Atherosclerosis 286 (2019) 135–141

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Intra-individual variability in high density lipoprotein cholesterol and risk of end-stage renal disease: A nationwide population-based study

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HIGHLIGHTS

- Studies have demonstrated an association between dyslipidemia and progression of kidney disease.
- Results on the effects of high-density lipoprotein cholesterol (HDL-C) on renal outcome have been conflicting.
- Greater intra-individual variability in HDL-C is associated with higher incidence of end-stage renal disease.

ARTICLE INFO

Keywords:
HDL-cholesterol
Variability
ESRD

ABSTRACT

Background and aims: There is a growing evidence demonstrating an association between dyslipidemia and progression of chronic kidney disease (CKD), but results on the effects of high-density lipoprotein cholesterol (HDL-C) on renal outcome have been conflicting. In this study, the relationship between HDL-C variability and the risk for progression to end-stage renal disease (ESRD) was investigated.

Methods: This study analyzed data of 4,283,318 subjects who were free of ESRD at the time of enrollment, received more than three medical examinations from 2009 to 2012, and were followed to the end of 2015, based on the Korean National Health Insurance Service database. HDL-C variability was measured using the standard deviation, coefficient of variation, average real variability and variability independent of the mean (VIM).

Results: A total of 2,095 new cases of ESRD were observed during a median follow up of 3.38 years. There was a graded association between higher HDL-C variability and incident ESRD. In the multivariable adjusted model, hazard ratio comparing the highest and lowest quartiles of VIM of HDL-C was 1.82 (95% confidence interval, 1.58–2.09). The results were consistent when the variability of HDL-C was modeled using standard deviation, coefficient of variation and average real variability and were independent of other confounding factors, including the presence of CKD.

Conclusions: HDL-C variability independently predicted an increased risk for developing ESRD. Our findings suggest that identification of HDL-C variability may help improve risk stratification for the prevention of ESRD.

1. Introduction

Chronic kidney disease (CKD) and end-stage renal disease (ESRD) are emerging public health issues worldwide with the growing prevalence of obesity and metabolic disease. Although dyslipidemia is recognized as a causative determinant of atherosclerosis, it remains unclear whether it can cause renal microvascular disease and influence kidney function. Dyslipidemia is common among patients with CKD, and previous studies have showed that dyslipidemia might affect CKD progression [1–3]. Dyslipidemia in CKD patients is characterized by a

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https://doi.org/10.1016/j.atherosclerosis.2019.05.018
Received 16 November 2018; Received in revised form 15 May 2019; Accepted 23 May 2019
Available online 24 May 2019
0021-9150/

mixed phenotype: elevated levels of triglycerides (TG) and reduced levels of high-density lipoprotein cholesterol (HDL-C) with variations [4]. HDL-C functions to recycle cholesterol esters from the vessel wall back to the liver via the so-called reverse cholesterol pathway. HDL-C protects against plaque formation and progression and prevents or reverses low-density lipoprotein (LDL) oxidation via the reverse cholesterol pathway. Thus, HDL-C is associated with decreased atherosclerosis risk, and its level appears to be linked to a reduction of cardiovascular mortality in the general population [5]. In addition, several epidemiologic studies have demonstrated an association between low HDL-C and progression of CKD [2]. However, other reports showed inconsistencies between HDL-C and renal function outcomes, including in genetic study and in intervention with drugs increasing HDL-C [6]. Previous studies have therefore elicited several conflicting opinions and interpretations as to the association between HDL-C metabolism and clinical outcomes in CKD patients.

Notably, blood lipid profiles in CKD patients are likely influenced by distinct features different from the general population, including change of glomerular filtration rate (GFR), the presence of diabetes mellitus, severity of proteinuria, use of some specific agents, comorbidity, and nutritional status [7,8]. For these reasons, and owing to the lack of data to support prior guidelines in populations with CKD, the Kidney Disease: Improving Global Outcomes (KDIGO) Work Group does not recommend previous guidelines emphasizing the potential value of LDL cholesterol (LDL-C) as an indication for lipid-lowering treatment [7]. The Work Group also suggests that HDL-C should be measured as part of the initial lipid panel, although low HDL-C by itself does not imply specific therapy in people with CKD [7]. Therefore, it is necessary to explore alternative and reliable markers of dyslipidemia for patients with CKD and to investigate whether knowledge of such novel values would have any influence on clinical outcomes.

Recently, research on the intra-individual variability of various physiological measures has revealed their role as a risk factor for clinical outcomes. This observation aligns with our previous reports that increased total cholesterol (TC) variability was associated with increased incidence of ESRD [9]. It was observed that high visit-to-visit variability in TC could have a possible role as a predictor of ESRD; there was a graded association between higher TC variability and incident ESRD. Therefore, substantial within-person variability in lipid levels might be associated with adverse health outcomes, including progression of kidney disease. In the present study, we aimed to concretely investigate whether HDL-C variability was associated with the incidence of ESRD using a nation-wide, population-based cohort.

2. Patients and methods

2.1. Data source and study population

The Korean National Health Insurance Service (NHIS), managed by the government, is a health insurance program mandatory for nearly all residents in South Korea and provides regular health check-up programs for all insured subjects. Enrollees are recommended to have get check-ups at least biennially. In current study, we used data of subjects who had taken a health examination in 2012 (index year) and three or more health examinations between January 1, 2009, and December 31, 2012. In total, 12,144,205 subjects over age 20 received health examination in the index year, and among them 4,285,410 individuals took three or more health examinations before till 2012. We excluded 214,524 subjects with missing data for at least one variable and 2,092 subjects who had ESRD prior to the index year. Finally, the study population consisted of 4,283,318 subjects. This study was conducted according to the Declaration of Helsinki and approved by the Institutional Review Board of The Catholic University of Korea (No. SC18ZESI0087). Anonymized and deidentified information was used for analyses, and thus informed consent was not required.

