Retinal Artery Occlusion and Cardiovascular Disease

Risk Factors, Potential Pathophysiology, and Prognosis

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BY
MARIE ØRSKOV

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AALBORG UNIVERSITY
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Marie Ørskov

AALBORG UNIVERSITY
DENMARK

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PhD supervisor: Professor Torben Bjerregaard Larsen, MD, PhD
Department of Cardiology, Aalborg University Hospital
Department of Clinical Medicine. Aalborg University

Assistant PhD supervisors: Associate Professor Flemming Skjøth, MSc, PhD
Department of Clinical Medicine. Aalborg University
Unit for Clinical Biostatistics, Aalborg University Hospital

Professor Henrik Vorum, MD, PhD
Department of Ophthalmology, Aalborg University Hospital
Department of Clinical Medicine. Aalborg University

PhD committee: Professor Mette Grønkær
Aalborg University, Denmark

Associate Professor Bob Siegerink
Leiden University Medical Center, The Netherlands

Clinical Associate Professor Yousif Subhi
Rigshospitalet, Denmark

PhD Series: Faculty of Medicine, Aalborg University

Department: Department of Clinical Medicine

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ENGLISH SUMMARY

Retinal artery occlusion is a debilitating disease that, in the worst cases, causes blindness in affected patients. We know that there are associations between retinal artery occlusion and cardiovascular diseases, but there are still major gaps in our knowledge of these occlusions. There are no definite guidelines for management of these patients and no effective treatment have been determined.

The overall aim of this thesis was to elucidate associations between retinal artery occlusion and cardiovascular diseases. This thesis is based on three studies, all of which use data from the Danish national registers.

In the first study, we examined cardiovascular diseases, ophthalmic diseases, systemic diseases and inflammatory diseases as risk factors for retinal artery occlusion. The results indicated that systemic atherosclerosis and changes in the pressure gradients over the lamina cribrosa between the intraocular and the intracranial environment and the transmural pressure over the vascular wall may be associated with the development of retinal artery occlusion.

In the second study, we investigated whether the CHA_2DS_2-VASc Stroke Risk score or the ESSEN Stroke Risk score could be used to identify patients with retinal artery occlusion who are at increased risk of stroke. We found an association between the risk of stroke and an increasing CHA_2DS_2-VASc score or ESSEN Stroke Risk score, where the ESSEN Stroke Risk score separated patients more accurately according to their risk of stroke. However, the discriminative properties of the risk scores were poor and the predictive ability was no better than for the null model.

In the third study, we investigated the risk of macrovascular complications in patients with diabetes with or without retinal artery occlusion. We found that the risk of macrovascular complications was significantly higher in patients with both diabetes and retinal artery occlusion compared to patients with diabetes and no diagnosis of retinal artery occlusion. This indicated that retinal artery occlusion is a potential predictor of macrovascular complications in patients with diabetes.

This thesis has contributed knowledge concerning risk factors and potential pathogeneses that may lead to retinal artery occlusion. Furthermore, we focused on risk stratification of complications following retinal artery occlusion. Evidence-based risk stratification that effectively identify patients at increased risk of complications can be used as clinical tools to make treatment decisions. Combined with other scientific research, the knowledge gained in these studies may contribute to the preparation of guidelines for management of patients with retinal artery occlusion.

DANSK RESUME

Retinal arterie okklusion er en invaliderende sygdom, der i værste tilfælde forårsager blindhed hos berørte patienter. Vi ved, at der er sammenhænge mellem retinale arterie okklusioner og kardiovaskulære sygdomme, men der er stadig store mangler i vores viden om disse okklusioner. Der er ingen definerede retningslinjer for håndtering af patienterne, og der er ingen effektiv behandling er blevet beskrevet.

Det overordnede mål med denne afhandling var at belyse sammenhænge mellem retinale arterie okklusioner og kardiovaskulære sygdomme. Denne afhandling er baseret på tre studier, som alle anvender data fra de danske nationale registre.

I første studie undersøgte vi om en række udvalgte kardiovaskulære sygdomme, øjensygdomme, systemiske sygdomme og inflammatoriske sygdomme var risikofaktorer for retinale arterie okklusioner. De estimerede effektmål indikerede at systemisk aterosklerose og ændringer i trykforholdene over lamina cribrosa mellem øjets ydre og indre og over den vaskulære væg inden i øjet kunne være associeret med udviklingen af retinal arterie okklusion.

