Retinal Vein Occlusion is Associated with Low Blood High-Density Lipoprotein Cholesterol: A Nationwide Cohort Study

JAERYUNG KIM, DONG HUI LIM, KYUNGDO HAN, SE WOONG KANG, DON-IL HAM, SANG JIN KIM, AND TAE-YOUNG CHUNG

• PURPOSE: To investigate association between the development of retinal vein occlusion (RVO) and blood high-density lipoprotein cholesterol (HDL-C).

• DESIGN: A retrospective, nationwide, population-based cohort study.

• METHODS: This study was set in the Republic of Korea and included 23,149,403 people ≥20 years of age who underwent the Korean National Health Screening Program examination between January 2009 and December 2012. Among them, the RVO group was composed of patients with an initial diagnosis of RVO made between 2009 and 2015 (n = 117,639). The earliest claim with an RVO diagnostic code was considered as the incident time. The predictive value of HDL-C level for RVO was analyzed using hazard ratios. The primary outcome measure was the incident cases of RVO.

• RESULTS: Subjects with RVO were generally older; had high body mass index, waist circumference, fasting blood glucose, blood pressure, total and low-density lipoprotein cholesterol, and triglyceride values, and low glomerular filtration rate and HDL-C values; and were more likely to experience diabetes mellitus and hypertension compared with the non-RVO group. The fully adjusted hazard ratio of RVO was 1.12 (95% confidence interval 1.10–1.14) in the lowest quartile of HDL-C versus in the highest quartile. The association between the development of RVO and HDL-C was higher those with a younger age, male sex, current smoking habit, diabetes mellitus, and hypercholesterolemia. In addition, we observed a significant synergistic effect of low HDL-C level with obesity and hypertension.

• CONCLUSION: This is the first nationwide population-based epidemiologic study evaluating the association between HDL-C level and the risk of RVO development. A significant association between low HDL-C and RVO development was found. (Am J Ophthalmol 2019;205: 35–42. © 2019 Elsevier Inc. All rights reserved.)

RETINAL VEIN OCCLUSION (RVO) IS THE SECOND most common form of retinal vascular disease.[1] There are 2 types of RVO: branch RVO (BRVO) and central RVO (CRVO). Of the 2 main types of RVO, BRVO is up to 5 times more prevalent than CRVO.[2] Although the fundamental pathogenic mechanisms of RVO are not yet fully understood, a combination of complex elements is believed to contribute to the development of RVO, including vein compression of the vein at the arteriovenous crossing,[3] increased arterial rigidity and arteriosclerosis, formation of thrombus after degenerative changes in vessel walls,[4] dysregulated hematologic factors,[5,6] and elevated levels of proinflammatory mediators and decreased levels of anti-inflammatory cytokines in the vitreous fluid of patients with RVO.[7,8] Previous studies have reported that risk factors for RVO include old age, hypertension, diabetes mellitus (DM), myocardial infarction, cerebral vascular accidents, and chronic kidney disease (CKD).[9–11] In addition, although hyperlipidemia has also been considered to be a risk factor for RVO,[12] few studies to date have evaluated the association between high-density lipoprotein cholesterol (HDL-C) and RVO development, especially on the basis of extensive nationwide data. The purpose of this study was to evaluate the risk of RVO in Korean patients with low blood HDL-C.

METHODS

• DATA SOURCE AND STUDY POPULATION: All Korean nationals are obligated to enroll in the Korean National Health Insurance Service (KNHIS). A total of 97% of the Korean population is covered by the KNHIS, while the remaining 3% of the population is covered by the Medical Assistance Program and the Medical Care for Patriots and Veterans Affairs Scheme. Thus, nearly all data in the health system are centralized in large databases. The KNHIS provides a biennial National Health

AJO.com Supplemental Material available at AJO.com.

Accepted for publication Apr 1, 2019.

From the Department of Ophthalmology (J.K., D.H.L., S.W.K., D-I.H., S.J.K., T-Y.C.), Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul; Department of Preventive Medicine (D.H.L.), Graduate School, and the Department of Biostatistics (K.H.), College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea.

