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Risk of Retinal Vascular Occlusive Disease in Patients with Aortic Stenosis

A Nationwide Korean Cohort Study

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Objective: The intersection of aortic stenosis (AS) and retinal vascular occlusive disease (RVOD) underscores the need for comprehensive cardiovascular and ophthalmic evaluations in patients with either condition. We aimed to evaluate the risk of RVOD in the entire Korean population with AS.

Design: A population-based retrospective cohort study.

Participants: We included 4094 patients with AS (2088 males) and 4094 age-, sex-, and index year-matched controls. Clinical and follow-up data of all patients diagnosed with AS and healthy controls from 2004 to 2015 were extracted from the Korean National Health Insurance Claim database.

Methods: The risk of RVOD, including retinal vein occlusion and retinal artery occlusion, was compared between the AS and control groups. Competing analysis was used to obtain aHRs. The covariates used in the final analysis included age, sex, income, body mass index, fasting glucose, systolic blood pressure, cholesterol level, smoking, alcohol consumption, atrial fibrillation (AF), and myocardial infarction (MI).

Main Outcome Measures: Adjusted hazard ratio (aHR) of RVOD, incidence rate of RVOD.

Results: The incidence rate of RVOD per 100 000 was 495.3 in the AS group and 366.2 in the control group ($P < 0.001$). During a mean follow-up period of 8 years, the aHR of RVOD was 1.48 (95% confidence interval [CI]: 1.19–1.83) in the AS group compared with the control group. Even after adjusting for AF and MI, the incidence of RVOD remained consistently and significantly higher in patients with AS (aHR 1.29, 95% CI: 1.03–1.63). In the subgroup analysis based on age, the risk of RVOD was significantly higher in patients with AS across all age groups. However, this significance weakened after adjusting for MI in patients ≥80 years (aHR 7.47, 95% CI: 0.97–57.55) and for AF in patients ≥65 years (aHR 1.36, 95% CI: 0.92–2.03).

Conclusions: The results suggest a possible clinical association between AS and subsequent RVOD. Continuous screening for ≥5 years for RVOD would be recommended in patients with AS.

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Aortic stenosis (AS) is a condition where the aortic valve narrows, restricting blood flow from the left ventricle to the aorta. Its prevalence is rising in the aging population and is associated with significant mortality. Therefore, AS is increasingly recognized as an important medical condition today.[1,2] The pathogenesis of AS is multifactorial, including calcification and fibrosis of the aortic valve leaflets, as well as several conditions linked to vascular diseases, such as endothelial damage, inflammation of the vessel, and atherosclerosis.[3]

Retinal vascular occlusive diseases (RVODs) include 2 main conditions: retinal artery occlusion (RAO) and retinal vein occlusion (RVO).[4] Retinal artery occlusion is primarily caused by an embolus that can originate from atherosclerotic plaques in the carotid arteries or cardiac sources such as valvular heart diseases and arrhythmia.[5] Retinal vein occlusion is commonly associated with systemic conditions that affect the vascular endothelium and blood flow dynamics, such as hypertension, diabetes mellitus, and hyperlipidemia.[6] Both conditions can cause subsequent retinal hemorrhages, edema, and ischemia,[7,8] which can lead to irreversible vision loss if not treated promptly. Therefore, the development and management of RVOD is considered very important in the field of ophthalmology.

It has been reported that RVOD is significantly associated with cardiovascular diseases. Retinal vascular abnormalities are predictors of cardiovascular conditions such as coronary artery disease and heart failure. In addition, RVOD has significant associations with atrial fibrillation (AF) and myocardial infarction (MI).[9,10] Although there is limited research on RVOD risk in patients with valvular heart disease, RAO and RVO share common pathophysiological pathways with AS, particularly through systemic

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atherosclerosis or vascular injury caused by inflammation and oxidative stress.[11] The intersection of AS and RVOD underscores the need for comprehensive cardiovascular and ophthalmic evaluations in patients with either condition. Thus, we aimed to investigate the actual prevalence and risk of RVOD in patients with AS and to propose the shared mechanisms between the 2 conditions to provide targeted prevention and management strategies for treating these diseases.

