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Risk of Retinal Vascular Occlusive Disease According to Type and Low-Density Lipoprotein-Cholesterol Control after Acute Coronary Syndrome

Minjeong Kim[1,2], Ji Hyun Lee[3], Yun-Hyeong Cho[3], Kunho Bae[4], and Ju-Yeun Lee[5,6]

[1]Department of Cardiology, Ewha Womans University Hospital, Ewha Womans University College of Medicine, Seoul, Korea;
[2]Department of Medicine, Graduate School, Yonsei University College of Medicine, Seoul, Korea;
[3]Department of Cardiology, Myongji Hospital, Hanyang University College of Medicine, Goyang, Korea;
[4]Department of Ophthalmology, Seoul National University Hopital, Seoul National University College of Medicine, Seoul, Korea;
[5]Department of Ophthalmology, Myongji Hospital, Hanyang University College of Medicine, Goyang, Korea;
[6]Department of Ophthalmology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA.

Purpose: Retinal vascular occlusive disease (RVOD) may occur as a consequence of systemic vascular dysfunction. Although RVOD has been associated with coronary artery disease, its incidence after acute coronary syndrome (ACS) and the influence of lipid control remain unclear.

Materials and Methods: Using data from the Korean National Health Information Database (2002–2022), we conducted a nationwide retrospective cohort study including 55040 patients with newly diagnosed ACS [unstable angina (UA) or myocardial infarction (MI)] and age- and sex-matched controls. RVOD outcomes included retinal artery occlusion (RAO) and retinal vein occlusion (RVO). Low-density lipoprotein-cholesterol (LDL-C) control was stratified into four categories (excellent, good, suboptimal, poor) based on guideline-recommended targets. Competing risk analysis was performed to estimate adjusted hazard ratios (aHRs).

Results: The risk of RVOD was higher in both the UA group [aHR=1.67, 95% confidence interval (CI): 1.56–1.79] and MI group (aHR=1.34, 95% CI: 1.15–1.56) compared with controls. Stratified analysis showed elevated risk in older patients (≥65 years) and males. Among LDL-C groups, poor LDL-C control (≥100 mg/dL) was associated with the highest RVOD risk (aHR = 2.27), compared with both the ACS-free control group and the excellent control group (<55 mg/dL).

Conclusion: ACS is independently associated with increased RVOD risk, particularly among patients with UA, older age, and poor LDL-C control. Intensive lipid-lowering therapy and ophthalmologic follow-up may reduce vision-threatening vascular events in this high-risk population.

Key Words: Retinal vascular occlusive disease, acute coronary syndrome, low-density lipoprotein, unstable angina, myocardial infarction

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Corresponding author: Ju-Yeun Lee, MD, PhD, Department of Ophthalmology, Myongji Hospital, Hanyang University College of Medicine, 55 Hwasu-ro 14beon-gil, Deogyang-gu, Goyang 10475, Korea.
E-mail: leejy5293@gmail.com

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INTRODUCTION

Acute coronary syndrome (ACS) is characterized by myocardial infarction (MI) and unstable angina (UA).[1] Following ACS, vascular inflammation and oxidative stress not only harm the cardiovascular system but also affect blood vessels in peripheral tissues, potentially contributing to retinal vascular occlusive disease (RVOD).[2,3] Previous studies suggest that retinal vascular diseases, especially microangiopathy, often coincide with cerebrovascular and renal vascular diseases[4,5] and are associated with various cardiovascular conditions such as coronary artery disease (CAD).[6-9] CAD involves vascular endothelium damage caused by atherosclerosis, a key pathological mechanism implicated in RVOD.[10]

While several previous studies have suggested that RVOD is associated with an increased risk of subsequent cardiovascular disease,[11,12] few have investigated the risk of RVOD specifically in patients with ACS. Most of these studies were based on relatively small cohorts. Furthermore, despite the differing pathophysiological mechanisms of ACS subtypes—such as chronic vascular stress and progressive atherosclerosis in UA versus acute plaque rupture and thrombosis in MI—studies specifically assessing RVOD risk across these subtypes remain scarce.

