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Similarities and Differences in Systemic Risk Factors for Retinal Artery Occlusion and Stroke: A Nationwide Case-Control Study

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Background: Retinal artery occlusion (RAO) has been considered a stroke equivalent. This study compares risk factor profiles for thromboembolism among patients with RAO and stroke, respectively. *Methods:* This case-control study is based on 5683 RAO patients entered in the Danish National Patient Register between 1st of January 2000 and 31st of December 2018. Cases were matched on sex, year of birth, and age at event with 28,415 stroke patients. The Danish nationwide registries were used to collect information about age, sex, previous diagnoses, and drug prescriptions. Adjusted conditional logistic regression models were used to investigate the association between hypothesised risk factors and the patient outcome. *Results:* For atrial fibrillation, a substantially stronger association to stroke was found, with an odds ratio (OR) of 0.52 (95% CI: 0.47-0.58) when comparing RAO patients with stroke patients. RAO was stronger associated with arterial hypertension, peripheral artery disease, retinal vein occlusion, cataract, and glaucoma with OR's ranging from 1.21-11.70. The identified effect measures reached equivalence or was close to equivalence for diabetes, heart failure, ischemic heart disease, and renal disease. *Conclusion:* The differences in risk factor profiles between RAO and stroke suggests differences in the pathophysiology of the two diseases. These variations in pathophysiologies between the two diseases may indicate that different interventions are needed to ensure the optimal long-term prognosis for the patients.

Keywords: Retinal artery occlusion—Stroke—Epidemiology—Risk factors—Pathophysiology

Introduction

Retinal artery occlusion (RAO) has a number of characteristics in common with ischemic stroke.[1,2] Embolism is a potential cause of RAO, and the emboli have been categorized according to their composition and origin. The emboli can be composed of cholesterol, platelet-fibrin, or calcific.[3,4] Retinal emboli most frequently originate from the aortic valves in the heart or from plaques in the carotid artery.[3] Overall, this corresponds to the pathophysiology described in the existing literature for embolic stroke,[5] but it is unknown whether the two manifestations of embolism share common risk factors.

RAO is categorized according to the location of the occlusion as a central retinal artery occlusion (CRAO) or a branch retinal artery occlusion (BRAO). The incidence rate of RAO is generally low and because of the potentially transient nature of RAO the rate may generally be

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underestimated.[6] The incidence rate has been determined to be 1.8-1.9 per 100.000 person years for CRAO, symptomatic BRAO have an lower rate.[7,8] The incidence of RAO increases with age and mainly affects middle aged and elderly people.[9] The overall incidence rate of stroke is 17.7 per 1000 person-years,[10] which is much higher than for RAO. The incidence rate of stroke differs for different types of stroke and similarly to RAO the incidence rate increases with age.[11,12]

Aims and/or hypothesis

The purpose of the present study was to use nationwide register data to study similarities and differences between systemic and ocular risk factors for developing RAO or stroke. The identification of such risk factors requires larger data sets that can be obtained from nationwide registry data.

Methods

Registry Data sources

The data used in this study were extracted from three Danish nationwide registers. Data concerning date of birth, sex, vital status, migration, and date of death were collected from the Danish Civil Registration System.[13] Information about hospital admissions in the Danish public health system was identified in the Danish National Patent Register (DNPR), including diagnoses, procedures, patient category (hospitalized or outpatient), and diagnosis type (primary or secondary diagnoses). The DNPR was established in 1977 [14] and with diagnoses coded using the International Classification of Diseases version 10 (ICD-10) since 1997. The Danish National Prescription Registry contains information about all drug prescriptions sold in the Danish pharmacies,[15] using the global Anatomical Therapeutic Chemical classification (ATC) code. Data from the different registries were cross-linked, using the personal identification number held by all Danish residents.

Study population

This study was a case-control study. The case population consisted of all RAO patients, both inpatients and outpatients, with a first-time hospital diagnosis of RAO. The diagnoses were collected from the DNPR using the ICD-10 codes H340, H341, and H342. The control population consisted of patients with incident acute ischemic stroke identified in the DNPR with the ICD-10 codes I63 and I64. These ICD-10 codes included both hemispheric and subcortical ischemia. Each RAO case was matched with 5 stroke controls of the same sex and with both date of birth and date of diagnosis within 1 year from that of the case. All ICD-10 and ATC codes used to identify the population, risk factors and other variables are summarized in Table 1.