Methods

This nationwide study was approved by the Institutional Review Board of Myongji Hospital (IRB No. 2023-07-001-001). The requirement for informed consent was waived owing to the retrospective study design and deidentified data.

Data Source

We accessed health claims from 2002 to 2022, recorded via the National Health Information Database (NHID) from the National Health Insurance Service of South Korea. The NHID records contained personal information, demographics, lifestyle questionnaires, health checkup data, and medical treatment data of the Korean population. In this study, we established an entire cohort by considering all medical records using nationally representative cohort data from the National Health Insurance Service.

Study Population

We extracted data from patients diagnosed with AS between January 2002 and December 2022 using the International Classification of Diseases code (I35) from the NHID. The definition for detecting AS cases in this study was the same as that in previous epidemiologic studies on AS in Korea.[12] Index date referred to the first enrollment date of study groups (first diagnosis date of AS or first date of controls). A 2-year washout period was applied to exclude a previous history of AS and to define newly diagnosed cases of AS (January 2002 and December 2003). The exclusion criteria were as follows: (1) age $<$20 years and (2) any history of AS before the index date of AS. A fixed-cohort design was used to ensure sufficient follow-up. All participants with AS first identified between January 2004 and December 2015 were enrolled in the established cohort and followed longitudinally. The controls were also retrieved from the NHID using a random number generator. For every patient with AS, AS-free individuals with health checkup data were randomly sampled from the NHID and matched by age and sex. The same exclusion criteria were applied before matching the AS group.

In the subanalysis, among the AS group, to evaluate the risk of RVOD depending on whether aortic valve replacement (AVR) was performed, patients identified as undergoing a treatment code of AVR (O1793, O1799) were identified within the AS group. Patients who underwent AVR before the development of RVOD during the study period were classified into the AVR group, and those who did not undergo AVR before the development of RVOD were classified into the non-AVR group.

For all participants in this study, data on age, sex, type of insurance for income, records of medical visits, date of diagnosis and treatment, and comorbidities were obtained. The baseline characteristics, health checkup data, anthropometric measurements, and lifestyle questionnaires of the AS and control groups, which were obtained within 2 years based on the index date, were included in the final statistical results.

Definition of Outcomes and Covariates

Retinal vascular occlusive disease was identified based on the diagnostic codes confirmed by ophthalmologists as possible outcomes.[13,14] The primary outcomes were as follows: (1) entire RVOD (H34), including all retinal vascular obstructive problems, such as retinal microembolism, (2) RAO (H340-2), and (3) RVO (H348-9). The covariates for RVOD, including demographics, lifestyle, and basic comorbidities, were included in the final analysis. The following covariates were collected: (1) age, (2) sex (male or female), (3) body mass index, (4) income (quartiles), (5) death, (6) smoking (none, former, or current), (7) alcohol consumption (no or yes), (8) total cholesterol and fasting glucose, (9) systolic blood pressure, and (10) the presence of AF or MI. Data were collected based on anthropometric measurements and lifestyle questionnaires using the National Health Insurance Service system. Covariates were used in the final regression model. Follow-up was censored at the end of this study (December 31, 2022).

Statistical Analysis

Data handling and statistical analyses were performed by an independent data analyst (J.-Y.L.) specially trained by the Health Insurance Review and Assessment Institute for big data.[15] Continuous variables were compared between the groups using the Wilcoxon rank-sum test, and the comparison of the proportion of each variable between the groups was analyzed using the chi-square test. In the presence of competing risks, traditional survival analysis, such as the Kaplan−Meier method or Cox proportional hazard regression, introduces biases into the estimation of survival probability. Therefore, regarding the competing risks of death in patients with AS, we used competing analysis to estimate the cause-specific hazard of RVOD in the AS group compared with the control group. The covariates mentioned earlier were adjusted to compute the hazard ratios of RVOD in the final analysis. Herein, different models were set up to reflect various combinations of AF and MI, and each adjusted hazard ratio (aHR) with 95% confidence interval (CI) is presented. Stratified analysis was additionally performed according to sex and age group based on the age of 80 years (very old age). A 95% confidence level was used for this analysis. All results are presented as mean ± standard deviation. SAS Enterprise Guide version 6.1 software (SAS Inc) was used for all the analyses.

