascular outcomes in chronic kidney disease. Lipids Health Dis 2015; 14: 29
16. Kronenberg F. High-density lipoprotein in chronic kidney diseases—the devil is in the detail. J Am Soc Nephrol 2018; 29: 1356–1371
17. Abdullah SM, Defina LF, Leonard D et al. Long-term association of low-density lipoprotein cholesterol with cardiovascular mortality in individuals at low 10-year risk of atherosclerotic cardiovascular disease. Circulation 2018; 138: 2315–2325
18. Tonelli M, Muntner P, Lloyd A et al. Association between LDL-C and risk of myocardial infarction in CKD. J Am Soc Nephrol 2013; 24: 979–986
19. Hager MR, Narla AD, Tannock LR. Dyslipidemia in patients with chronic kidney disease. Rev Endocr Metab Disord 2017; 18: 29–40
20. Di Angelantonio E, Gao P, Pennells L et al. Lipid-related markers and cardiovascular disease prediction. JAMA 2012; 307: 2499–2506
21. Silverman MG, Ference BA, Im K et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. JAMA 2016; 316: 1289–1297
22. Elam MB, Ginsberg HN, Lovato LC et al. Association of fenofibrate therapy with long-term cardiovascular risk in statin-treated patients with type 2 diabetes. JAMA Cardiol 2017; 2: 370–380
23. Sarwar N, Sandhu MS, Ricketts SL et al. Triglyceride-mediated pathways and coronary disease: collaborative analysis of 101 studies. Lancet 2010; 375: 1634–1639
24. Varbo A, Benn M, Tybjærg-Hansen A et al. Remnant cholesterol as a causal risk factor for ischemic heart disease. J Am Coll Cardiol 2013; 61: 427–436
25. Sultan R, Tong DC, Peverelle M et al. Elevated triglycerides to high-density lipoprotein cholesterol (TG/HDL-C) ratio predicts long-term mortality in high-risk patients. Heart Lung Circ 2019; 29: 414–421