2.2. Data collection

Blood samples for the measurement of serum glucose, creatinine (Cr), TC, TG, HDL-C, LDL-C levels were drawn after an overnight fast. Estimated glomerular filtration rate (eGFR) was calculated using the abbreviated Modification of Diet in Renal Disease formula [10]. Low GFR was defined as an eGFR < 60 mL/min per 1.73 m^2, according to the U.S. National Kidney Foundation guidelines [11]. Proteinuria was defined as a grade of $+1$ or greater by urine dipstick test. Comorbidities were defined primarily by a combination of medical history (ICD code and self-reported) and use of one or more drugs for the corresponding disease. Hypertension was defined according to the presence of at least one claim per year under ICD-10 codes I10 or I11 and at least one claim per year for the prescription of an antihypertensive agent or systolic/diastolic blood pressure $\geq$140/90 mmHg. Diabetes mellitus was defined according to the following criteria: (1) at least one claim per year under ICD-10 codes E10–14 and at least one claim per year for the prescription of antidiabetic medication, or (2) fasting glucose level $\geq$ 126 mg/dL. Dyslipidemia was defined according to the presence of at least one claim per year under ICD-10 code E78 and at least one claim per year for the prescription of lipid-lowering agent, or TC $\geq$ 240 mg/dL. Use of lipid-lowering medications was defined as at least one prescription of lipid-lowering medications during the 3 years before the index date. Obesity was defined as BMI $\geq$25 kg/m^2 [12].

2.3. Definition of HDL-C variability

HDL-C variability was defined as the variation in HDL-C values between health examinations. Three measurements of variability were calculated: standard deviation (SD), coefficient of variation (CV), average real variability (ARV) and variability independent of the mean (VIM). VIM was first used by Rothwell to minimize the correlation between the measurement of variability and the mean value [13,14]. VIM was defined as SD/(mean to the power of x), multiplied by the population mean to the power of x. The power of x is derived from fitting a curve by a plot of SD against mean using the model SD = a times mean^x, where x was derived by nonlinear regression analysis as implemented in the SAS PROC NLIN procedure [14].

2.4. Study outcomes and follow-up

The study population was followed from the date of the last health exam to the date of ESRD diagnosis or until December 31, 2015, whichever came first. The primary endpoint was incident ESRD, defined using the combination of ICD-10 code (N18-19, Z49, Z94.0, Z99.2) and initiation of renal replacement therapy and/or kidney transplantation (KT) during hospitalization. All medical care expenses for dialysis are reimbursed using the Korean Health Insurance Review and Assessment Service database. These patients are also registered as special medical aid beneficiaries. Therefore, we were able to identify every ESRD patient in the whole of the South Korean population and to analyze the data for all ESRD patients who had started dialysis. Codes for treatment or medical expense claims included R3280 for KT, O7011-O7020 or V001 for hemodialysis, and O7071-O7075 or V003 for peritoneal dialysis. We excluded individuals without previous chronic kidney disease who had a transplant or dialysis code on the same date as an acute renal failure code. Subjects on continuous renal replacement therapy or acute peritoneal dialysis were also excluded.

2.5. Statistical analysis

Multivariable-adjusted proportional-hazards models were applied as follows: model 1 was adjusted for age, sex, smoking, alcohol drinking, regular exercise, and income status; model 2 was further adjusted for BMI, hypertension, diabetes, and dyslipidemia; model 3 was further adjusted for HDL-C level, fasting blood glucose, baseline

Table 1
Baseline characteristics of subjects according to the HDL cholesterol variability (VIM).

	Q1	Q2	Q3	Q4
	n = 1,070,914	n = 1,070,754	n = 1,070,889	n = 1,070,761
Age, years	43.79 ± 11.68	44.31 ± 11.53	45.07 ± 11.66	46.71 ± 12.1
Male, n (%)	635,673 (59.36)	706,839 (66.01)	755,792 (70.58)	807,644 (75.43)
BMI, kg/m^2	23.16 ± 3.15	23.61 ± 3.16	24 ± 3.15	24.51 ± 3.14
Body weight, kg	63.98 ± 11.65	65.79 ± 11.8	67.21 ± 11.86	68.85 ± 11.92
Height, cm	165.83 ± 8.8	166.56 ± 8.74	166.98 ± 8.69	167.25 ± 8.61
Current smoker, n (%)	277,346 (25.9)	313,609 (29.29)	340,016 (31.75)	375,292 (35.05)
Heavy drinker, n (%)	83,627 (7.81)	88,629 (8.28)	89,610 (8.37)	87,094 (8.13)
Regular exercise, n (%)	227,672 (21.26)	231,397 (21.61)	232,459 (21.71)	229,123 (21.4)
Income lower 25%, n (%)	172,938 (16.15)	173,088 (16.17)	181,433 (16.94)	198,195 (18.51)
Diabetes, n (%)	58,329 (5.45)	69,282 (6.47)	82,707 (7.72)	110,015 (10.27)
Hypertension, n (%)	195,878 (18.29)	214,856 (20.07)	237,514 (22.18)	279,801 (26.13)
Dyslipidemia, n (%)	100,617 (9.4)	100,651 (9.4)	100,643 (9.4)	100,630 (9.4)
CKD[a], n (%)	19,797 (1.85)	21,274 (1.99)	24,623 (2.3)	34,055 (3.18)
Proteinuria[b], n (%)	36,091 (3.38)	37,157 (3.48)	38,236 (3.58)	42,386 (3.97)
At index year				
Waist circumference, cm	78.49 ± 9.05	79.96 ± 8.92	81.22 ± 8.75	82.89 ± 8.53
Systolic BP, mmHg	120.31 ± 13.81	121.22 ± 13.74	122.02 ± 13.69	123.11 ± 13.73
Diastolic BP, mmHg	75.58 ± 9.57	76.2 ± 9.55	76.7 ± 9.52	77.3 ± 9.52
Fasting glucose, mg/dL	95.02 ± 18.51	96 ± 19.8	96.99 ± 21.13	98.83 ± 23.76
Serum creatinine, mg/dL	0.90 ± 0.31	0.92 ± 0.33	0.93 ± 0.34	0.94 ± 0.36
eGFR, mL/min per 1.73 m^2	93.3 ± 37.85	92.9 ± 38.05	92.43 ± 37.32	91.79 ± 37.07
Total cholesterol, mg/dL	196.39 ± 34.18	195.32 ± 34.87	194.24 ± 35.4	191.86 ± 36.51
HDL-cholesterol, mg/dL	61.83 ± 13.09	57.03 ± 12.28	53.07 ± 12.92	48.09 ± 18.59
LDL-cholesterol, mg/dL	112.73 ± 32.76	114.07 ± 33.28	114.55 ± 34.77	113.1 ± 36.78
Triglyceride, mg/dL	96.31 (96.21–96.41)	106.77 (106.66–106.88)	117.81 (117.68–117.93)	137.53 (137.37–137.68)