Results

Baseline Characteristics

After considering the washout periods and exclusion criteria, 4094 patients were newly diagnosed with AS, and 4094 age- and sex-matched individuals were finally included during the enrollment period (January 2004 and December 2015) (Fig S1, available at www.ophthalmologyscience.org). The mean age of the patients in each group was 66.8 ± 10.1 years, and 2088 (51%) were males. The median follow-up duration was 10.3 years, comprising 9.9 years in the AS group and 10.7 years in the control group. Within the AS group, 1527 patients (37.3%) underwent AVR treatment before the development of RVOD. The baseline characteristics were compared between the AS and control groups (Table 1).

Risk of RVOD in Patients with AS Compared with Controls

During the follow-up period, RVOD developed in 353 (8.6%) patients in the entire cohort. The mean age at development of total RVOD was 72.2 ± 9.6 years in the AS group and 75.1 ± 8.5 years in the control group, with significant differences ($P < 0.001$). In the AS group, 194 (4.7%), 30 (0.7%), and 119 (2.9%) cases of total RVOD, RAO, and RVO, respectively, newly occurred. The incidence rates per 100 000 person-years were 495.32, 73.28, and 297.98, respectively. In the control group, 159 (3.9%), 13 (0.3%), and 94 (2.2%) cases of total RVOD, RAO, and RVO, respectively, newly occurred. The incidence rates per 100 000 person-years were 366.21, 29.20, and 214.69, respectively (Table 2).

In multivariate competing analysis without AF or MI, the risk (aHR, 95% CI) of total RVOD (1.48, 1.19−1.83), RAO (2.54, 1.31−4.90), and RVO (1.47, 1.12−1.93) were all significantly higher in the AS group than in the control group. When only AF was added as a variable, the AS group had a higher risk of RVOD (1.45, 1.16−1.83), RAO (2.21, 1.06−4.26), and RVO (1.53, 1.14−2.05) than the control group. However, when MI was added as a variable, the significance of AS in RAO and RVO was attenuated, except for RVOD (1.34, 1.06−1.69). When both AF and MI were added, only the risk of total RVOD (1.29, 1.03−1.63) was significantly higher in the AS group than in the control group.

The mean interval between exposure and total RVOD was 6.3 ± 4.5 years in the AS group and 8.6 ± 4.8 years in the control group. Incidence rate ratios (IRRs) for total RVOD according to the follow-up periods are presented in Figure 1. Based on the index date, IRR (95% CI) of total RVOD was 2.40 (1.89−2.88) within 1 year, 2.54 (2.06−3.13) from 1 to 3 years, 2.21 (1.79−2.73) from 3 to 5 years, and 0.98 (0.80−1.22) after 5 years.

Stratified Analysis According to Age Group

The risk of total RVOD stratified according to age group in the AS and control groups is shown in Table 3. In the very elderly patient group (≥80 years), the incidence rate of total RVOD was 868.72 in the AS group and 105.61 in the control group. In multivariate Cox analysis without AF or MI, the aHR (95% CI) of total RVOD was 9.95