Inquiries to Dong Hui Lim, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irown-ro, Gangnam-gu, Seoul 06351, Republic of Korea; e-mail: ldhlse@gmail.com

0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2019.04.001

Screening Program (NHSP) to all subjects ≥20 years of age. The KNHIS gathers all essential details for reimbursement of each medical claim, including diagnostic codes, procedures, prescription drugs, personal information about the patient, information about the hospital, and the direct medical costs of both inpatient and outpatient care. For diagnostic code registration, the KNHIS uses the *Korean Classification of Diseases*, which is similar to the *International Classification of Diseases* (ICD). In this retrospective, nationwide population-based cohort study, a total of 23,503,802 subjects who participated in the NHSP at least once between 2009 and 2012 were initially enrolled. Among these subjects, we excluded 50,940 individuals who were <20 years of age, 107,228 subjects with missing data, and 196,231 subjects diagnosed with RVO during the washout period (2002–2008). Thus, this study included 23,149,403 people ≥20 years of age who underwent the NHSP examination at least once between January 1, 2009 and December 31, 2012, together with monitoring for development of RVO (*Korean Classification of Diseases* code H34.8 corresponding to the *International Classification of Diseases, 10th revision, Clinical Modification* code H34.81, CRVO, or H34.83, venous tributary [branch] occlusion) until December 31, 2015. The earliest claim with an RVO diagnostic code for an individual was selected and considered as the incident time. This study adhered to the tenets of the Declaration of Helsinki, and the study protocol was reviewed and approved by the Institutional Review Board of Samsung Medical Center (2018-05-190). The need for written informed consent was waived.

• **MEASUREMENTS AND DEFINITIONS:** According to the Korean NHSP examination procedures, the personal information of each patient was gathered, including age, sex, average monthly insurance premium, and residential area, categorized as city area, metropolitan area, or rural area. In addition, the results of a questionnaire regarding medical history and health behavior, anthropometric measurement including body mass index (BMI), waist circumference, and blood pressure (BP), and laboratory tests, such as fasting blood glucose and cholesterol level, were also provided.[13] BMI was calculated as the weight in kilograms divided by the square of the height in meters (kg/m^2). According to the Clinical Practice Guidelines for Overweight and Obesity by Korean Society for the Study of Obesity,[14] the BMI cutoff of 25 kg/m^2 was adopted to define obesity for the Korean population enrolled in our study. Hypertension was defined as a systolic BP ≥ 140 mm Hg or a diastolic BP of ≥ 90 mm Hg or the use of oral antihypertensive medications with diagnosis based on ICD-10 codes (10–13, I15). BP was measured while the subject was in a seated position after 5 minutes of rest during the daytime. DM was defined as a fasting blood glucose level of ≥126 mg/dL or the use of insulin or oral hypoglycemic agents with diagnosis (ICD-10 codes E11–E14). Hypercholesterolemia was defined as a total cholesterol of ≥240 mg/dL or the use of cholesterol-lowering medications with diagnosis (ICD-10 code E78). CKD was defined as a glomerular filtration rate (GFR) of <60 mL/min/1.73 m^2. Blood samples were collected after overnight fasting and measured for serum levels of HDL-C together with glucose, total cholesterol (TC), triglycerides, low-density lipoprotein cholesterol, and creatinine. Stroke was defined according to ICD-10 codes (I63 and I64) for diagnoses made during hospitalization together with brain computed tomography or magnetic resonance imaging. Heart disease included myocardial infarction (ICD-10 codes I21 and I22) and heart failure (ICD-10 code I50) diagnosed during hospitalization. In addition, the definitions of lifestyle variables were as follows: smoking status was categorized into the 3 groups of nonsmokers, current smokers who had smoked ≥100 cigarettes in their lifetime, and ex-smokers who had smoked in the past but had since quit at least 1 month ago. Alcohol consumption status was categorized into the 3 groups of nondrinkers, those who drank <30 g of pure alcohol a day on average, and heavy drinkers who drank >30 g per day. Regular exercise was defined as strenuous physical activity that was performed for ≥30 minutes, and subjects were asked if they performed such ≥5 times per week.

• **STATISTICAL ANALYSIS:** Baseline characteristics were presented as numbers with percentages (%) for categorical variables or mean values with standard deviations (SDs) for continuous variables. Kaplan–Meier survival analysis was used to draw the RVO-free survival curve. Participants were classified into 4 groups according to HDL-C concentration quartiles. Associations between HDL-C and the risk of RVO were analyzed using multivariable-adjusted Cox regression models, and the hazard ratio (HR) and 95% confidence interval (CI) for each HDL-C quartile, relative to the reference group (the highest quartile, Q4), were presented for each of the 3 models. Model 1 was adjusted for age and sex; model 2 was further adjusted for smoking, alcohol drinking, regular exercise, and income status; and model 3 was further adjusted for BMI and systolic BP. We also presented the HR and 95% CI according to HDL-C deciles after adjusting for the same confounders as mentioned in model 3. Thereafter, we calculated the HRs and 95% CI of Q4 group versus the lower 3 quartiles (Q1−Q3), stratified by age (<65 or ≥65 years), sex (male or female), smoking (none or current), alcohol drinking (none or heavy), regular exercise (no or yes), income (Q2−Q4 or Q1), DM (no or yes), high TC (no or yes), stroke (no or yes), heart disease (no or yes), CKD (no or yes), obesity (no or yes), and hypertension (no or yes). Statistical analysis was performed with SAS software (version 9.4; SAS Institute Inc, Cary, North Carolina, USA), and $P < .05$ was considered statistically significant.