Managing low-density lipoprotein-cholesterol (LDL-C) levels in ACS patients has become a cornerstone strategy for preventing disease recurrence and systemic vascular complications. LDL-C targets in ACS patients are progressively being lowered, with recent guidelines recommending a target of less than 55 mg/dL for individuals with a history of ACS.[13,14] However, while the relationship between LDL-C levels and RVOD remains underexplored, particularly in individuals with prior cardiovascular events, some evidence suggests a significant increase in RVOD risk with elevated LDL-C levels.[15,16]

This study aimed to investigate the risk of RVOD following ACS, stratified by its subtypes, UA and MI, to explore potential differences in RVOD incidence based on their distinct pathophysiological characteristics. Additionally, it assessed the incidence of RVOD in relation to LDL-C levels, highlighting the importance of effective LDL-C control. By incorporating subtype-specific analysis, this study seeks to provide nuanced clinical guidance for maintaining retinal vascular health and preventing complications in ACS patients.

MATERIALS AND METHODS

This nationwide study, approved by the Institutional Review Board of Myongji Hospital (IRB NO. 2023-07-003-003), was conducted retrospectively using de-identified data, thus waiving the need for informed consent.

Data source

We utilized health claims data from 2002 to 2022 obtained from the National Health Information Database (NHID), managed by the National Health Insurance Service (NHIS) of South Korea. The NHID contains comprehensive data, including personal demographics, lifestyle information, health checkup results, and medical treatment records for the Korean population. For this study, a comprehensive cohort was constructed by integrating all available medical records and leveraging the nationally representative datasets provided by the NHIS.

Study population

Patients with MI diagnosed between January 2002 and December 2022 were identified using the most recent version of the Korean Classification of Disease codes, based on the International Classification of Diseases, from the NHID. To ensure accuracy, ACS cases were defined by the following criteria: 1) presence of a relevant diagnosis code (I20, I21.0–I21.4, I24); 2) undergoing an muscle and brain fraction of creatine kinase or troponin test at the first diagnosis (index date) of ACS; and 3) undergoing coronary angiography, percutaneous coronary intervention, or coronary artery bypass grafting. Patients with ACS were categorized into two main groups: UA and MI, including non-ST-segment elevation MI (NSTEMI) and ST elevation MI (STEMI). The index date was defined as the first date of ACS diagnosis or the first date of enrollment in the control group. A 2-year washout period (January 2002 to December 2003) was applied to exclude individuals with a prior history of ACS and to include only incident cases, in accordance with previous nationwide cohort studies using claims data.[17-19] The following exclusion criteria were applied: 1) age <20 years and 2) history of RVOD prior to the index date of ACS (UA/MI).

Among the entire cohort of ACS patients, individuals were classified into four groups based on the degree of LDL-C control: 1) excellent: LDL-C <55 mg/dL with ≥50% reduction from baseline; 2) good: 55 mg/dL ≤ LDL-C <70 mg/dL with ≥50% reduction from baseline; 3) suboptimal: 70 mg/dL ≤ LDL-C <100 mg/dL or <50% reduction from baseline; and 4) poor: LDL-C ≥100 mg/dL. The LDL-C reduction rate was calculated based on follow-up lipid panels performed within 2 years after the index ACS event. These cutoff values were determined in reference to the current guidelines, which emphasize more intensive LDL-C lowering in patients at very high cardiovascular risk, including those with ACS. The guidelines recommend achieving an LDL-C level of <55 mg/dL and a ≥50% reduction from baseline as optimal targets in this population.

The control cohort was selected from the NHID using a random number generator. For each ACS patient, ACS-free individuals with health checkup data were randomly sampled from the NHID and matched by age and sex. The same exclusion criteria were applied to both cohorts before matching.

For all participants, data on age, sex, type of insurance (as a proxy for income), medical visit records, dates of diagnosis and treatment, and comorbidity data were included in the analysis. Baseline characteristics, health checkup data, anthropometric measurements, and lifestyle questionnaires obtained within 2 years of the index date were incorporated into the final statistical analyses for both the ACS (UA/MI) and control groups.

Definition of outcomes and covariates

RVOD was identified as a potential outcome based on diagnostic codes confirmed by ophthalmologists.[20,21] The primary outcomes included: 1) entire RVOD (H34), including all retinal vascular obstructive conditions such as retinal microembolism; 2) retinal artery occlusion (RAO), defined by H340–2; and

3) retinal vein occlusion (RVO), defined by H348–9.