Table 1. Baseline Characteristics of Aortic Stenosis and Control Cohorts

Variable	Aortic Stenosis (N = 4094)	Control (N = 4094)	*P* Value
Age (yrs, SD)	66.76 + 10.14	66.76 + 10.14	0.999
Age group (N, %)			
<65	1423 (34.8)	1423 (34.8)	0.999
65 to 80	2451 (59.8)	2451 (59.8)	0.999
≥80	220 (5.4)	220 (5.4)	0.999
BMI (kg/m2)	24.28 + 3.31	23.49 + 3.32	<0.001
Male sex (N, %)	2088 (51.0)	2088 (51.0)	0.999
Systolic BP (mmHg)	129.88 + 17.98	131.99 + 18.83	<0.001
Smoking (N, %)			<0.001
None	2767 (69.9)	2884 (70.4)	
Former	643 (16.2)	329 (8.0)	
Current	550 (13.9)	881 (21.5)	
Alcohol consumption (N, %)			<0.001
No	2968 (74.7)	2912 (71.1)	
Yes	1003 (25.3)	1182 (28.9)	
Income (N, %)			<0.001
Upper	588 (14.7)	1257 (30.7)	
Middle upper	605 (15.1)	965 (23.6)	
Middle lower	863 (21.6)	784 (19.2)	
Lower	1941 (48.6)	1088 (26.6)	
Atrial fibrillation (N, %)	60 (1.5)	12 (0.3)	<0.001
Hypertension (N, %)	3383 (82.6)	1455 (35.5)	<0.001
Diabetes mellitus (N, %)	2359 (57.6)	977 (23.9)	<0.001
Dyslipidemia (N, %)	2995 (73.2)	800 (19.5)	<0.001
Myocardial infarction (N, %)	175 (4.3)	9 (0.2)	<0.001
Total cholesterol (mg/dL)	191.12 + 42.14	198.12 + 41.43	<0.001
HDL cholesterol (mg/dL)	51.92 + 15.83	51.90 + 15.69	<0.001
LDL cholesterol (mg/dL)	110.52 + 6.88	112.48 + 40.44	<0.001
Creatinine (mg/dL)	1.07 + 0.98	0.95 + 0.63	<0.001
CCI			<0.001
0	425 (10.4)	995 (24.4)	
1	548 (13.4)	692 (17.0)	
≤2	3121 (76.2)	2384 (58.6)	

BMI = body mass index; BP = blood pressure; CCI = Charlson Comorbidity Index; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SD = standard deviation.

Table 2. Risk of Retinal Vascular Occlusive Disease in Participants with Aortic Stenosis Compared with Controls in the Established Cohort from the National Health Insurance Service Data of South Korea

Retinal Disease	Aortic Stenosis		Control		HR (95% CI)*	HR (95% CI)†	HR (95% CI)‡	HR (95% CI)§
	Number of Events	*IR*¶ *(95% CI)*	*Number of Events*	*IR*¶ *(95% CI)*				
RVOD‖	194	495.32 (429.26–568.47)	159	366.21 (328.01–448.74)	1.48 (1.19–1.83)	1.45 (1.16–1.83)	1.34 (1.06–1.69)	1.29 (1.03–1.63)
RAO	30	73.28 (47.15–99.40)	13	29.20 (14.52–48.99)	2.54 (1.31–4.90)	2.21 (1.06–4.26)	1.34 (0.53–3.37)	1.34 (0.53–3.37)
RVO	119	297.98 (239.21–342.13)	94	214.69 (183.72–275.48)	1.47 (1.12–1.93)	1.53 (1.14–2.05)	1.33 (0.99–1.80)	1.33 (0.99–1.80)

BMI = body mass index; CI = confidence interval; HR = hazard ratio; IR = incidence rate; RAO = retinal artery occlusion; RVO = retinal vein occlusion; RVOD = retinal vascular occlusive disease.
*Adjusted for age and sex. BMI, income, death, smoking, alcohol consumption, total cholesterol, blood pressure, and fasting glucose.
†Adjusted for age and sex. BMI, income, death, smoking, alcohol consumption, total cholesterol, blood pressure, fasting glucose, and history of atrial fibrillation.
‡Adjusted for age and sex. BMI, income, death, smoking, alcohol consumption, total cholesterol, blood pressure, fasting glucose, and history of myocardial infarction.
§Adjusted for age and sex. BMI, income, death, smoking, alcohol consumption, total cholesterol, blood pressure, fasting glucose, history of myocardial infarction, and atrial fibrillation.
‖Entire RVOD includes all retinal vascular obstructive problems including RAO, RVO, and retinal microembolism.
¶Per 100 000.