Data are expressed as the mean ± SD or n (%).
VIM, variability independent of the mean; BP, blood pressure; eGFR, estimated glomerular filtration rate.
[a] CKD was defined as eGFR < 60 mL/min per 1.73 m^2.
[b] Proteinuria was defined as having urinary protein ≥1 + on dipstick testing in fasting morning urine.

serum creatinine and presence of proteinuria. The potential effect modifications of age group, sex, presence or absence of diabetes mellitus, hypertension, obesity, use of lipid-lowering agents, CKD, and proteinuria were evaluated through stratified analysis and interaction testing using a likelihood ratio test. In subgroup analyses, the hazard ratio (HR; with 95% confidence interval [CI]) of the higher three quartiles (Q2–Q4) groups of VIM were compared with the lowest quartile (Q1) as a reference group. Also, HR and 95% CI values of ESRD in each group according to age, sex, with or without diabetes, hypertension, preexisting CKD or proteinuria were analyzed using the Cox proportional hazards model for decile groups of HDL-C variability.

3. Results

3.1. Baseline characteristics of the study population

Characteristics of participants by quartiles of VIM for HDL-C are described in Table 1. Subjects in higher quartiles of HDL-C variability were more likely to be older, men, and current smokers, and to have a lower income and higher prevalence of diabetes, hypertension, CKD, and proteinuria. The mean HDL-C levels in the Q1–Q4 groups were 61.83 ± 13.09 mg/dL, 57.03 ± 12.28 mg/dL, 53.07 ± 12.92 mg/dL, and 48.09 ± 18.59 mg/dL, respectively. Subjects in higher quartiles of HDL-C variability had lower eGFR, higher prevalence of proteinuria, and higher triglyceride level. Similar patterns of baseline characteristics were noted by quartiles of SD, CV and ARV.

3.2. HDL-C variability and the risk of ESRD

During a median 3.38 years of follow-up after the HDL-C variability assessment period, 2,095 subjects developed ESRD. The incidence of ESRD increased progressively with higher levels of HDL-C variability (Fig. 1). The incidence rate was four times higher in the VIM Q4 group compared with the VIM Q1 group (Table 2). An incrementally higher risk of ESRD was observed for higher VIM quartiles compared with the lowest quartile group in all models. After adjusting for age, sex, alcohol drinking, smoking, regular exercise, and income, the hazard ratios (HR) for incident ESRD were 1.139 (95% CI, 0.973–1.333,), 1.521 (95% CI, 1.314–1.761), and 2.517 (95% CI, 2.202–2.877) for the second, third, and fourth quartiles versus the first quartile of VIM of HDL-C, respectively (Table 2, model 1). After further controlling for other confounding factors, including HDL-C, fasting blood glucose, baseline serum creatinine and presence of proteinuria, the association between the HDL-C variability and incident ESRD remained significant (HR [95% CI]: Q2, 1.044 [0.89–1.223]; Q3, 1.253 [1.80–1.454]; Q4, 1.816 [1.576–2.092]; Table 2, model 3). HDL-C variability as measured by SD, CV or ARV was also an independent predictor of ESRD, even after full multivariable adjustment (see Fig. 2).

3.3. Subgroup analyses and the risk of ESRD by deciles of HDL-C variability

Stratified analysis by age, sex, presence or absence of diabetes mellitus, hypertension, obesity, use of lipid-lowering agents, CKD, and proteinuria was conducted (Table 3 and Supplemental Fig. 1). Higher HDL-C variability remained predictive of worse renal outcomes in subgroups compared with lower HDL-C variability. The risk of ESRD according to HDL-C variability was significantly different divided by age (> 55 years) and sex. Thus, impact of HDL-C variability on ESRD development was stronger in older and male individuals.

4. Discussion

The results of the current study indicate that measures of intra-individual visit-to-visit HDL-C variability is an independent risk factor for ESRD, even after adjusting for possible confounding factors, including HDL-C level and basal renal function, in a Korean population. After these adjustments, the incremental risk for ESRD for Q1 *versus* Q4 of VIM was 59% for HDL-C. The results confirm our prior reports