Covariates for RVOD, including demographics, lifestyle factors, and basic comorbidities, were included in the final analysis. The following variables were collected: 1) age; 2) sex (male or female); 3) income; 4) smoking status (none, former, or current); 5) alcohol consumption (no or yes); 6) presence of atrial fibrillation (AF); 7) body mass index (kg/m^2); 8) total cholesterol (mg/dL); 9) fasting glucose (mg/dL); and 10) systolic and diastolic blood pressure (mm Hg). These data were obtained through anthropometric measurements and lifestyle questionnaires using the NHIS System. The collected covariates were incorporated into the final regression model. Follow-up was censored at the end of the study period (December 31, 2022).

Statistical analysis

Data handling and statistical analyses were performed by an independent data analyst (J. L.) trained in big data analytics at the Health Insurance Review and Assessment Institute. Continuous variables were compared among the three groups using one-way analysis of variance, and categorical variables were analyzed using the chi-square test. Incidence rates of RVOD in the UA, MI, and control groups were evaluated using the log-rank test. Given the issue of competing risks, traditional survival methods such as Kaplan–Meier or Cox proportional hazards regression may yield biased survival estimates. Therefore, competing risk analysis was employed to estimate the cause-specific hazards of RVOD in the ACS group relative to the control group. Hazard ratios (HRs) were calculated after adjusting for covariates. Additionally, stratified analyses were conducted by sex and age (≤65 years vs. >65 years). All analyses were performed at a 95% confidence level and results are reported as mean±standard deviation. Statistical analyses were conducted using SAS Enterprise Guide version 6.1 (SAS Inc., Cary, NC, USA).

RESULTS

Baseline characteristics

After applying the washout periods and exclusion criteria, 55040 patients newly diagnosed with ACS and 55040 age- and sex-matched controls were included during the enrollment period (January 2004 to December 2022) (Fig. 1). The mean age was 64.0±9.0 years in the control group and 64.1±9.3 years in the ACS group. The proportion of male participants was 70.7% in the control group and 70.8% in the ACS group. The median follow-up duration was 10.8 years overall, 9.8 years in the ACS group, and 13.2 years in the control group. Within the ACS group, 49475 patients were diagnosed with UA, and 5565 patients were diagnosed with MI. Baseline characteristics of the ACS and control groups are compared in Table 1.