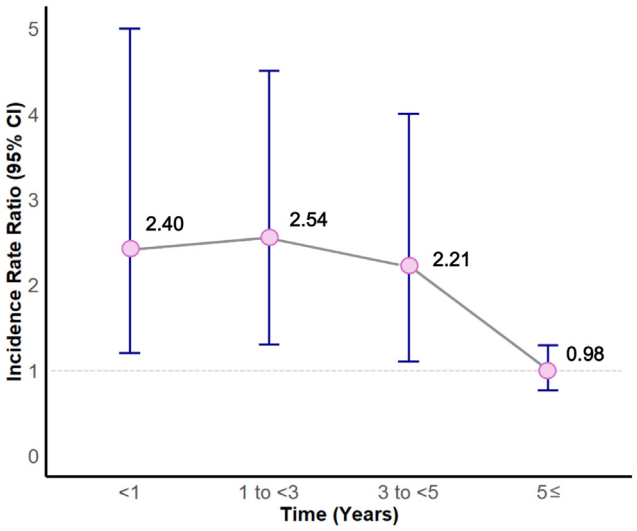

Figure 1. Incidence rate ratios for total retinal vascular occlusive disease in the aortic stenosis and control groups according to the follow-up periods. CI = confidence interval.

(1.53−64.73) in the AS group. When adding only AF as a covariate, the aHR of total RVOD was 9.84 (1.45−66.80) in the AS group, but the significance of AS for RVOD was attenuated when MI was added. In the younger age group (<65 years), the incidence rate of total RVOD was 459.68 in the AS group and 315.52 in the control group. In the analysis without AF or MI, the aHR of total RVOD was 1.71 (1.16−2.52) in the AS group. When adding only MI, the aHR of total RVOD was 1.72 (1.17−2.54) in the AS group; however, the significance of AS was attenuated when AF was added as a covariate.

Subanalysis: Risk of RVOD According to the Performance of AVR

The results of the subanalysis according to the performance of AVR in the AS group are presented in Table 4. The aHRs (95% CI) of total RVOD, RAO, and RVO were 0.86 (0.62−1.17), 0.50 (0.22−1.14), and 0.99 (0.67−1.48), respectively, in the AVR group compared with the non-AVR group. All showed aHR values in the direction of protection in the AVR group but were not statistically significant (all $P > 0.05$).

Discussion

While AS is known to be associated with various systemic vascular problems,[16–18] its relationship with RVOD has not been well evaluated. This is the first to elucidate the relationship between AS and RVOD. Aortic stenosis contributes to RVOD through distinct mechanisms independent of traditional vascular risk factors like hypertension, atherosclerosis, and diabetes mellitus. Chronic hemodynamic overload from AS induces systemic circulatory dysfunction and localized ischemia, making microvascular systems such as retinal vessels particularly vulnerable. Additionally, the

Table 3. Risk of Retinal Vascular Occlusive Disease in Participants with Aortic Stenosis Compared with Controls According to Age in the Established Cohort from the National Health Insurance Service Data of South Korea

	Aortic Stenosis		Control				
RVOD	*Number of Events*	*IR*‖ (95% *CI*)	*Number of Events*	*IR*‖ (95% *CI*)	HR (95% CI)*	HR (95% CI)†	HR (95% CI)‡	HR (95% CI)§
Age ≥80	10	868.72 (850.45–886.99)	2	105.61 (91.37–119.85)	9.95 (1.53–64.73)	9.84 (1.45–66.80)	7.47 (0.97–57.55)	1.41 (0.94–2.10)
Age <65	81	459.67 (455.00–464.34)	55	315.53 (310.84–320.22)	1.71 (1.16–2.52)	1.36 (0.92–2.03)	1.72 (1.17–2.54)	4.93 (0.49–49.46)

BMI = body mass index; CI = confidence interval; HR = hazard ratio; IR = incidence rate; RVOD = retinal vascular occlusive disease.
*Adjusted for age and sex. BMI, income, death, smoking, alcohol consumption, total cholesterol, blood pressure, and fasting glucose.
†Adjusted for age and sex. BMI, income, death, smoking, alcohol consumption, total cholesterol, blood pressure, fasting glucose, and history of atrial fibrillation.
‡Adjusted for age and sex. BMI, income, death, smoking, alcohol consumption, total cholesterol, blood pressure, fasting glucose, and history of myocardial infarction.
§Adjusted for age and sex. BMI, income, death, smoking, alcohol consumption, total cholesterol, blood pressure, fasting glucose, history of myocardial infarction, and atrial fibrillation.
‖Per 100 000.