TABLE 1. Characteristics of Subjects with and Without RVO

Variable	RVO (n = 117,639)	Non-RVO (n = 23,031,764)	*P* Value[a]
Age (y)	60.4 ± 11.4	47.6 ± 14.4	<.0001
BMI (kg/m^2)	24.4 ± 3.1	23.7 ± 3.3	<.0001
WC (cm)	82.8 ± 8.6	80.0 ± 9.3	<.0001
GFR (mL/min/1.73m^2)	83.2 ± 33.8	89.6 ± 39.5	<.0001
Fasting glucose (mg/dL)	106.6 ± 35.0	97.5 ± 23.3	<.0001
Systolic BP (mm Hg)	128.7 ± 16.0	122.2 ± 15.2	<.0001
Diastolic BP (mm Hg)	79.1 ± 10.3	76.0 ± 10.1	<.0001
Total cholesterol (mg/dL)	198.6 ± 38.8	194.7 ± 36.9	<.0001
HDL cholesterol (mg/dL)	53.2 ± 13.6	55.2 ± 13.9	<.0001
LDL cholesterol (mg/dL)	117.4 ± 35.2	113.8 ± 33.3	<.0001
Log [triglyceride] (mg/dL)	4.8 ± 0.5	4.7 ± 0.6	<.0001
Age (≥65 y)	45,826 (38.95%)	3,157,415 (13.71%)	<.0001
Sex (male)	52,925 (44.99%)	11,690,000 (50.77%)	<.0001
Current smoker	18,100 (15.39%)	5,676,364 (24.65%)	<.0001
Heavy drinker	6102 (5.19%)	1,526,184 (6.63%)	<.0001
Exercise	52,401 (44.54%)	11,430,000 (49.64%)	<.0001
Diabetes	25,422 (21.61%)	2,112,579 (9.17%)	<.0001
Hypertension	61,692 (52.44%)	6,003,374 (26.07%)	<.0001
Hypercholesterolemia	37,667 (32.02%)	4,409,068 (19.14%)	<.0001
Stroke	2530 (2.9%)	226,843 (1.53%)	<.0001
Heart disease	5710 (6.53%)	470,752 (3.18%)	<.0001
CKD	13,865 (11.79%)	1,259,361 (5.47%)	<.0001

Continuous data are presented as mean ± standard deviation.

BMI = body mass index; BP = blood pressure; CKD = chronic kidney disease; GFR = glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; RVO = retinal vein occlusion; WC = waist circumference.

[a]Calculated using the Student *t* test for continuous variables and the χ^2 test for categorical variables.

RESULTS

AMONG THE 23,149,403 SUBJECTS, 117,639 (0.51%) CLINICAL RVO cases were newly diagnosed during the study period. The main characteristics of the study population are shown in Table 1. The subjects with RVO were older, had higher BMI, waist circumference (WC), fasting blood glucose, systolic and diastolic BP, total and low-density lipoprotein cholesterol, and triglyceride values compared with the non-RVO group (all $P < .0001$). In addition, RVO patients had low GFR and HDL-C values and were more likely to experience DM, hypertension, hypercholesterolemia, stroke, heart disease, and CKD versus the non-RVO control group (all $P < .0001$). When Kaplan–Meier survival analyses were performed with RVO development as the dependent variable, the group with the lowest quartile of HDL-C concentration showed the lowest disease-free survival rate for RVO among the 4 quartile groups of HDL-C concentration (Figure 1).

In Table 2, multivariable-adjusted Cox regression models (models 1–3) demonstrate the influence of HDL-C on the development of RVO in Korean population. The adjusted HRs of RVO were 1.17 (95% CI 1.15–1.19; *P* for trend < .0001 for model 1), 1.18 (95% CI 1.16–1.20; *P* for trend < .0001 for model 2), and 1.12 (95% CI 1.10–1.14; *P* for trend < .0001 for model 3) in the lowest quartile of HDL-C compared with their highest quartile counterparts.

When the HRs for RVO development in the total study population were expressed as the risk in deciles versus the highest decile of HDL-C, the HR for the first decile of HDL-C was the highest and the HRs decreased in a concentration-dependent manner (Figure 2). Intriguingly, the association between the development of RVO and HDL-C was higher in younger patients (20–39 years of age and 40–64 years of age, respectively) compared with patients >65 years of age.