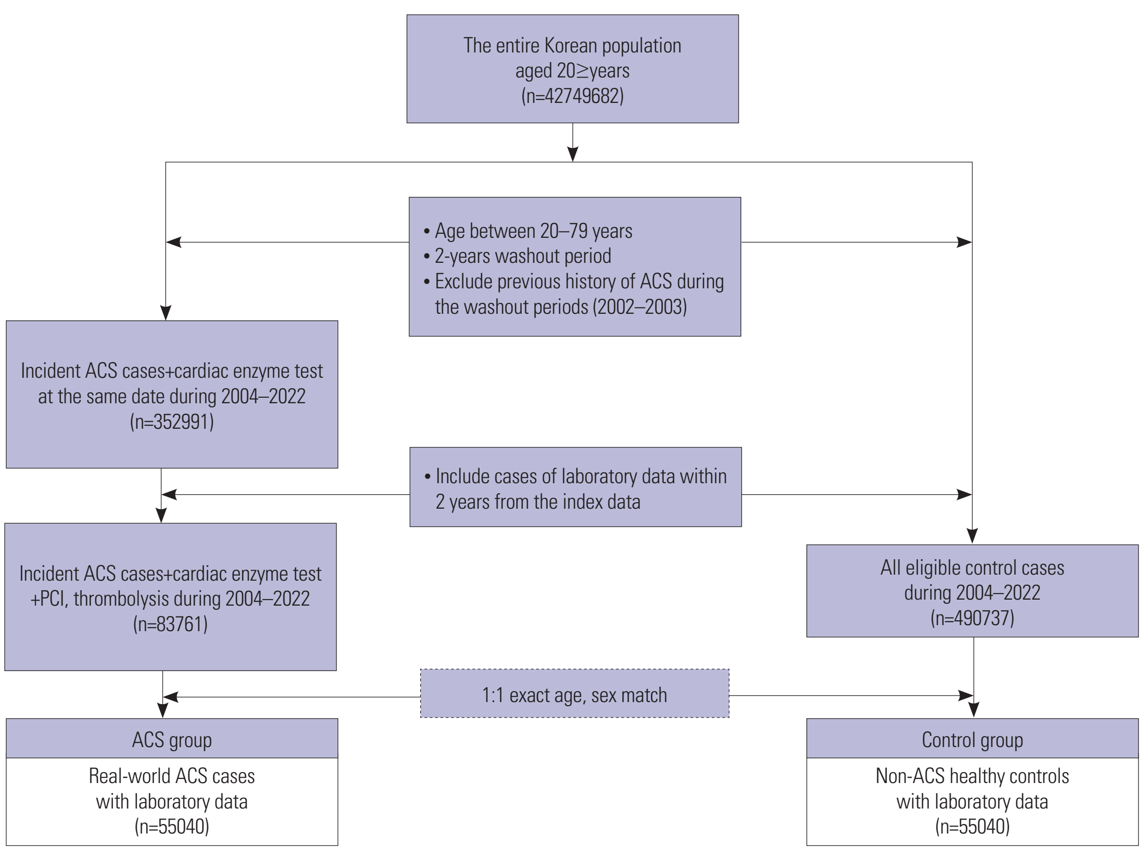

Fig. 1. Flow diagram of the cohort identification process. ACS, acute coronary syndrome; PCI, percutaneous coronary intervention.

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Table 1. Baseline Characteristics of Acute Coronary Syndrome Cohorts and the Control Group

Variables	Control cohort (n=55040)	UA cohort (n=49475)	MI cohort (n=5565)	*p*
Continuous variables				
Age (yr)	64.0±9.0	64.3±9.0	64.0±13.3	<0.001
BMI (kg/m^2)	23.55±17.39	24.77±3.02	24.58±3.00	<0.001
Systolic BP (mm Hg)	131.13±18.72	128.79±16.48	128.68±17.00	<0.001
Total cholesterol (mg/dL)	197.76±46.63	174.64±45.26	185.91±49.33	<0.001
HDL-C (mg/dL)	55.14±14.96	49.15±19.92	47.55±13.76	<0.001
LDL-C (mg/dL)	105.96±37.06	93.55±44.33	106.15±52.19	<0.001
Categorical variables				
Age group (yr)				
<65	25813 (46.9)	22683 (45.8)	3130 (56.2)	<0.001
≥65	29227 (53.1)	26792 (54.2)	2435 (43.8)	<0.001
Male sex	38950 (70.7)	34496 (69.7)	4453 (80.0)	<0.001
Smoking				
None	33579 (61.0)	26158 (52.8)	2443 (43.8)	<0.001
Former	5739 (10.4)	12836 (25.9)	1351 (24.3)	<0.001
Current	15725 (28.6)	8306 (21.3)	1575 (31.9)	<0.001
Alcohol consumption				
No	31899 (57.9)	32404 (65.4)	3534 (63.5)	<0.001
Yes	23141 (42.1)	17071 (34.6)	2031 (36.5)	<0.001
Income				
Upper	9470 (17.2)	7193 (14.5)	903 (16.2)	<0.001
Middle upper	10433 (18.9)	7067 (14.2)	834 (14.9)	<0.001
Middle lower	12111 (22.0)	10667 (21.6)	1321 (23.7)	<0.001
Lower	23026 (41.9)	23463 (49.7)	2399 (45.2)	<0.001
Atrial fibrillation	44 (0.001)	266 (0.005)	11 (0.001)	<0.001
Hypertension	10395 (18.8)	45899 (92.7)	4635 (83.2)	<0.001
Diabetes mellitus	7198 (13.0)	37330 (75.4)	3530 (63.4)	<0.001
Dyslipidemia	630 (1.14)	46686 (94.3)	4846 (87.1)	<0.001

UA, unstable angina; MI, myocardial infarction; BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol.
Data are presented as mean±standard deviation or n (%).