progression of AS involves chronic inflammation and elevated cytokines (e.g., interleukin 6 and tumor necrosis factor alpha),[19,20] worsening endothelial dysfunction and vascular damage. Recent studies highlight that AS is an actively regulated process involving oxidative stress, endothelial dysfunction, inflammation, and biomechanical stress rather than a purely degenerative condition.[21–24] Calcified valves contribute to retinal vascular occlusion, particularly RAO, through micro-emboli formation.[4–6] Even after adjusting for major cardiovascular risk factors such as MI and AF, AS remains an independent risk factor for RVOD. Moreover, conventional atherosclerosis treatments, including statins and antihypertensives, have not been effective in slowing AS progression,[25] underscoring the need for a deeper understanding of its pathophysiology, including chronic inflammation, endothelial interactions, and mechanical stress.[22]

When analyzing RAO and RVO separately, the significance of AS in RAO was attenuated after adjusting for MI but remained significant after adjusting for AF. This is likely because atherosclerosis is more closely associated with coronary artery disease, which appears earlier and serves as a more definitive and stronger surrogate marker than AS in RAO. Another potential possibility is combining carotid atherosclerosis in patients with MI, which is a possible source of embolism in RAO. In RVO, the *P* value was marginal after adjusting for MI, suggesting a complex and multifactorial influence on the development of RVO in AS, not just systemic atherosclerosis. However, due to the rarity of RVOD, the sample size was relatively small, even in this nationwide cohort study, which may have influenced the significance of the results. Thus, we combined them and focused on total RVOD to avoid bias in the results due to small sample size.

The IRR of RVOD in the AS group remained over 2 compared with the control group for up to 5 years after the initial diagnosis. However, after 5 years, the difference in IRR between the 2 groups disappeared. This could be due to the higher mortality, comorbidities, older age, and higher follow-up loss rates in patients with AS, not just from the vanished influence of AS on RVOD. To support the findings of this study and better understand the relationship between AS and RVOD, future research is needed to investigate the risk of RVOD according to the severity of AS or the effects of pharmacological treatments, as well as the physiological associations through the assessment of inflammatory cytokines or coagulation factors related to AS and RVOD.

In the age-based subgroup analysis, the incidence of RVOD in the very old age group (≥80 years) was approximately 10 times higher in the AS group than in controls, even after adjusting for age. This difference remained significant after adjusting for AF but was attenuated after adjusting for MI. In the younger group (<65 years), the RVOD incidence was about 1.7 times higher in the AS group, remaining significant after MI adjustment but attenuated after AF adjustment. These findings suggest that key cardiovascular risk factors for RVOD vary by age group, reflecting different underlying pathophysiology. In those ≥80 years of age, MI appears to be a stronger contributor to RVOD than AF, indicating atherosclerosis as the main mechanism. While the role of statins in AS is uncertain,

Table 4. Risk of Retinal Vascular Occlusive Disease in Participants with Aortic Stenosis Who Received AVR Compared with Non-AVR in the Established Cohort from the National Health Insurance Service Data of South Korea

Retinal Disease	AVR Group		Non-AVR Group		HR (95% CI)*
	Number of Events	*IR‡ (95% CI)*	*Number of Events*	*IR‡ (95% CI)*	
RVOD†	85	514.54 (509.70–519.40)	109	481.30 (477.20–485.40)	0.86 (0.62–1.17)
RAO	10	73.28 (68.00–78.60)	20	29.20 (26.85–31.60)	0.50 (0.22–1.14)
RVO	55	297.98 (294.88–301.08)	64	241.69 (238.55–244.84)	0.99 (0.67–1.48)

AVR = aortic valve replacement; BMI = body mass index; CI = confidence interval; HR = hazard ratio; IR = incidence rate; RAO = retinal artery occlusion; RVO = retinal vein occlusion; RVOD = retinal vascular occlusive disease.
*Adjusted for age and sex. BMI, income, death, smoking, alcohol consumption, total cholesterol, blood pressure, and fasting glucose.
†Entire RVOD includes all retinal vascular obstructive problems including RAO, RVO, and retinal microembolism.
‡Per 100 000.

their use may be justified in very elderly AS patients to prevent RVOD by slowing atherosclerosis. In patients <65 years of age, AF had a greater impact than MI, suggesting embolic mechanisms may be more prominent. This group likely includes more patients with mild to moderate AS, reducing the impact of hemodynamic changes. Additionally, younger AS patients are more likely to have rheumatic or bicuspid aortic valve disease, often accompanied by mitral valve involvement. Given the higher prevalence and impact of AF in AS patients <65 years of age, regular electrocardiogram or Holter monitoring may be recommended to prevent RVOD.