The selection process for both the case and the control populations are visualized in the flowchart in Fig. 1. The inclusion period was from January 1st 2000 through December 31st 2018. The exclusion criteria for both populations included inconsistent information in the Danish Civil Registration System or age below 18 years at the index date. Furthermore, controls were excluded from the population if they had received a RAO diagnosis before their matched index date.

Exposure

Potential risk factors for RAO and stroke were identified from the literature,[7,16,25–29,17–24] and included atrial fibrillation, diabetes, heart failure, arterial hypertension, ischemic heart disease, peripheral artery disease, retinal vein occlusion, renal disease, cataract, and glaucoma. All exposures were identified using ICD-10 codes in the DNPR or ATC codes in the Danish National Prescription

Table 1. *ICD 10 and ATC codes used in this study.*

Disease	ICD 10 & ATC codes
Retinal artery occlusion	H340 H341 H342
Stroke	I63 I64
Atrial fibrillation	I48
Cataract	H25 H26 H281 H282
Diabetes	E100 E101 E109 E110 E111 E119 A10
Glaucoma	H40 H42
Heart failure	I 110 I130 I132 I420 I50 I501 I509 C03C C09
Arterial hypertension	C02A C02B C02C C02DA C02L C03A C03B C03D C03EA C03 X C07C C07D C08G C09BA C09DA C09XA52 C02DB C02DD C02DG C04 C05 C07 C07F C08 C09BB C09DB C09
Ischemic heart disease	I20 I21 I23 I24 I25
Peripheral arterial disease	I70 I71 I72 I73 I74 I77
Retinal vein occlusion	H348
Renal disease	I12 I13 N00 N01 N02 N03 N04 N05 N07 N11 N14 N17 N18 N19 Q61

Abbreviations: ICD, International Classification of Diseases; ATC, Anatomical Therapeutic Chemical classification.

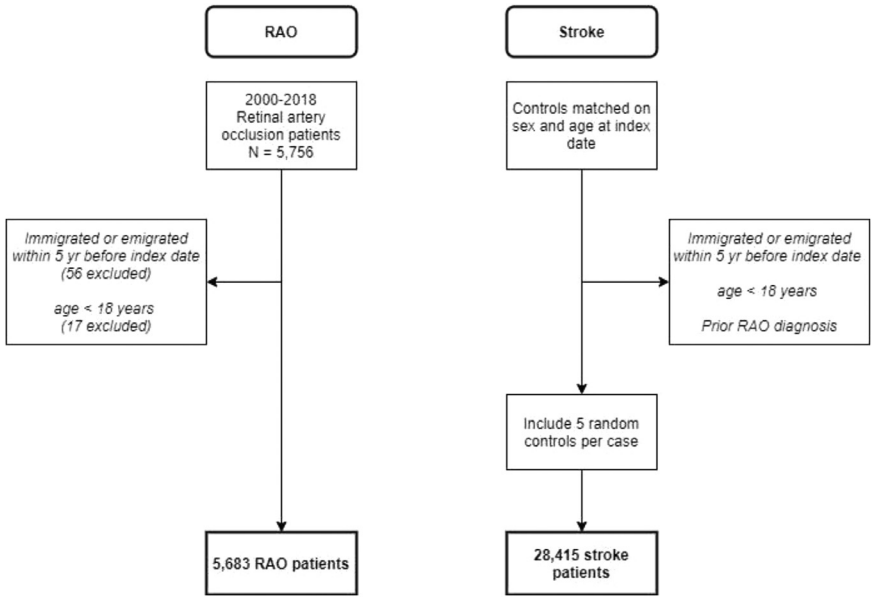

Fig. 1. *Patient flow-chart*
Abbreviations: RAO, retinal artery occlusion.

Registry. A study subject was defined as exposed if a diagnosis or prescription had been registered within 5 years prior to the index date. The diagnosis of arterial hypertension required at least two prescriptions of antihypertensive drugs.