Table 2. Risk of Retinal Occlusive Diseases in Participants with Acute Coronary Syndrome Compared with Controls in the Established Cohort from the National Health Insurance Service Database of South Korea

Retinal diseases	Control cohort		UA cohort		MI cohort		HR_UA (95% CI)*	HR_MI (95% CI)*
	N of events	IR* (95% CI)	N of events	IR* (95% CI)	N of events	IR* (95% CI)		
RVOD	2059	283.67 (283.63–283.71)	2260	509.21 (509.14–509.28)	197	361.76 (361.60–361.92)	1.67 (1.56–1.79)	1.34 (1.15–1.56)
RAO	223	30.12 (30.11–30.13)	501	108.48 (108.45–108.51)	34	60.70 (60.64–60.76)	2.05 (1.69–2.50)	1.08 (0.66–1.78)
RVO	1450	198.44 (198.41–198.47)	2214	494.75 (494.68–494.82)	191	348.80 (348.64–348.96)	1.43 (1.31–1.56)	1.34 (1.11–1.63)

UA, unstable angina; MI, myocardial infarction; IR, incidence rate; CI, confidence interval; HR, hazard ratio; RVOD, retinal vascular occlusive disease; RAO, retinal artery occlusion; RVO, retinal vein occlusion.
*Adjusted for age, sex, body mass index, income, mortality, smoking, alcohol consumption, total cholesterol, systolic blood pressure, fasting glucose, and history of atrial fibrillation.

Risk of RVOD in each ACS group (UA/MI) compared to control group

During the follow-up period, total RVOD developed in 4516 (4.1%) patients across the entire cohort. In the UA group, 2260 (4.7%) patients developed total RVOD, 501 (0.7%) had RAO, and 2214 (4.5%) had RVO (Table 2). In the MI group, 197 patients (3.5%) had total RVOD, 34 (0.6%) had RAO, and 191 (3.4%) had RVO. The incidence rates (per 100000 person-years) were as follows: UA group, 509.21 for total RVOD, 108.48 for RAO, and 494.75 for RVO; MI group, 361.76 for total RVOD, 60.70 for RAO, and 348.80 for RVO; control group, 2059 (3.7%) patients developed total RVOD, 223 (0.4%) had RAO, and 1450

Table 3. Risk of Retinal Vascular Occlusive Disease in Patients with Acute Coronary Syndrome Compared with Controls, Stratified by Age Group and Sex, in the Established Cohort from the National Health Insurance Service Database of South Korea

Strata	Control cohort		UA cohort		MI cohort		HR_UA (95% CI)*	HR_MI (95% CI)*
	N of events	IR* (95% CI)	N of events	IR* (95% CI)	N of events	IR** (95% CI)		
RVOD according to age group (yr)								
Age <65	959	254.38 (254.33–354.43)	936	390.64 (390.56–390.72)	92	261.74 (261.57–261.91)	1.45 (1.31–1.60)	1.07 (0.86–1.34)
Age ≥65	1100	315.32 (315.26–315.38)	1324	648.34 (648.23–648.45)	105	543.87 (543.54–544.20)	1.79 (1.63–1.96)	1.53 (1.24–1.89)
RVOD according to sex								
Male	1350	265.88 (265.84–265.92)	1481	476.10 (476.02–476.18)	159	354.83 (354.66–355.00)	1.65 (1.51–1.79)	1.40 (1.18–1.66)
Female	709	325.09 (325.01–325.17)	779	586.81 (586.68–586.94)	38	393.98 (393.58–394.38)	1.65 (1.47–1.85)	1.16 (0.83–1.64)

UA, unstable angina; MI, myocardial infarction; IR, incidence rate; CI, confidence interval; HR, hazard ratio; RVOD, retinal vascular occlusive disease.
*Adjusted for age, sex, body mass index, income, mortality, smoking, alcohol consumption, total cholesterol, systolic blood pressure, fasting glucose, and history of atrial fibrillation.

(2.6%) had RVO, with incidence rates of 283.68, 30.12, and 198.44 per 100000 person-years for total RVOD, RAO, and RVO, respectively.

In the competing risk analysis adjusted for AF, the UA group demonstrated a higher risk than the control group for total RVOD [adjusted HR (aHR)=1.67; 95% confidence interval (CI): 1.56–1.79], RAO (aHR=2.05; 95% CI: 1.69–2.50), and RVO (aHR=1.43; 95% CI: 1.31–1.56). In the MI group, the risks were also elevated compared with the control group: total RVOD (aHR=1.34; 95% CI: 1.15–1.56) and RVO (aHR=1.34; 95% CI: 1.11–1.63). The mean interval between exposure and total RVOD diagnosis was 5.8±4.2 years in the UA group, 7.0±4.9 years in the MI group, and 9.2±4.9 years in the control group.