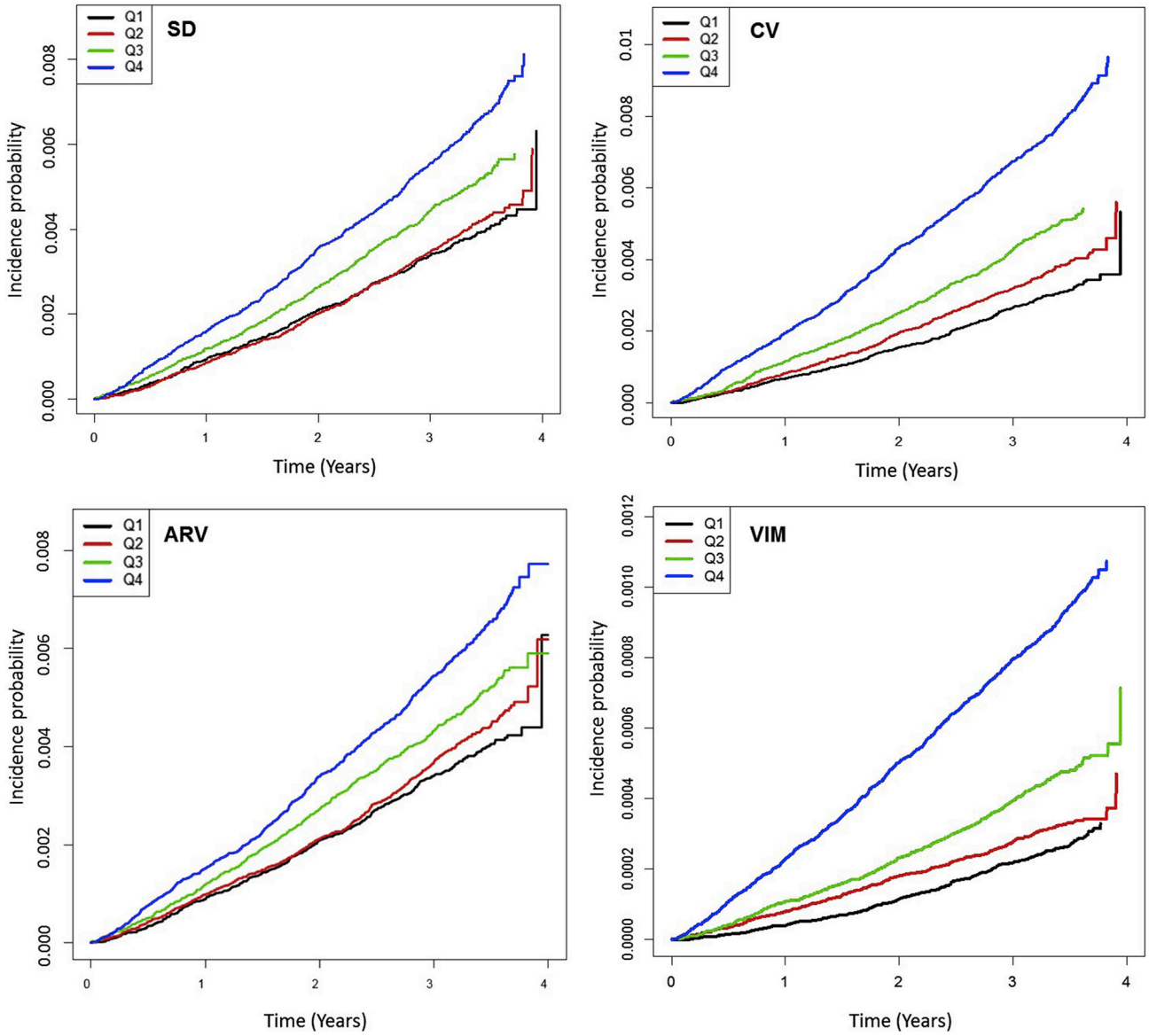

Fig. 1. Kaplan–Meier estimates of disease-free probability by quartiles of high-density lipoprotein (HDL) cholesterol variability measured as the standard deviation (SD), coefficient of variation (CV), average real variation (ARV) and the variability independent of the mean (VIM).
The lowest quartile, Q1, is illustrated in black, Q2 is illustrated in red, Q3 is illustrated in green, and the highest quartile, Q4, is illustrated in blue. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

demonstrating TC variability as a predictor of ESRD in the general population and further extend across a range of HDL-C variability. Furthermore, our study presented a greater impact of HDL-C variability on the incidence of ESRD in general populations, including even low-risk subjects without diabetes, hypertension, and preexisting CKD.

HDL-C has been shown to have a variety of beneficial protective actions, and it has long been considered 'good cholesterol'. This is because of reverse cholesterol transport, whereby HDL-C transfers cholesterol from the periphery to the liver for excretion [5]. Beyond this general property, HDL-C appears to exert an influence, not only on cardiovascular risk, but also on CKD and its progression to ESRD [1,6,15,16]. A recent, large study by Bowe et al. showed the association between HDL-C levels and renal outcomes in a general population cohort of almost 2 million. They demonstrated that individuals with lowest and highest deciles of HDL-C had a higher risk for CKD and CKD progression, with a U-shaped trend [2]. However, another study revealed an inverse association between lower HDL-C level and eGFR decline, contrary to expectations [17]. Anacetrapib, an orally active cholesteryl ester transfer protein (CETP) inhibitor, has an action of raising HDL-C levels. The Randomized Evaluation of the Effects of Anacetrapib through Lipid-modification (REVEAL) trial reported a higher frequency of decline in eGFR, although HDL-C level was higher in the anacetrapib-treated group during the study period [17].

The reason for those conflicting results is probably that the measured HDL-C level could not reflect the main pathogenesis of dyslipidemia in CKD, including low cholesterol efflux capacity and disturbed HDL-C functionality [4,18–20]. Cholesterol efflux capacity of HDL-C is, as mentioned above, the first step in reverse cholesterol transport and a key mechanism of the athero-protective effect of HDL-C; low cholesterol efflux capacity of HDL-C is observed in advanced CKD [21,22]. Circulating HDL-C level may not be a suitable surrogate marker to reflect real cholesterol efflux capacity. Meanwhile, it has been known that HDL-C serves as a potent antioxidant, anti-inflammatory, and antithrombotic factor [23]. Because oxidative stress and chronic

Table 2
Hazard ratios and 95% confidence intervals of ESRD by quartiles of HDL cholesterol variability.