When we evaluated the effects of several confounding factors on RVO development according to HDL-C concentration (Q1–Q3 vs. Q4), age, sex, smoking, regular exercise, income, DM, hypercholesterolemia, heart disease, and CKD significantly affected the relationship of HDL-C concentration with RVO development (Table 3). When we evaluated the effects of obesity and hypertension on the development of RVO according to HDL-C level, there was an inverse relationship between the level of HDL-C and the development of RVO regardless of obesity and hypertension. We observed a significant synergistic effect of low HDL-C level with obesity

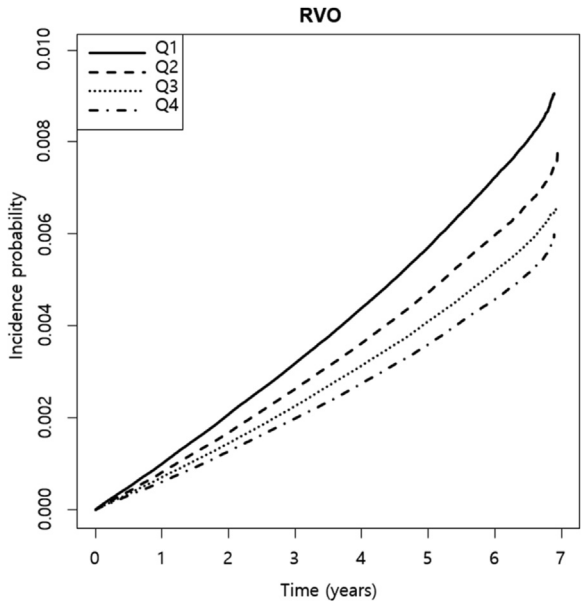

FIGURE 1. Kaplan–Meier curves showing the incidence of retinal vein occlusion (RVO) according to quartiles (Q1–Q4) of high-density lipoprotein cholesterol (HDL-C) concentration. The group with the lowest quartile of HDL-C concentration showed the lowest disease-free survival rate for RVO among the 4 quartile groups.

(HR 1.40 [95% CI 1.38–1.43], *P* value for interaction < .001) and hypertension (HR 1.70 [95% CI 1.67–1.72], *P* value for interaction < .001; Figure 3). In addition, although the risk of RVO in nonobese patients with low HDL-C levels (HR 1.29 [95% CI 1.27–1.31]) was significantly higher than that in obese patients with high HDL-C levels (HR 1.22 [95% CI 1.20–1.24]), the risk of RVO in nonhypertensive patients with low HDL-C levels (HR 1.25 [95% CI 1.23–1.27]) was significantly lower than that in hypertensive patients with high HDL-C levels (HR 1.55 [95% CI 1.52–1.57]; Figure 3).

DISCUSSION

IN THE PRESENT STUDY, WE DEMONSTRATED THAT A LOW blood level of HDL-C was associated with a significantly higher risk of RVO after adjusting for potential confounders, including age, sex, current smoking habit, heavy drinking habit, exercise, income, BMI, and systolic BP in a nationwide population-based cohort of Koreans. The risk of RVO continuously decreased in a concentration-dependent manner as the blood level of HDL-C increased. We observed a synergistically increased RVO risk between low HDL-C level and hypertension, obesity, young age (<65 years of age), male sex, current smoking, DM, or hypercholesterolemia. To the best of our knowledge, this study is the first to examine the association between HDL-C level and RVO risk thoroughly using a nationwide, population-based cohort study.

RVO is the second most common vision-threatening retinal vascular disease.[2] CRVO is an extremely frustrating problem that results in a permanently poor visual outcome. In spite of treatment with antivascular endothelial growth factor agents for visual impairment caused by macular edema secondary to RVO, approximately 50% of patients with CRVO and approximately 30% of patients with BRVO do not present resolution of macular edema and their visual improvement after the treatment was insufficient, especially in the case of CRVO patients gaining only approximately 1 Snellen line.[15] Therefore, the

TABLE 2. Multivariable-Adjusted Cox Regression Analysis of RVO Incidence by HDL-C Concentration