Stratified analysis according to age group and sex

The risk of total RVOD stratified by age group and sex in the ACS and control groups is presented in Table 3. Among individuals aged ≥65 years, the aHR for total RVOD was 1.79 (95% CI: 1.63–1.96) in the UA group and 1.53 (95% CI: 1.24–1.89) in the MI group, compared with the control group. In the younger age group, the aHR for total RVOD was 1.45 (95% CI: 1.31–1.60) in the UA group and 1.07 (95% CI: 0.86–1.34) in the MI group.

In the male population, the aHR for total RVOD was 1.65 (95% CI: 1.51–1.79) in the UA group and 1.40 (95% CI: 1.18–1.66) in the MI group, compared with the control group. In the female population, the aHR for total RVOD was 1.65 (95% CI: 1.47–1.85) in the UA group and 1.16 (95% CI: 0.83–1.64) in the MI group.

Risk of RVOD according to the LDL-C control groups in ACS patients

Based on LDL-C control, 2435 patients were categorized in the excellent group, 1467 in the good group, 16530 in the suboptimal group, and 6260 in the poor group. The baseline characteristics of each LDL-C group are detailed in Supplementary Table 1 (only online) (https://www.aaojournal.org).

The incidence rates for RVOD (per 100000 person-years) were: 491.89 in the excellent group, 486.57 in the good group, 560.02 in the suboptimal group, and 643.95 in the poor group compared with 283.66 in the control group. In the competing risk analysis, the aHR for total RVOD was 1.80 (95% CI: 1.44–2.15) in the excellent group, 1.85 (95% CI: 1.40–2.43) in the good group, 1.93 (95% CI: 1.74–2.13) in the suboptimal group, and 2.27 (95% CI: 2.00–2.58) in the poor group, compared with the control group (Fig. 2).

In the sub-analysis, the risk of total RVOD was also assessed across LDL-C control groups, using the excellent group as the reference (Table 4). Compared with the excellent group, the aHR for total RVOD was 1.02 (95% CI: 0.85–1.23) in the good group and 1.02 (95% CI: 0.86–1.22) in the suboptimal group, neither of which reached statistical significance (all $p>0.05$). In the poor group, the aHR for total RVOD was 1.24 (95% CI: 1.02–1.50) compared with the excellent group, indicating a statistically significant increased risk.

DISCUSSION

Herein, we found that the risk of RVOD remained elevated after all types of ACS and that the risk increased as the LDL-C levels remained uncontrolled after ACS. Several studies have demonstrated an association between the occurrence of RVOD following MI. This study stratified ACS into UA and MI to explore differences in RVOD risk based on their distinct pathophysiological mechanisms and associated vascular complications. UA, driven by chronic vascular stress and progressive atherosclerosis, is often linked to localized and systemic vascular inflammation.[22,23] In contrast, MI, primarily resulting from acute plaque rupture and thrombosis, is associated with systemic embolic events and acute ischemic complications, such as stroke.[24] Analysis of the association between RVOD and the mechanistic distinction of ACS subtypes was hypothesized to provide a deeper understanding of their respective vascular risks. This study was also based on the fact that tight LDL-C control should be recommended after the diagnosis of ACS and that vascular pathology caused by LDL-C can be associated

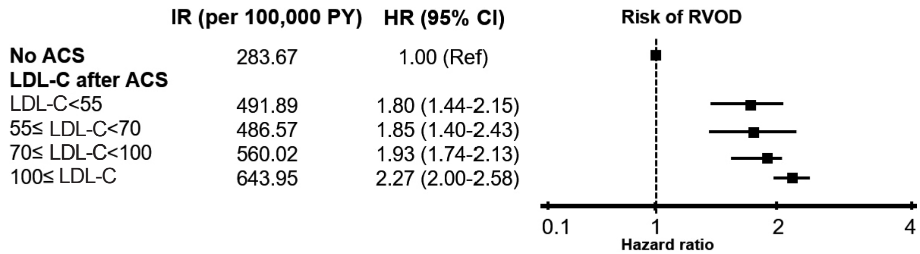

Fig. 2. Risk of RVOD in control and ACS cohorts according to LDL-C strata in the established cohort from the National Health Insurance Service database of South Korea. ACS, acute coronary syndrome; LDL-C, low-density lipoprotein cholesterol; CI, confidence interval; HR, hazard ratio; RVOD, retinal vascular occlusive disease.