		N	Event (n)	Follow-up duration (person-years)	Incidence rate (per 1000 person-years)	Model 1	Model 2	Model 3
SD	Q1	1,066,186	414	3,616,866.64	0.11446	1 (ref.)	1 (ref.)	1 (ref.)
	Q2	1,075,654	440	3,649,012.63	0.12058	1.007 (0.859,1.18)	1.175 (1.016,1.359)	1.088 (0.951,1.245)
	Q3	1,070,806	547	3,628,155.42	0.15077	1.183 (1.019,1.372)	1.288 (1.122,1.479)	1.411 (1.24,1.605)
	Q4	1,070,672	694	3,614,285.87	0.19202	1.429 (1.24,1.646)	1.540 (1.353,1.752)	1.784 (1.574,2.021)
				p for trend		< 0.0001	< .0001	< .0001
CV	Q1	1,070,926	330	3,632,100.21	0.09086	1 (ref.)	1 (ref.)	1 (ref.)
	Q2	1,070,772	403	3,632,699.94	0.11094	1.123 (0.959,1.315)	1.197 (1.035,1.385)	1.176 (1.017,1.361)
	Q3	1,070,889	529	3,628,633.13	0.14578	1.483 (1.28,1.717)	1.486 (1.295,1.705)	1.439 (1.254,1.651)
	Q4	1,070,731	833	3,614,887.29	0.23044	2.427 (2.122,2.777)	2.036 (1.791,2.314)	1.86 (1.635,2.115)
				p for trend		< 0.0001	< 0.0001	< 0.0001
ARV	Q1	1,032,468	401	3,502,100.41	0.11450	1 (ref.)	1 (ref.)	1 (ref.)
	Q2	1,123,583	487	3,811,160.44	0.12778	1.132 (0.992,1.292)	1.132 (0.992,1.292)	1.173 (1.027,1.339)
	Q3	1,040,225	521	3,523,523.01	0.14786	1.279 (1.122,1.457)	1.253 (1.099,1.427)	1.399 (1.227,1.596)
	Q4	1,087,012	686	3,671,536.71	0.18684	1.523 (1.345,1.724)	1.538 (1.359,1.742)	1.753 (1.545,1.99)
				p for trend		< 0.0001	< 0.0001	< 0.0001
VIM	Q1	1,070,914	282	3,630,789.33	0.07767	1 (ref.)	1 (ref.)	1 (ref.)
	Q2	1,070,754	342	3,630,512.53	0.09420	1.139 (0.973,1.333)	1.211 (1.047,1.4)	1.044 (0.89,1.223)
	Q3	1,070,889	498	3,627,907.61	0.13727	1.521 (1.314,1.761)	1.522 (1.327,1.747)	1.253 (1.08,1.454)
	Q4	1,070,761	973	3,619,111.09	0.26885	2.517 (2.202,2.877)	2.100 (1.848,2.387)	1.816 (1.576,2.092)
				p for trend		< 0.0001	< 0.0001	< 0.0001

Model 1, adjusted for age, sex, smoking, alcohol consumption, regular exercise and income.
Model 2, adjusted for Model 1 plus BMI, diabetes, hypertension and dyslipidemia.
Model 3, adjusted for Model 2 plus HDL-cholesterol level, fasting blood glucose, serum creatinine and presence of proteinuria at index year.
SD, standard deviation; CV, coefficient of variation; ARV, average real variability; VIM, variability independent of the mean.

inflammation are common features of CKD, these sterile inflammatory processes are known to be primarily involved in the modulation of the composition and function of HDL-C in patients with CKD [24]. Thus, CKD-induced abnormalities of HDL-C structure and function have a wide range of adverse consequences far beyond the impairment of the reverse cholesterol transport process [25]. Accordingly, mere measured HDL-C level in blood seems not to reliably reflect the degree of disturbance of HDL-C in CKD patients.

Several factors related to lipid metabolism are involved in the pathogenesis of decline of renal function in CKD to ESRD. Recently, research on the intra-individual variability of various physiological measures has revealed their role as risk factors for clinical outcomes [26–29]. Bangalore et al. demonstrated that in patients with previous myocardial infarction, variabilities in LDL-C and blood pressure are powerful and independent predictors of cardiovascular events including death [26]. Also, some reports elucidated the risk of visit-to-visit