Statistical analyses

Baseline characteristics for both the case and the control population were described using proportions for categorical measures and means, including standard deviations, for continuous measures.

Each exposure was investigated as a risk factor for RAO using conditional logistic regression with RAO patient id defining the match group. The reported OR were adjusted for sex, age at index date, and other potential confounders present prior to index date. Adjustments were based on knowledge from existing literature,[16,18,19,21,24,25] where potential confounders of the association between each exposure and RAO were identified. The models were adjusted for atrial fibrillation, ischemic heart disease, diabetes, heart failure, arterial hypertension, renal disease, cataract, glaucoma, and retinal vein occlusion.

A subanalysis stratified on RAO subtype was conducted to investigate whether the effects differed between BRAO and CRAO.

A significance level of 0.05 was used. All statistical analyses were performed using Stata Statistical Software: Release 16 (StataCorp LP, College Station, TX)

Results

This retrospective case-control study included 5683 RAO patients and 28,415 matched stroke patients. Of the 5683 RAO patients, 2338 were BRAO patients, 2881 were CRAO patients, and the remaining 464 patients were unspecified RAO patients. Baseline characteristics are summarized in Table 2. The mean age of the populations was 68.4 years (sd 12.6 years) and 44.5% was female.

Risk factors for developing both RAO and stroke with a prevalence above 10% at index date included diabetes, heart failure, arterial hypertension, and ischemic heart disease, making them the most prevalent risk factors. The prevalence was higher for cataract, glaucoma, and retinal vein occlusion among the RAO patients, whereas atrial fibrillation was more prevalent among the stroke patients.

A forest plot of all effects are summarized in Table 2 and visualized in Fig. 2, with an indication of whether the risk factor was more or less associated with RAO or stroke. The largest differences in effect between cases and controls were estimated for atrial fibrillation, cataract, glaucoma, and RVO. The association was stronger in RAO compared to stroke, for all the investigated eye diseases, including cataract, glaucoma, and retinal vein occlusion, with OR of 2.37 (95% CI: 2.16-2.59), 3.61 (95% CI: 3.00-4.34), and 11.70 (95% CI: 9.18-14.93), respectively. For stroke, a substantially stronger association was found for atrial fibrillation compared to RAO, with an OR of 0.52 (95% CI: 0.47-0.58). The effect of arterial hypertension and peripheral arterial disease were slightly stronger for RAO than stroke, where the estimated OR were 1.21 (95% CI: 1.13-1.29) and 1.31 (95% CI: 1.18-1.46), respectively. Small differences with the least significant effect of less than 10% increase or decrease in risk were identified for diabetes, heart failure, and renal disease. Diabetes showed a stronger association with stroke, whereas heart failure and renal disease showed a stronger association with

Table 2. *Comparing risk factors between RAO and stroke.*

	Baseline characteristics		Effect	
Exposure	RAO	Stroke	OR	95% CI
N	5683	28415		
Female % (N)	44.5 (2528)	44.5 (12640)		
Age mean (sd)	68.4 (12.6)	68.4 (12.6)		
Arterial hypertension % (N)*	40.0 (2273)	35.3 (10026)	1.21	(1.13-1.29)
Atrial fibrillation % (N)	8.0 (453)	13.0 (3695)	0.52	(0.47-0.58)
Cataract % (N)	17.8 (1010)	7.9 (2238)	2.37	(2.16-2.59)
Diabetes % (N)*	15.3 (868)	15.4 (4364)	0.85	(0.78-0.93)
Glaucoma % (N)	4.9 (280)	1.0 (280)	3.61	(3.00-4.34)
Heart failure % (N)	12.4 (703)	10.8 (3067)	1.15	(1.04-1.28)
Ischemic heart disease % (N)	14.3 (814)	13.0 (3702)	1.04	(0.94-1.13)
Peripheral arterial disease % (N)	9.1 (515)	6.6 (1884)	1.31	(1.18-1.46)
Renal disease % (N)	4.2 (236)	3.1 (882)	1.19	(1.02-1.40)
Retinal vein occlusion % (N)	4.8 (271)	0.3 (96)	11.70	(9.18-14.93)

Demographic and clinical characteristics of the case population comprising RAO patients and matched control population of stroke patients. RAO patients were used as reference in the analyses. Adjusted conditional logistic regressions estimating odds ratio, 95% confidence interval and p-value.