Table 4. Risk of Retinal Vascular Occlusive Diseases in Control and ACS Cohorts according to LDL-C Strata in the Established Cohort from the National Health Insurance Service Database of South Korea

Group	N of events	PY per 100,000	IR (95% CI)	Adjusted HR† (95% CI)
LDL-C control after ACS*				
LDL-C<55	89	18093.46	491.89 (389.70–594.08)	1.00
55≤LDL-C<70	56	11508.99	486.57 (359.12–613.99)	1.02 (0.85–1.23)
70≤LDL-C<100	717	128029.09	560.02 (519.02–600.62)	1.02 (0.86–1.22)
100≤LDL-C	313	48605.65	643.95 (572.66–715.24)	1.24 (1.02–1.50)

ACS, acute coronary syndrome; PY, person-years; CI, confidence interval; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol.
*All units of LDL-C are expressed in mg/dL; †Adjusted for age, sex, body mass index, income, mortality, smoking, alcohol consumption, total cholesterol, systolic blood pressure, fasting glucose, and history of atrial fibrillation.

with RVOD.[15,25] Investigating whether RVOD varies with the degree of LDL-C management could provide meaningful insights. This study focused on the risk of RVOD after ACS, stratified by ACS type and LDL-C management level, addressing a significant gap in existing research.

We found that patients with ACS, including both UA and MI, had a higher risk of RVOD compared with the control group. RVOD and ACS share common pathophysiological mechanisms related to systemic vascular pathology, including atherosclerosis.[26-28] Additionally, endothelial dysfunction is a key pathophysiological mechanism that may contribute to a prothrombotic and proinflammatory state, impaired retinal vasodilation, vascular ischemia, and atherosclerotic changes.[29] Interestingly, the risks of RVO, RAO, and RVOD were consistently higher in the UA group than in the MI group. Although MI is generally considered more severe and is typically associated with acute plaque rupture and a robust systemic inflammatory response,[30] our findings suggest that UA—despite its less acute presentation—may confer a greater long-term risk of retinal vascular events. This could be explained by the older age and higher burden of chronic vascular comorbidities commonly observed in UA patients, as well as by the progressive nature of atherosclerosis in this group. Importantly, RVOD does not necessarily arise solely from overt vascular occlusion in the arterial or venous systems. Rather, it may reflect a broader spectrum of retinal microvascular dysfunction, including chronic endothelial injury, increased vascular stiffness, and impaired retinal hemodynamics. In particular, UA is often associated with longstanding systemic vascular stress, which may predispose patients to these non-occlusive forms of microvascular compromise. These mechanisms may underlie the consistently elevated HRs for RVOD observed in the UA group compared to both controls and MI patients. Furthermore, the correlation between RAO and UA differed from that observed in the MI cohort. The risk of RAO was not significantly higher in the MI group than in the control group, whereas RAO incidence was significantly higher in the UA group. RAO, another component of RVOD, is primarily caused by embolic sources originating from the carotid artery or heart.[31] AF is a leading cause of cardioembolic events. Our findings may be primarily attributed to the approximately fourfold higher prevalence of AF in the UA group compared to the MI and control groups. In addition, the possibility exists that meaningful results may not have been derived because of the significantly lower number of events in the MI group than in the UA group.

In a subgroup analysis, we did not observe an increased risk in the younger or female MI group. Younger MI patients are known to have a higher proportion of males and a lower prevalence of conventional risk factors such as diabetes mellitus (DM), hypertension, and dyslipidemia compared to older patients.[32] These chronic vascular conditions are closely associated with RVOD, which may explain why the risk of RVOD was not significantly elevated in young MI patients. Additionally, the proportion of males in the MI group was markedly higher than that in the UA and control groups, resulting in a smaller sample size of female patients with MI. This limited sample size may have contributed to the lack of statistical significance for RVOD risk in female MI patients.

Interestingly, the risk of RVOD in the ACS group was approximately 1.8 times higher than in the control group, even with successful LDL-C control (<55 mg/dL). Among all LDL-C control groups after ACS, the group with LDL-C levels >100 mg/dL demonstrated a significantly higher risk of RVOD compared to the group with LDL-C levels <55 mg/dL. Furthermore, there was a sequential increase in RVOD risk as LDL-C levels rose. The results of this study suggest that LDL-C levels should be maintained below 100 mg/dL to prevent RVOD after ACS. Controlling LDL-C levels is a fundamental treatment strategy for ACS. Current guidelines for LDL-C control after ACS recommend maintaining LDL-C levels below 70 mg/dL or 55 mg/dL in high-risk patients.[13,14] Although there are slight discrepancies among the guidelines, there is a trend toward lower target levels and stricter control recommendations. To reflect both earlier and more recent guidelines,[13,14,33] LDL-C levels were divided into four groups in this study. Our findings suggest that LDL-C control after ACS may be associated not only with reducing ACS recurrence but also with preventing complications such as RVOD. These results further support existing guidelines for lipid-lowering therapy and highlight its importance in preventing ophthalmological complications following ACS.