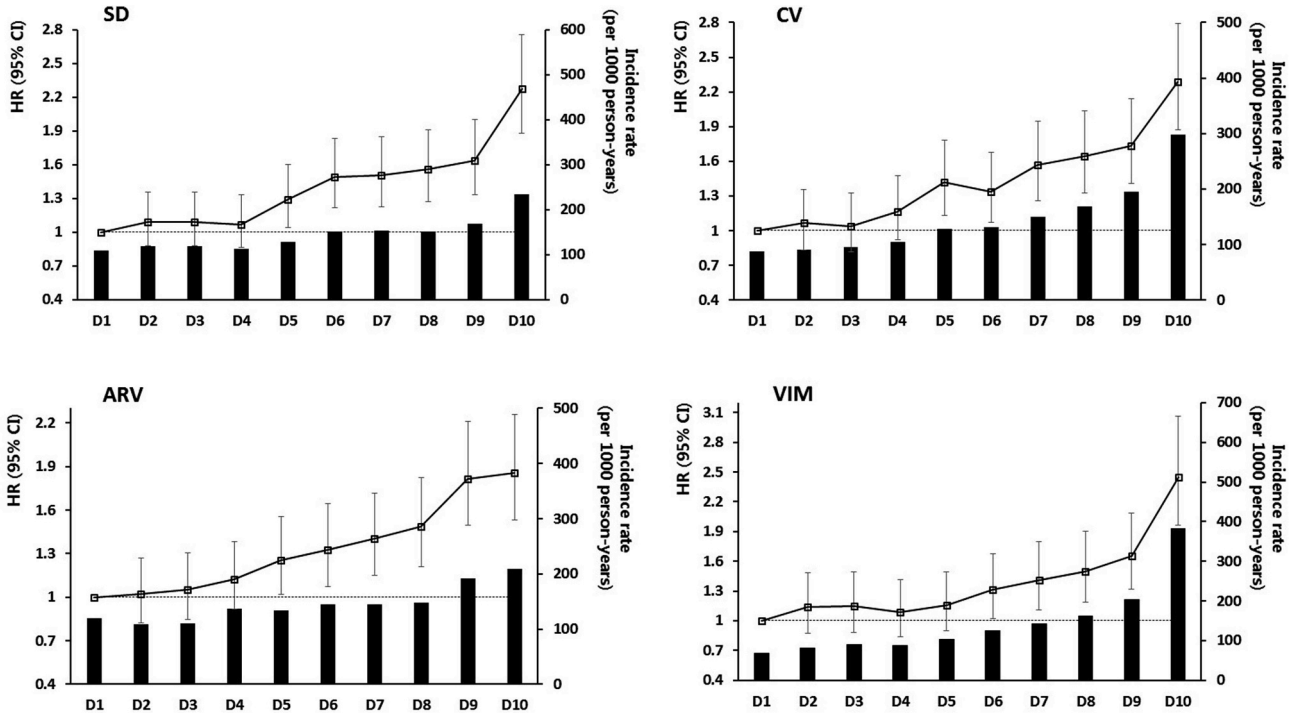

Fig. 2. Adjusted hazard ratios, 95% confidence intervals, and incidence rates of end-stage renal disease by deciles of HDL cholesterol variability.
The hazard ratio was adjusted for age, sex, body mass index, smoking, alcohol consumption, regular exercise, income, diabetes mellitus, hypertension, HDL-C level, use of lipid lowering-agent, fasting blood glucose, serum creatinine and presence of proteinuria. HDL-C variability measured as the standard deviation (SD), coefficient of variation (CV), average real variation (ARV) and the variability independent of the mean (VIM).

Table 3
Hazard ratios and 95% confidence intervals of ESRD by quartile of HDL cholesterol variability (VIM) in subgroups adjusting confounding factors.

Subgroups		VIM				*p* for interaction
		Q1	Q2	Q3	Q4	
Age, years	< 55	1 (ref.)	0.928 (0.74–1.165)	1.308 (1.061–1.613)	1.666 (1.355–2.049)	0.010
	≥55	1 (ref.)	1.188 (0.95–1.485)	1.247 (1.008–1.543)	1.957 (1.604–2.386)	
Sex	Male	1 (ref.)	1 (0.829,1.206)	1.294 (1.089,1.537)	1.917 (1.628,2.257)	0.017
	Female	1 (ref.)	1.242 (0.922,1.673)	1.173 (0.869,1.582)	1.499 (1.117,2.011)	
Diabetes	No	1 (ref.)	0.908 (0.741,1.113)	1.159 (0.959,1.401)	1.568 (1.304,1.885)	0.313
	Yes	1 (ref.)	1.261 (0.976,1.63)	1.383 (1.085,1.763)	2.173 (1.733,2.725)	
Hypertension	No	1 (ref.)	1.015 (0.721,1.429)	1.133 (0.812,1.582)	1.599 (1.161,2.203)	0.910
	Yes	1 (ref.)	1.064 (0.889,1.273)	1.295 (1.096,1.53)	1.882 (1.606,2.205)	
Obesity	No	1 (ref.)	1.164 (0.961,1.408)	1.323 (1.102,1.589)	1.912 (1.605,2.278)	0.330
	Yes	1 (ref.)	0.82 (0.616,1.093)	1.123 (0.87,1.451)	1.589 (1.248,2.024)	
Use of lipid lowering agents	No	1 (ref.)	0.944 (0.763,1.168)	1.046 (0.855,1.281)	1.622 (1.344,1.958)	0.090
	Yes	1 (ref.)	1.19 (0.937,1.511)	1.547 (1.24,1.93)	2.073 (1.671,2.572)	
Chronic kidney disease	No	1 (ref.)	1.046 (0.791,1.383)	1.111 (0.846,1.46)	1.534 (1.185,1.987)	0.666
	Yes	1 (ref.)	1.032 (0.852,1.252)	1.272 (1.065,1.519)	1.615 (1.364,1.911)	
Presence of proteinuria	No	1 (ref.)	0.862 (0.676,1.099)	1.056 (0.842,1.324)	1.483 (1.196,1.839)	0.155
	Yes	1 (ref.)	1.075 (0.87,1.329)	1.329 (1.089,1.622)	1.574 (1.296,1.911)	

Model, adjusted for age, sex, BMI, smoking, alcohol consumption, regular exercise, income, diabetes, hypertension, dyslipidemia, HDL-cholesterol level, fasting blood glucose, serum creatinine and presence of proteinuria at index year.
Obesity was defined as BMI $> 25\,kg/m^2$.

variability of blood pressure on development of renal or cardiovascular outcomes and mortality [30,31]. In addition, Ceriello and his colleague showed that variability in hemoglobin $A1_C$, blood pressure, lipid profiles and serum uric acid elevates risk of development of CKD in type 2 diabetes [27]. These observations align with our previous reports that increased total cholesterol variability was associated with increased incidence of ESRD [9]. The present study also demonstrated that HDL-C variability was a potent marker of renal function outcomes. Higher HDL-C variability can reflect disturbed lipid metabolism leading to increased lipotoxicity of CKD and consequent increase in the risk of ESRD [32]. Given that the disturbed metabolism of HDL-C in CKD is related to impairment of reverse cholesterol transport and maturation of HDL-C, HDL-C variability might be presumed to reflect the unstable process of HDL-C metabolism in pathologic conditions in diverse kidney diseases.

Another interesting point is that HDL-C variability showed a different risk of ESRD by age and sex. Thus, the impact of HDL-C variability was significantly stronger in older and male subjects in the subgroup analysis. Previous studies have focused on the hypothesis that menopause-related hormonal changes ultimately affect the HDL-C metabolism [33]. Thus, the pronounced difference in the age- and sex-related risks of ESRD may occur as the result of several biologic factors, mainly driven by hyperandrogenism, insulin resistance, and the linked increase of central obesity and HDL-cholesterol reduction occurring after menopause [33]. Of course, the association between menopause-linked hormonal changes and HDL-C variability and the reason why the impact of HDL-C variability on ESRD development was attenuated in females compared with males are both unclear. Further research is required to better understand these findings.