*Diagnoses based on both hospital diagnoses and drug prescriptions. Abbreviations: RAO, retinal artery occlusion; OR, Odds ratio; CI, confidence interval.

RAO. No differences in effect estimates were identified for ischemic heart disease.

The subanalysis stratified on RAO subtype showed comparable results overall (Table 3). The only differences observed were that the effect reached equivalence for arterial hypertension in CRAO patients and for peripheral arterial disease in BRAO patients.

Discussion

The present study contributes with novel information on risk factors for the development of RAO. Based on the results of this study, RAO and stroke had some differences in their risk factor profiles and the association with several of the investigated risk factors varied considerably

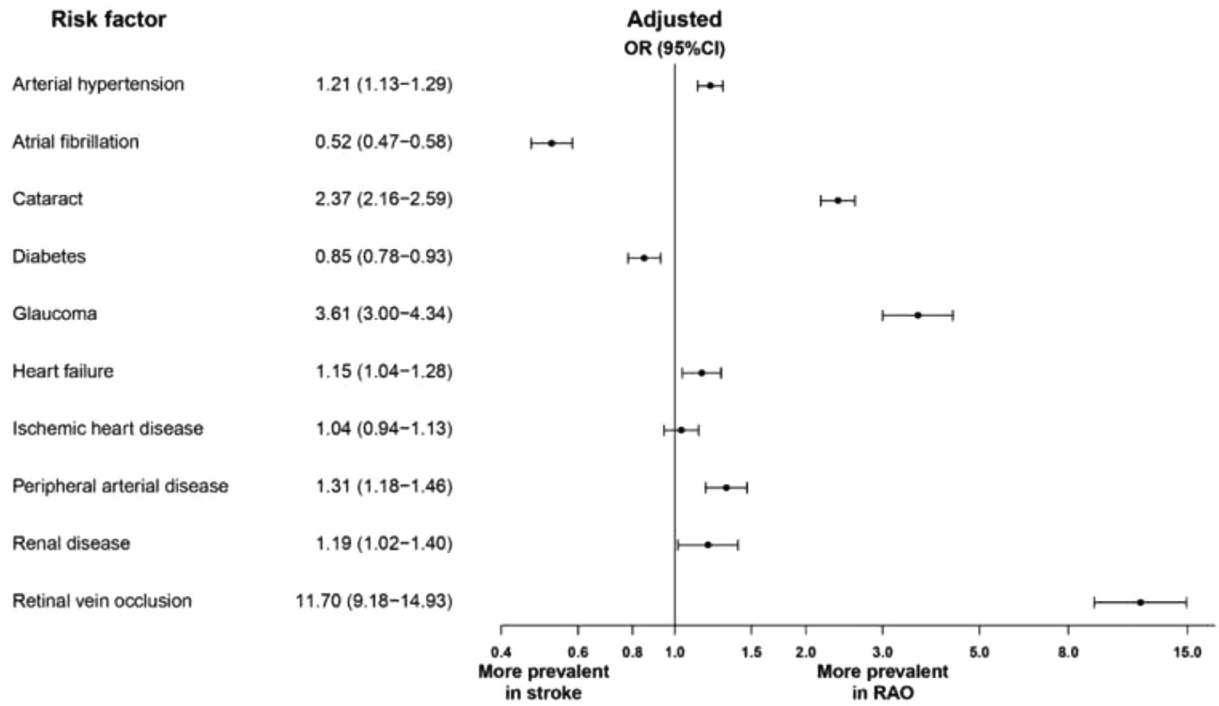

Fig. 2. *Effect measures of the investigated risk factors*

Forestplot of the effect measures for all investigated risk factors. Below the scale it can be visualized whether an association is stronger for RAO or stroke.Abbreviations: RAO, retinal artery occlusion; OR, odds ratio.