Previous studies have shown that carotid intima-media thickness significantly decreases and coronary flow reserve improves after AVR in patients with AS.[26,27] However, the preventive effect of AVR on AS-related vascular diseases remains unclear. Although the AVR group tended to have a lower risk of RVOD, this was not statistically significant. Aortic valve replacement is generally performed in severe AS to correct hemodynamic load and eliminate calcium embolism sources. Several explanations may account for the findings: RVOD development in severe AS may be more influenced by irreversible systemic factors such as age, diabetes, hypertension, dyslipidemia, endothelial dysfunction, vessel inflammation, and atherosclerosis than by hemodynamic changes, which show limited improvement post-AVR. Additionally, even if retinal vascular function improves after AVR, its impact on disease progression may be minimal. The small sample size may also have limited statistical significance. Further studies are needed to verify it.

The current study is meaningful in that we attempted to adjust as thoroughly as possible to investigate the independent effect of AS on RVOD. Consequently, there was a high rate of loss to follow-up and mortality. Lastly, the NHID data were based on registered diagnoses from medical clinics or hospitals, and there could have been a considerable number of patients with undiagnosed RVOD.

There are several limitations. First, we could not obtain information on AS severity. Therefore, the linear relationship between AS severity and RVOD occurrence was not calculated. In addition, although AF and MI were included as confounders, information on other important vascular risk factors such as atherosclerosis, carotid artery disease, coagulopathy, and medication use was not available. Future studies should include these variables to further clarify the relationship between AS and RVOD. Second, the number of RVOD events was small, with even fewer RAO occurrences, resulting in borderline statistical significance. This is because the incidence rates of AS and RVOD are low, and RAO is particularly rare. Despite the few events, analyzing the association between these conditions would be even more challenging without a big data study. Third, AS primarily occurs in the elderly population. The mean age of the study and control groups was approximately 67 years and included a large proportion of elderly individuals. In the AVR subgroup analysis, selection bias may be present, as surgical patients were generally younger and healthier, while most were expected to have severe AS. Fourth, rather than focusing solely on the diagnosis of specific conditions such as hypertension, hyperlipidemia, or diabetes, we aimed to incorporate a concept that reflects how well these conditions are managed by including blood pressure and related laboratory data. While it is true that there were limitations in selecting adjustment factors due to the use of health screening data, many previous studies on RVOD and cardiac diseases did not apply comprehensive adjustments. In addition, the study included patients with AS diagnosed between 2004 and 2015 with a mean follow-up of 8 years. Given recent advances in cardiovascular risk management and the increasing incidence and diagnosis of AS, caution should be exercised when interpreting the results in the context of contemporary clinical practice.

In conclusion, we found that RVOD occurs more frequently in patients with AS than in those without AS. Based on our results, patients with AS and their physicians should be informed of the potential association with retinal vascular dysfunction and advised to promptly consult an ophthalmologist if visual symptoms develop ≥5 years after AS diagnosis, and it can be important to prevent atherosclerosis to preclude RVOD in very elderly patients with AS.

Footnotes and Disclosures

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No animal subjects were used in this study.

Author Contributions:

Conception and design: Lee, Kim, Choi

Data collection: Lee

Analysis and interpretation: Lee, Kim, Bae

Obtained funding: Kim

Overall responsibility: Lee, Kim, Choi, Bae

Abbreviations and Acronyms:
AF = atrial fibrillation; **aHR** = adjusted hazard ratio; **AS** = aortic stenosis; **AVR** = aortic valve replacement; **CI** = confidence interval; **IRR** = incidence rate ratio; **MI** = myocardial infarction; **NHID** = National Health Information Database; **RAO** = retinal artery occlusion; **RVO** = retinal vein occlusion; **RVOD** = retinal vascular occlusive disease.

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