HDL-C				HR (95% CI)		
Quartile	Sex	Mean (mg/dL)	Median (mg/dL)	Model 1[a]	Model 2[b]	Model 3[c]
Q1	Male	37.93	39	1.17 (1.15–1.19)	1.18 (1.16–1.20)	1.12 (1.10–1.14)
	Female	41.97	43			
Q2	Male	47.02	47	1.12 (1.10–1.14)	1.13 (1.11–1.15)	1.09 (1.07–1.10)
	Female	53.03	53			
Q3	Male	54.68	55	1.07 (1.05–1.09)	1.07 (1.05–1.09)	1.05 (1.03–1.07)
	Female	61.76	62			
Q4	Male	69.45	67	1 (reference)	1 (reference)	1 (reference)
	Female	76.85	74			
P value for trend				< 0.0001	< 0.0001	< 0.0001

CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; HR = hazard ratio; RVO = retinal vein occlusion.
[a]Adjusted for age and sex.
[b]Adjusted for age, sex, current smoking habit, heavy drinking habit, exercise, and income.
[c]Adjusted for age, sex, current smoking habit, heavy drinking habit, exercise, income, body mass index, and systolic blood pressure.

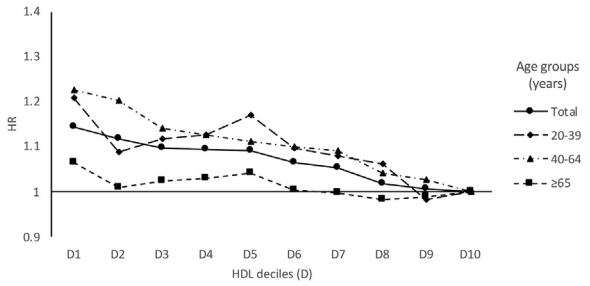

FIGURE 2. Hazard ratios (HRs) for retinal vein occlusion development according to deciles (D) of high-density lipoprotein cholesterol (HDL-C) concentration. The HR in this graph expresses the risk in deciles compared with the risk in the highest decile of HDL-C, adjusted for age, sex, smoking, drinking, exercise, income, body mass index, and systolic blood pressure. Compared with the highest decile of HDL-C, the HR for the first decile of HDL-C was the highest and the HRs continuously decreased in a concentration-dependent manner. The association between the development of RVO and HDL-C was higher in younger patients (20–39 years of age and 40–64 years of age, respectively) compared with patients ≥65 years of age.

prevention as well as the early treatment of RVO is of the utmost importance.

Decreased HDL-C concentration is traditionally associated with an increased risk of cardiovascular disease.[16] The 2018 guidelines on the management of blood cholesterol reported by the American College of Cardiology and American Heart Association indicate that HDL-C concentration <40 mg/dL in men and <50 mg/dL in women is a risk-enhancing factor for atherosclerotic cardiovascular disease.[17] There have been controversies on the effects of extremely elevated HDL-C levels (by cutoff values ranging from 75–100 mg/dL).[18,19] Although some studies have reported that extremely high HDL-C may indicate dysfunctional HDL particles and paradoxically confer an increased risk of cardiovascular disease,[20,21] others have reported that the highest quintile of HDL-C was independently associated with lower levels of markers of subclinical cardiovascular disease.[22] Further research to demonstrate the effect of extremely high HDL-C on the risk of cardiovascular disease is needed.

Despite the evidence from various previous reports including 4 case-control studies[23–26] and 3 prospective cohort studies,[10,27,28] the association between HDL-C level and the risk of RVO development has remained controversial. While some studies have shown a protective effect of high HDL-C level against RVO,[26,28] other studies have indicated no significant effect[10,25,27] or even an opposite effect.[23,24] Unfortunately, even in the prospective cohort studies, the total patient sample size was <5000. Therefore, our study, based on a large nationwide population cohort covering almost the entire population of South Korean adults, reveals novel insights into the association between HDL-C and RVO. Meanwhile, intriguingly, the association between HDL-C level and the risk of RVO development was higher in younger patients compared with patients who were ≥65 years of age. Along with a previous report demonstrating that compositional changes in HDL-C in elderly subjects, without a significant decrease in HDL-C level, are linked to a loss of antiatherogenic properties,[29] we can postulate that higher association between the development of RVO and HDL-C in younger patients is attributed to alterations in HDL composition and subsequent functional impairment.