Table 3. *Stratified analysis comparing risk factors between RAO subtypes and stroke.*

Branch retinal artery occlusion				
	Baseline characteristics		Effect	
Exposure	BRAO	Stroke	OR	95% CI
N	2338	11690		
Female % (N)	44.0 (1028)	44.0 (5140)		
Age mean (sd)	66.9 (13.5)	66.9 (13.4)		
Arterial hypertension % (N)*	41.7 (976)	34.6 (4044)	1.37	(1.23-1.51)
Atrial fibrillation % (N)	7.7 (181)	12.5 (1465)	0.54	(0.46-0.64)
Cataract % (N)	16.0 (374)	7.6 (892)	2.13	(1.84-2.47)
Diabetes % (N)*	14.8 (346)	15.4 (1798)	0.81	(0.71-0.93)
Glaucoma % (N)	4.3 (100)	0.9 (100)	3.59	(2.65-4.88)
Heart failure % (N)	12.2 (286)	10.4 (1221)	1.14	(0.97-1.34)
Ischemic heart disease % (N)	14.6 (341)	12.9 (1507)	1.07	(0.93-1.24)
Peripheral arterial disease % (N)	8.0 (186)	6.7 (789)	1.09	(0.91-1.30)
Renal disease % (N)	4.0 (94)	2.9 (344)	1.19	(0.92-1.53)
Retinal vein occlusion % (N)	4.8 (112)	0.3 (35)	12.80	(8.63-18.99)
Central retinal artery occlusion.				
	Baseline characteristics		Effect	
Exposure	CRAO	Stroke	OR	95% CI
N	2881	14405		
Female % (N)	44.8 (1292)	44.8 (6460)		
Age mean (sd)	69.9 (11.7)	69.9 (11.7)		
Arterial hypertension % (N)*	38.9 (1121)	36.2 (5221)	1.09	(0.99-1.20)
Atrial fibrillation % (N)	8.0 (231)	13.6 (1955)	0.49	(0.42-0.57)
Cataract % (N)	19.0 (548)	8.2 (1175)	2.43	(2.15-2.75)
Diabetes % (N)*	16.0 (461)	15.4 (2223)	0.90	(0.80-1.01)
Glaucoma % (N)	5.5 (159)	1.0 (151)	3.83	(2.98-4.93)
Heart failure % (N)	12.4 (358)	11.1 (1595)	1.16	(1.01-1.34)
Ischemic heart disease % (N)	14.2 (410)	13.3 (1916)	0.99	(0.87-1.13)
Peripheral arterial disease % (N)	9.9 (286)	6.5 (938)	1.48	(1.28-1.72)
Renal disease % (N)	4.5 (130)	3.3 (475)	1.24	(1.00-1.53)
Retinal vein occlusion % (N)	4.5 (129)	0.3 (49)	11.22	(7.96-15.82)

Abbreviations: BRAO, branch retinal artery occlusion; CRAO, central retinal artery occlusion; OR, odds ratio; CI, confidence interval.

between the two diseases. This variation may be important in the management of patients at risk for RAO and stroke because different interventions could be necessary for these two diseases, to prevent development of the diseases and in the end to ensure the most efficient long-term prognosis. Previously, RAO and stroke have been described as equivalents,[1,2] indicating a shared risk factor profile, matching comorbidities, pointing at similar management of affected patients.

A stronger association was found between stroke and atrial fibrillation compared with the association with RAO. The association between stroke and atrial fibrillation have been described in detail.[5,20,24] Atrial fibrillation is a common cardiac arrhythmia, causing thrombus formation in the left atrium, which can reach the brain and cause a stroke.[30] These types of strokes are defined as cardiogenic strokes,[24,25,31] and constitute between 14-30.6% of all ischemic strokes.[32–35] The stronger association between atrial fibrillation and stroke may indicate that emboli arising from the heart are not the primary causes of RAO, which previously has been described as one of the main pathophysiologies of RAO.[3] The reason for this difference between RAO and stroke may be explained by the composition and size of the emboli, but further clinical studies are needed to determine the specific reason.