Several limitations and strengths may apply to the interpretation of our findings. First, the median follow-up period of the current study to investigate the risk of ESRD development in the general population. Second, reverse causality is plausible, because it seems that the renal function status might affect HDL-C variability. Higher HDL-C variability could relate to other systemic conditions that increase events, including frailty, and could also be a marker for the proportion of time that the patient is not meeting the treatment goal. Third, although we used SD, CV, ARV and VIM as index of variability, there is no consensus on the ideal statistical measure of intra-individual HDL-C variability. Namely, their predictive power does not mean that HDL-C variability measurements would be clinically useful for risk prediction, because most risk predictors used in clinical practice should be readily available. Also, HDL-C variability may not be completely independent of HDL-C values. Although we used the adjusted model for HDL-C values (model 3) to minimize the limitation, it needs to be considered that HDL-C variability reflects HDL-C mean values to some extent. Fourth, the underlying causes of ESRD were not identifiable in this study. The most common causes of ESRD are diabetes, hypertension and primary glomerulonephritis. Individual clinical renal outcomes can show distinct prognoses, depending on the underlying renal cause. However, to overcome this limitation of pathogenetic heterogeneity where possible, we conducted a subgroup analysis for the presence of diabetes, hypertension, renal dysfunction and the presence of proteinuria and there were still significant associations between HDL-C variability and the risk of ESRD development. Finally, because of the limitations of the data, we could not include variables for the severity of disease such as the duration of diabetes and hypertension, or the degree of diabetes control. Instead, we have performed an analysis adjusted for the fasting blood glucose level.

However, the current study has several distinguishing points. To our knowledge, it is the first study to report the relationship between HDL-C variability and ESRD development in a large general population, using a well-established and validated longitudinal national database. Identification of novel markers in the lipid profile may provide valuable information regarding risk of kidney disease, and those markers, in turn, may be used as potential therapeutic targets. Second, our study demonstrated a greater impact of lipid variability on low-risk groups. Diabetes and hypertension are currently the most common causes of ESRD, but the exact cause of kidney disease is uncertain in a considerable proportion of ESRD cases [34]. The fluctuation of HDL-C *per se* may be another risk factor that affects renal outcome. A more uniform and less variable lipid level might be important for preventing progression to ESRD, especially in low-risk subjects. It is necessary to investigate whether a therapeutic strategy to minimize the variability in lipid parameters could decrease the risk of CKD and its progression to ESRD.

In conclusion, greater visit-to-visit variability in HDL-C levels is significantly associated with higher incidence of ESRD in a South Korean general population. These observations highlight the dual importance of achieving stability of lipid metabolism with lowering atherogenic lipoprotein. Further studies are needed to unravel mechanisms promoting lipoprotein variability that could be associated with CKD.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Financial support

This research was supported by the Basic Science Research Program through the National Research Foundation (NRF) of Korea funded by the Ministry of Science, ICT & Future Planning, Republic of Korea (2017R1D1A1B03031133 and 2018R1A1A1A05020740).

Author contributions

Conceived and designed the experiments: ESK KH SC. Analyzed the data: ESK KH MKK HSK SJS CWP. Contributed reagents/materials/analysis tools: ESK KH YGP. Wrote the paper: ESK SC.

Acknowledgements

This study was performed using the database from the National Health Insurance System (NHIS-2019-1-135), and the results do not necessarily represent the opinion of the National Health Insurance Corporation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2019.05.018.