TABLE 3. Multivariable-Adjusted Cox Regression Analysis Showing Association Between HDL Concentration and RVO Development According to Other Characteristics of Subjects

Variable	HR (95% CI)	*P* Value[a]
Age (y)		
< 65	1.23 (1.21–1.25)	<.0001
≥ 65	1.10 (1.08–1.13)	
Sex		
Male	1.26 (1.23–1.28)	<.0001
Female	1.18 (1.16–1.20)	
Smoker		
None	1.20 (1.19–1.22)	<.0001
Current	1.29 (1.25–1.33)	
Drinker		
None	1.21 (1.20–1.23)	.0558
Heavy	1.26 (1.19–1.33)	
Regular exercise		
No	1.21 (1.19–1.23)	.0079
Yes	1.21 (1.19–1.24)	
Income		
Q2–Q4	1.20 (1.18–1.22)	.0128
Q1	1.24 (1.21–1.27)	
Diabetes		
No	1.13 (1.11–1.15)	<.0001
Yes	1.18 (1.15–1.21)	
Hypercholesterolemia		
No	1.07 (1.05–1.08)	<.0001
Yes	1.43 (1.40–1.47)	
Stroke		
No	1.21 (1.20–1.23)	.9094
Yes	1.32 (1.22–1.44)	
Heart disease		
No	1.21 (1.19–1.23)	.0059
Yes	1.19 (1.12–1.26)	
CKD		
No	1.20 (1.18–1.21)	.0065
Yes	1.29 (1.25–1.34)	

CI = confidence interval; CKD = chronic kidney disease; HDL = high-density lipoprotein; HR = hazard ratio; Q = quartile; RVO = retinal vein occlusion.

[a]*P* value for trend.

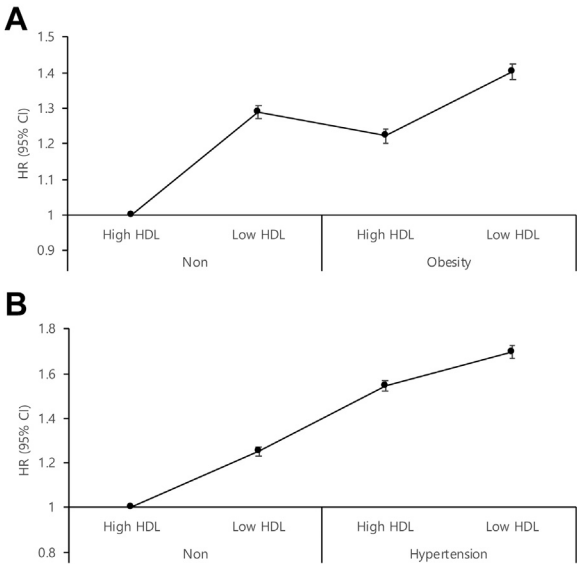

FIGURE 3. Retinal vein occlusion risk based on the combined effect of the concentration of high-density lipoprotein (HDL) with obesity (A) or hypertension (B). High HDL represents the highest quartile of HDL and low HDL represents the lower 3 quartiles of HDL. (A) Obesity (adjusted by age, sex, smoking, drinking, exercise, income, and systolic blood pressure). (B) Hypertension (adjusted by age, sex, smoking, drinking, exercise, income, and body mass index). There was an inverse relationship between the level of HDL and the development of retinal vein occlusion regardless of obesity and hypertension, and a significant synergistic effect of low HDL level with obesity and hypertension was identified.

Although the exact pathogenic mechanisms of RVO remain unclear, it has been postulated that the pathophysiology of RVO consists of 3 causative factors known as Virchow's triad—abnormalities of the vessel wall, abnormalities in blood viscosity and coagulation, and abnormalities in blood flow, respectively.[30,31] Dyslipidemia is one of the key contributing factors to the development of arteriolar sclerosis.[32] In this regard, retinal arteries with sclerotic changes can compress further over the veins at the arteriovenous crossing site in RVO, ultimately leading to the occlusion of downstream retinal veins. Although the mechanisms underlying the direct relationship between HDL-C and the development of RVO still remain elusive, previous studies have suggested that HDL-C prevents atherosclerosis through several mechanisms, including the removal of excessive cholesterol from macrophages,[33] the alleviation of vascular endothelial dysfunction,[34] and antiapoptotic, antioxidative, and anti-inflammatory effects.[35] In this regard, we can speculate that low blood levels of HDL-C aggravate atherosclerotic changes in the vessel wall, facilitating RVO development. Meanwhile, in this study, when we evaluated the relationship between HDL-C concentration and RVO, we did not analyze CRVO and BRVO separately because the *Korean Classification of Diseases* code for RVO does not discriminate between CRVO and BRVO. However, considering that CRVO and BRVO share a common etiology as part of a systemic cardiovascular risk profile,[36] our results could confirm that a low blood level of HDL-C is an important risk factor for RVO development.

Several limitations should be mentioned regarding the interpretation of our results. First, because the KNHIS database relies on physicians' assignment of a diagnostic code for RVO and other comorbidities, there may be a possibility either of an underestimation of asymptomatic RVO or of a delayed diagnosis of RVO because of a delay in visiting the ophthalmologist. Second, the duration of low HDL-C level, which possibly influences RVO risk, could not be considered. Third, because of a lack of data, we did not consider dietary factors that may be potentially related to HDL-C level. Finally, our findings from the Korean population cannot be extrapolated to other ethnicities that were not considered in this study.