Cataract, glaucoma, retinal vein occlusion, arterial hypertension, and peripheral arterial disease were all stronger associated with RAO. Cataract, glaucoma, and retinal vein occlusion are diseases manifesting in the eye. They are all associated with age. Furthermore, the association identified between RAO and both retinal vein occlusion and glaucoma could be the result of their shared association with elevated intraocular pressure.[36–38] Especially, retinal vein occlusion and glaucoma are strongly associated with changes in the pressure gradients of the eye, including the intraluminal pressure and the

intraocular pressure. The eye has a special hydrostatic environment, because of the effect of the intraocular pressure. Therefore, the blood flow in the retinal veins is similar to that in a Starling resistor, while the laws of Laplace and Poiseuille describe the effect on the retinal arteries.[39,40] This implies that large changes in the pressure gradients of the eye or prolonged changes in hemodynamics of the retinal arteries predispose for RAO.[39,41]

Arterial hypertension and peripheral arterial disease are major risk factors for atherosclerosis and mainly cause atherothrombotic embolism, which has been described as the main pathogenesis of RAO.[3,4,22–24] The stronger association with RAO may be the result of atherothrombotic embolism being one in several mechanisms in the development of stroke, whereas other mechanisms may not contribute to the same extent in the development of RAO. The effect of arterial hypertension was strongest in the BRAO strata, while the effect of peripheral arterial disease was stronger in the CRAO strata.

Several of the investigated differences in risk factors for the two diseases were statistically insignificant or clinically irrelevant, including diabetes, heart failure, ischemic heart disease, and renal disease. This supports the close association already described for RAO and stroke. The risk factors with insignificant effect measures were all established associations of atherosclerosis, which similarly has been described as a primary pathophysiology of both RAO and stroke in the existing literature.

The pressure gradients were mainly associated with RAO and no evidence support an association with the development of stroke. Atherosclerosis is associated with the development of both RAO and stroke. However, the cardiogenic pathway was stronger associated with stroke, whereas the atherothrombotic pathway was more equally associated with both RAO and stroke.

Strengths and limitations

The size of the included populations is a strength of this study. With a case population of 5683 RAO patients and 5 stroke patients per RAO patient the total number of patients included in this study was 34,098. The matching between the two populations excludes confounding introduced by the sex and age of the patients. In addition, the matching reduces the risk of overall confounding and bias, since the two populations become more comparable. The study was conducted using the nationwide Danish registries, which ensured full coverage for all patients included.

The use of registries was also accompanied with limitations. The codes used could not be verified in the registries by e.g., patient journals or images, therefore incorrect codes may have introduced bias to the study. However, validation studies have investigated the positive prediction value (PPV) of several of the included ICD-10 codes. atrial fibrillation, heart failure, and arterial hypertension have been investigated and mean estimated PPVs ranging from 76 to 95% were determined.[42] This were assessed to be large enough PPVs not to cause significant bias in the study.

The four main clinical classifications of CRAO are thromboembolism, non-arteritic with cilioretinal artery sparing, transient, and arteritic.[43] The focus of this study was the thromboembolic type. However, the registries are disease specific rather than pathogenesis specific, preventing specifying the cohort to thromboembolic RAO patients.

There could be important factors, that were not included in this study, because they were not recorded in the registries. Lifestyle factors are not accessible in the Danish Civil Registration System, DNPR, or Danish National Prescription Registry. Therefore, adjustments could not be made for lifestyle factors, including smoking, BMI, and alcohol consumption, which could introduce confounding in the analyses.

Conclusion

This study supports that risk factors for RAO and stroke have both differences and similarities. This may be of importance in the understanding of the pathophysiology of RAO and when working on improving the management of the disease. Variations in the pathophysiology of the diseases may be an indication for different interventions for the two diseases to optimize the long-term prognosis of these patients.

Data availability

According to Danish law person level data may not be deposited.

Disclosures

HV has served as an advisory board member for Bayer and Novartis.

TBL has been an investigator for Janssen Scientific Affairs, LLC, Bayer AG and Boehringer Ingelheim; and has received speaker honorarium from Bayer, Bristol-Myers Squibb, Pfizer and Merck Sharp & Dome.

GYHL has been consultant and speaker for BMS/Pfizer, Boehringer Ingelheim and Daiichi-Sankyo. No fees are received personally.

FLS has received consultancy fees from Bayer.

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