References

[1] M. Rahman, W. Yang, S. Akkina, A. Alper, A.H. Anderson, et al., Relation of serum lipids and lipoproteins with progression of CKD: The CRIC study, Clin. J. Am. Soc. Nephrol. 9 (7) (2014) 1190–1198.
[2] B. Bowe, Y. Xie, H. Xian, S. Balasubramanian, Z. Al-Aly, Low levels of high-density lipoprotein cholesterol increase the risk of incident kidney disease and its progression, Kidney Int. 89 (4) (2016) 886–896.
[3] Y.P. Zhang, M.G. Lu, D.D. Duan, Y.L. Liu, M. Liu, et al., Association between high-density lipoprotein cholesterol and renal function in elderly hypertension: a cross-sectional study in Chinese population, Medicine (Baltim.) 94 (14) (2015) e651.
[4] N.D. Vaziri, M. Navab, A.M. Fogelman, HDL metabolism and activity in chronic kidney disease, Nat. Rev. Nephrol. 6 (5) (2010) 287–296.
[5] K.A. Rye, P.J. Barter, Cardioprotective functions of HDLs, J. Lipid Res. 55 (2) (2014) 168–179.
[6] M.B. Lanktree, S. Thériault, M. Walsh, G. Paré, HDL cholesterol, LDL cholesterol, and triglycerides as risk factors for CKD: A Mendelian randomization study, Am. J. Kidney Dis. 71 (2) (2018) 166–172.
[7] Chapter 1: assessment of lipid status in adults with CKD, Kidney Int. Suppl. 3 (3) (2011) 268–270.
[8] B.L. Kasiske, Hyperlipidemia in patients with chronic renal disease, Am. J. Kidney Dis. 32 (5 Suppl 3) (1998) S142–S156.
[9] M.K. Kim, K. Han, E.S. Koh, H.S. Kim, H.S. Kwon, et al., Variability in total cholesterol is associated with the risk of end-stage renal disease: a nationwide population-based study, Arterioscler. Thromb. Vasc. Biol. 37 (10) (2017) 1963–1970.
[10] E.J. Lamb, C.R. Tomson, P.J. Roderick, Estimating kidney function in adults using formulae, Ann. Clin. Biochem. 42 (Pt 5) (2005) 321–345.
[11] National Kidney Foundation, K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification, Am. J. Kidney Dis. 39 (2 Suppl 1) (2002) S1–S266.
[12] M. Chiu, P.C. Austin, D.G. Manuel, B.R. Shah, J.V. Tu, Deriving ethnic-specific BMI cutoff points for assessing diabetes risk, Diabetes Care 34 (8) (2011) 1741–1748.
[13] P.M. Rothwell, S.C. Howard, E. Dolan, E. O'Brien, J.E. Dobson, et al., Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension, Lancet 375 (9718) (2010) 895–905.
[14] Y. Yano, Visit-to-Visit blood pressure variability-what is the current challenge? Am. J. Hypertens. 30 (2) (2017) 112–114.
[15] H.T. Kang, J.K. Kim, J.Y. Kim, J.A. Linton, J.H. Yoon, et al., Independent association of TG/HDL-C with urinary albumin excretion in normotensive subjects in a rural Korean population, Clin. Chim. Acta Int J Clin Chem 413 (1–2) (2012) 319–324.
[16] J.C. Bae, J.M. Han, S. Kwon, J.H. Jee, T.Y. Yu, et al., LDL-C/apoB and HDL-C/apoA-1 ratios predict incident chronic kidney disease in a large apparently healthy cohort, Atherosclerosis 251 (2016) 170–176.
[17] L. Bowman, J.C. Hopewell, F. Chen, K. Wallendszus, et al., HPS3/TIMI55–REVEAL Collaborative Group, Effects of anacetrapib in patients with atherosclerotic vascular disease, N. Engl. J. Med. 377 (13) (2017) 1217–1227.
[18] M. Holzer, R. Birner-Gruenberger, T. Stojakovic, D. El-Gamal, V. Binder, et al., Uremia alters HDL composition and function, J. Am. Soc. Nephrol. 22 (9) (2011) 1631–1641.
[19] E.M. Miele, S.A.E. Headley, M. Germain, J. Joubert, S. Herrick, et al., High-density lipoprotein particle pattern and overall lipid responses to a short-term moderate-intensity aerobic exercise training intervention in patients with chronic kidney disease, Clin. Kidney J. 10 (4) (2017) 524–531.
[20] D.J. Kennedy, W.H. Tang, Y. Fan, Y. Wu, S. Mann, et al., Diminished antioxidant activity of high-density lipoprotein-associated proteins in chronic kidney disease, J. Am. Heart Assoc. 2 (2) (2013) e000104.
[21] R. Maeba, K.I. Kojima, M. Nagura, A. Komori, M. Nishimukai, et al., Association of cholesterol efflux capacity with plasmalogen levels of high-density lipoprotein: a cross-sectional study in chronic kidney disease patients, Atherosclerosis 270 (2018) 102–109.
[22] M. Holzer, G. Schilcher, S. Curcic, M. Trieb, S. Ljubojevic, et al., Dialysis modalities and HDL composition and function, J. Am. Soc. Nephrol. 26 (9) (2015) 2267–2276.
[23] H. Moradi, E. Streja, M.L. Kashyap, N.D. Vaziri, G.C. Fonarow, et al., Elevated high-density lipoprotein cholesterol and cardiovascular mortality in maintenance hemodialysis patients, Nephrol. Dial. Transplant. 29 (8) (2014) 1554–1562.
[24] S. Ruiz, P.E. Pergola, R.A. Zager, N.D. Vaziri, Targeting the transcription factor Nrf2 to ameliorate oxidative stress and inflammation in chronic kidney disease, Kidney Int. 83 (6) (2013) 1029–1041.
[25] N.D. Vaziri, Role of dyslipidemia in impairment of energy metabolism, oxidative stress, Clin. Exp. Nephrol. 18 (2) (2014) 265–268.
[26] S. Bangalore, R. Fayyad, F.H. Messerli, R. Laskey, D.A. DeMicco, et al., Relation of variability of low-density lipoprotein cholesterol and blood pressure to events in patients with previous myocardial infarction from the IDEAL trial, Am. J. Cardiol. 119 (3) (2017) 379–387.
[27] A. Ceriello, S. De Cosmo, M.C. Rossi, G. Lucisano, S. Genovese, et al., Variability in HbA1c, blood pressure, lipid parameters and serum uric acid, and risk of development of chronic kidney disease in type 2 diabetes, Diabetes Obes. Metab. 19 (11) (2017) 1570–1578.
[28] D. Clark 3rd, S.J. Nicholls, J. St John, M.B. Elshazly, S.R. Kapadia, et al., Visit-to-visit cholesterol variability correlates with coronary atheroma progression and clinical outcomes, Eur. Heart J. 39 (27) (2018) 2551–2558.
[29] M.K. Kim, K. Han, H.S. Kim, Y.M. Park, H.S. Kwon, et al., Cholesterol variability and the risk of mortality, myocardial infarction, and stroke: a nationwide population-based study, Eur. Heart J. 38 (48) (2017) 3560–3566.
[30] P. Muntner, J. Whittle, A.I. Lynch, L.D. Colantonio, L.M. Simpson, et al., Visit-to-Visit variability of blood pressure and coronary heart disease, stroke, heart failure, and mortality: a cohort study, Ann. Intern. Med. 163 (5) (2015) 329–338.
[31] J. Whittle, A.I. Lynch, R.M. Tanner, L.M. Simpson, B.R. Davis, et al., Visit-to-Visit variability of BP and CKD outcomes: results from the ALLHAT, Clin. J. Am. Soc. Nephrol. 11 (3) (2016) 471–480.
[32] N.D. Vaziri, Lipotoxicity and impaired high density lipoprotein-mediated reverse cholesterol transport in chronic kidney disease, J. Ren. Nutr. 20 (5 Suppl) (2010) S35–S43.
[33] G. Pucci, R. Alcidi, L. Tap, F. Battista, F. Mattace-Raso, et al., Sex- and gender-related prevalence, cardiovascular risk and therapeutic approach in metabolic syndrome: a review of the literature, Pharmacol. Res. 120 (2017) 34–42.
[34] Y. Kim, K.D. Yoo, H.J. Kim, J. Koh, Y. Yu, et al., Association of serum mineral parameters with mortality in hemodialysis patients: data from the Korean end-stage renal disease registry, Kidney Res. Clin. Pract. 37 (3) (2018) 266–276.