Despite these limitations, the present study has a major strong point, because it is an extremely large-scale cohort study that evaluated the influence of HDL-C level on RVO. Our study provides the first evidence that HDL-C is a risk factor for RVO in almost the entire population, because the KNHIS database including the NHSP examination covers the whole population of South Korean adults. Furthermore, we comprehensively analyzed coexisting illnesses and other factors, enabling adjustment for potential confounders.

In conclusion, we found that low blood HDL-C is an independent risk factor for RVO development. Careful monitoring of blood HDL-C level via regular health screening programs seems to be helpful in the general population, especially in subjects with other risk factors, such as hypertension, obesity, young age, male sex, current smoking habit, DM, or dyslipidemia. In addition, the assessment of lipid profiles including HDL-C level may be considered when encountering a newly diagnosed case of RVO. Future studies are warranted to examine whether the control of HDL-C level can decrease the risk of RVO development.

ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST. Funding/Support: Supported by a National Research Foundation of Korea grant funded by the Korean government's Ministry of Education (NRF-2018R1D1A1A02045884) to Dr. Lim. Financial Disclosures: The authors indicate no financial support or financial conflict of interest. All authors attest that they meet the current ICMJE criteria for authorship.

REFERENCES

1. Ehlers JP, Fekrat S. Retinal vein occlusion: beyond the acute event. *Surv Ophthalmol* 2011;56(4):281–299.
2. Rogers S, McIntosh RL, Cheung N, et al. The prevalence of retinal vein occlusion: pooled data from population studies from the United States, Europe, Asia, and Australia. *Ophthalmology* 2010;117(2):313–319.e311.
3. Zhao J, Sastry SM, Sperduto RD, Chew EY, Remaley NA. Arteriovenous crossing patterns in branch retinal vein occlusion. The Eye Disease Case-Control Study Group. *Ophthalmology* 1993;100(3):423–428.
4. Christoffersen NL, Larsen M. Pathophysiology and hemodynamics of branch retinal vein occlusion. *Ophthalmology* 1999;106(11):2054–2062.
5. Trope GE, Lowe GD, McArdle BM, et al. Abnormal blood viscosity and haemostasis in long-standing retinal vein occlusion. *Br J Ophthalmol* 1983;67(3):137–142.
6. Janssen MC, den Heijer M, Cruysberg JR, Wollersheim H, Bredie SJ. Retinal vein occlusion: a form of venous thrombosis or a complication of atherosclerosis? A meta-analysis of thrombophilic factors. *Thromb Haemost* 2005;93(6):1021–1026.
7. Noma H, Funatsu H, Mimura T, Eguchi S, Shimada K. Inflammatory factors in major and macular branch retinal vein occlusion. *Ophthalmologica* 2012;227(3):146–152.
8. Deobhakta A, Chang LK. Inflammation in retinal vein occlusion. *Int J Inflam* 2013;2013:438412.
9. Kolar P. Risk factors for central and branch retinal vein occlusion: a meta-analysis of published clinical data. *J Ophthalmol* 2014;2014:724780.
10. Yasuda M, Kiyohara Y, Arakawa S, et al. Prevalence and systemic risk factors for retinal vein occlusion in a general Japanese population: the Hisayama study. *Invest Ophthalmol Vis Sci* 2010;51(6):3205–3209.
11. Lee JY, Yoon YH, Kim HK, et al. Baseline characteristics and risk factors of retinal vein occlusion: a study by the Korean RVO Study Group. *J Korean Med Sci* 2013;28(1):136–144.
12. O'Mahoney PR, Wong DT, Ray JG. Retinal vein occlusion and traditional risk factors for atherosclerosis. *Arch Ophthalmol* 2008;126(5):692–699.
13. Lee JE, Shin DW, Jeong SM, et al. Association between timed up and go test and future dementia occurrence. *J Gerontol A Biol Sci Med Sci* 2018;73(9):1238–1243.
14. Kim MK, Lee WY, Kang JH, et al. 2014 clinical practice guidelines for overweight and obesity in Korea. *Endocrinol Metab (Seoul)* 2014;29(4):405–409.
15. Chatziralli I, Theodossiadis G, Chatzirallis A, Parikakis E, Mitropoulos P, Theodossiadis P. Ranibizumab for retinal vein occlusion: predictive factors and long-term outcomes in real-life data. *Retina* 2018;38(3):559–568.