This study had several limitations. First, the total number of RAO cases among RVOD events was low because RAO is a rare condition, and all RAO cases prior to the index date of ACS diagnosis were excluded. Despite the limited number of events, analyzing the association between these conditions would have been more challenging without access to a large-scale dataset. Further studies are needed to confirm this hypothesis. Second, the mean age of the study and control groups was approximately 67 years, resulting in a large proportion of elderly individuals. Consequently, a high rate of loss to follow-up was observed in both the study and control groups. To mitigate potential imbalances, an exact age- and sex-matched control group was used. Third, NSTEMI, STEMI, and UA are traditionally recognized subtypes of ACS. However, with advancements in high-sensitivity cardiac troponin assays, the distinction between UA and NSTEMI has become less clear, leading to the classification of ACS as NSTE-ACS or STE-ACS, based on ECG findings. This retrospective study employed the traditional UA and MI (STEMI and NSTEMI) classification based on cardiac enzyme levels, reflecting the data collected before high-sensitivity assays were widely available. Finally, this study did not account for the angiographic complexity or severity of CAD in patients with ACS. Moreover, NSTEMI, STEMI, and UA are the traditional types of ACS. With advancements in high-sensitivity cardiac troponin assays, some cases now blur the line between UA and NSTEMI, leading to the classification of ACS as NSTE-ACS or STE-ACS based on ECG findings. In addition, since the primary therapeutic target in lipid management after ACS is LDL-C, the associations of other lipid parameters such as triglycerides and high-density lipoprotein-cholesterol with clinical outcomes were not assessed. Further studies are needed to explore these relationships.

In conclusion, this study provides valuable insights for clinical practice. RVOD occurred more frequently after ACS, regardless of subtype, and ACS remained a significant independent risk factor for RVOD. Our findings highlight that ocular complications capable of causing blindness remain a significant concern after ACS, particularly in patients with poor LDL-C control. In UA patients, elderly individuals (≥65 years), and male MI patients, additional caution is warranted. For ACS patients with embolic risk factors, sudden vision loss should prompt evaluation for potential RAO. Furthermore, active LDL-C control and regular ophthalmological follow-up are strongly recommended to prevent RVOD after ACS.

DATA AVAILABILITY STATEMENT

The authors are restricted from sharing the data underlying this study because the Korean National Health Insurance Service (NHIS) owns the data. Researchers can request access through the NHIS website (https://nhiss.nhis.or.kr). Details of this process and the provisional guide are available at http://nhiss.nhis.or.kr/bd/ab/bdaba000eng.do.

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AUTHOR CONTRIBUTIONS

Conceptualization: Ju-Yeun Lee and Minjeong Kim. Data curation: Ju-Yeun Lee. Formal analysis: Ju-Yeun Lee. Funding acquisition: Minjeong Kim. Investigation: all authors. Methodology: Ju-Yeun Lee and Minjeong Kim. Project administration: : Ju-Yeun Lee. Resources: Ju-Yeun Lee and Minjeong Kim. Software: Ju-Yeun Lee. Supervision: Ju-Yeun Lee, Ji Hyun Lee, Yun-Hyeong Cho, and Kunho Bae. Validation: all authors. Visualization: Ju-Yeun Lee and Minjeong Kim. Writing—original draft: Minjeong Kim. Writing—review & editing: Ju-Yeun Lee. Approval of final manuscript: all authors.

ORCID iDs

Minjeong Kim	https://orcid.org/0000-0002-4937-2126
Ji Hyun Lee	https://orcid.org/0000-0003-1831-6735
Yun-Hyeong Cho	https://orcid.org/0000-0001-7581-9545
Kunho Bae	https://orcid.org/0000-0001-7387-1315
Ju-Yeun Lee	https://orcid.org/0000-0001-7540-7129

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