16. Emerging Risk Factors Collaboration, Di Angelantonio E, Sarwar N, et al. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* 2009;302(18):1993–2000.
17. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019;139(25):e1046–e1081.
18. Inazu A, Brown ML, Hesler CB, et al. Increased high-density-lipoprotein levels caused by a common cholesteryl-ester transfer protein gene mutation. *N Engl J Med* 1990;323(18):1234–1238.
19. Maruyama T, Sakai N, Ishigami M, et al. Prevalence and phenotypic spectrum of cholesteryl ester transfer protein gene mutations in Japanese hyperalphalipoproteinemia. *Atherosclerosis* 2003;166(1):177–185.
20. Hirano K, Yamashita S, Kuga Y, et al. Atherosclerotic disease in marked hyperalphalipoproteinemia - combined reduction of cholesteryl ester transfer protein and hepatic triglyceride lipase. *Arterioscler Thromb Vasc Biol* 1995;15(11):1849–1856.
21. Kontush A, de Faria EC, Chantepie S, Chapman MJ. Antioxidative activity of HDL particle subspecies is impaired in hyperalphalipoproteinemia: relevance of enzymatic and physicochemical properties. *Arterioscler Thromb Vasc Biol* 2004;24(3):526–533.
22. Laurinavicius AG, Santos IS, Santos RD, Bensenor IM, Conceicao RD, Lotufo PA. Extremely elevated HDL-cholesterol levels are not associated with increased carotid intima-media thickness: data from ELSA Brasil. *J Clin Lipidol* 2016;10(4):898–904.
23. Dodson PM, Galton DJ, Hamilton AM, Blach RK. Retinal vein occlusion and the prevalence of lipoprotein abnormalities. *Br J Ophthalmol* 1982;66(3):161–164.
24. Stojakovic T, Scharnagl H, Marz W, Winkelmann BR, Boehm BO, Schmut O. Low density lipoprotein triglycerides and lipoprotein(a) are risk factors for retinal vascular occlusion. *Clin Chim Acta* 2007;382(1-2):77–81.
25. Sofi F, Marcucci R, Fedi S, et al. High lipoprotein (a) levels are associated with an increased risk of retinal vein occlusion. *Atherosclerosis* 2010;210(1):278–281.
26. Risk factors for branch retinal vein occlusion. The Eye Disease Case-control Study Group. *Am J Ophthalmol* 1993;116(3):286–296.
27. Wong TY, Klein R, Sharrett AR, et al. The prevalence and risk factors of retinal microvascular abnormalities in older persons: The Cardiovascular Health Study. *Ophthalmology* 2003;110(4):658–666.
28. Klein R, Klein BE, Moss SE, Meuer SM. The epidemiology of retinal vein occlusion: the Beaver Dam Eye Study. *Trans Am Ophthalmol Soc* 2000;98:133–141.
29. Holzer M, Trieb M, Konya V, Wadsack C, Heinemann A, Marsche G. Aging affects high-density lipoprotein composition and function. *Biochim Biophys Acta* 2013;1831(9):1442–1448.
30. Rehak J, Rehak M. Branch retinal vein occlusion: pathogenesis, visual prognosis, and treatment modalities. *Curr Eye Res* 2008;33(2):111–131.
31. Gutman FA. Evaluation of a patient with central retinal vein occlusion. *Ophthalmology* 1983;90(5):481–483.
32. Martin SS, Blaha MJ, Blankstein R, et al. Dyslipidemia, coronary artery calcium, and incident atherosclerotic cardiovascular disease: implications for statin therapy from the multi-ethnic study of atherosclerosis. *Circulation* 2014;129(1):77–86.

33. Rosenson RS, Brewer HB Jr, Davidson WS, et al. Cholesterol efflux and atheroprotection: advancing the concept of reverse cholesterol transport. *Circulation* 2012;125(15):1905–1919.
34. Riwanto M, Rohrer L, Roschitzki B, et al. Altered activation of endothelial anti- and proapoptotic pathways by high-density lipoprotein from patients with coronary artery disease: role of high-density lipoprotein-proteome remodeling. *Circulation* 2013;127(8):891–904.
35. Camont L, Lhomme M, Rached F, et al. Small, dense high-density lipoprotein-3 particles are enriched in negatively charged phospholipids: relevance to cellular cholesterol efflux, antioxidative, antithrombotic, anti-inflammatory, and antiapoptotic functionalities. *Arterioscler Thromb Vasc Biol* 2013;33(12):2715–2723.
36. MacDonald D. The ABCs of RVO: A review of retinal venous occlusion. *Clin Exp Optometry* 2014;97(4):311–323.