I andet studie undersøgte vi om CHA_2DS_2-VASc Stroke Risk scoresystemet eller ESSEN Stroke Risk scoresystemet kunne anvendes til at identificere patienter med retinal arterie okklusion, som har øget risiko for apopleksi. Vi fandt en sammenhæng mellem risikoen for apopleksi og stigende CHA_2DS_2-VASc score og ESSEN Stroke Risk score. ESSEN Stroke Risk scoren adskilte patienter mere præcist efter deres risiko for apopleksi. De diskriminerende egenskaber ved risikoscorerne var dårlige og de prædiktive evner var ikke bedre end for nulmodellen.

I tredje studie undersøgte vi risikoen for makrovaskulære komplikationer i patienter med diabetes med eller uden retinal arterie okklusion. Vi fandt, at risikoen for makrovaskulære komplikationer var signifikant højere hos patienter med både diabetes og retinal arterie okklusion sammenlignet med patienter med diabetes og ingen retinal arterie okklusion diagnose. Dette indikerede at retinal arterie okklusion er en potentiel prædiktor for makrovaskulære komplikationer hos patienter med diabetes.

Afhandlingen har bidraget med viden om risikofaktorer og potentielle patogeneser, der kan føre til retinale arterie okklusioner. Desuden fokuserede vi på risikostratificering for komplikationer efter en retinal arterie okklusion. Evidensbaseret risikostratificering, der effektivt identificerer patienter med øget risiko for komplikationer, kan bruges som kliniske redskaber til at træffe behandlingsmæssige beslutninger. Kombineret med anden videnskabelig forskning, kan den viden opnået i disse studier bidrage til udarbejdelsen af retningslinjer for håndtering af patienter med retinale arterie okklusioner.

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LIST OF PAPERS

This dissertation is based on the following studies:

Study I

Ørskov M, Vorum H, Larsen TB, Lip GYH, Bek T, Skjøth F. Clinical risk factors for retinal artery occlusions: a nationwide case-control study. International Ophthalmology. 2022 Aug;42(8):2483–91.

Study II

Ørskov M, Vorum H, Larsen TB, Skjøth F. Evaluation of Risk Scores as Predictive Tools for Stroke in Patients with Retinal Artery Occlusion: A Danish Nationwide Cohort Study. TH Open. 2022;6(4):e429–36.

Study III

Ørskov M, Vorum H, Larsen TB, Larsen M, Skjøth F. Retinal artery occlusion as an early indicator of macrovascular complications in diabetes. American Journal of Medicine. 2022 Sep;(Epub ahead of print).

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CHAPTER 1. INTRODUCTION

Retinal artery occlusion is a small occlusion with a large negative clinical impact. However, there are no definite clinical guidelines or treatments to improve the natural course of the disease (1). Therefore, research in retinal artery occlusion is highly relevant to obtain the necessary knowledge to implement effective clinical guidelines for management of patients suffering from retinal artery occlusion and possibly identify an effective treatment to restore some of the vision loss these patients are experiencing.

Associations between retinal artery occlusion and cardiovascular diseases have been established (2–6). Especially, a strong association exists between retinal artery occlusion and stroke (2,7,8). Even with the associations already identified, there are still unknown aspects that need to be investigated.

The aim of this thesis was to investigate the interplay between retinal artery occlusion and cardiovascular diseases. What causes retinal artery occlusion events? Who are the patients at high risk and low risk of subsequent cardiovascular events? And is retinal artery occlusion an indicator of progressed systemic atherosclerosis and increased risk of cardiovascular diseases? These are some of the questions we found interesting when we decided to look into retinal artery occlusions.

CHAPTER 2. BACKGROUND

Retinal artery occlusion is a monocular ophthalmic emergency, causing visual impairment or even blindness in affected individuals (2,9). The incidence of central retinal artery occlusion is between 1.8-1.9 per 100,000 person-years (10,11). The variation in severity makes it difficult to estimate the incidence of branch retinal artery occlusion. The incidence of retinal artery occlusion increases with age, more than 90% of the affected patients are above 40 years and the mean age is 60-65 years (11–13). Stratified according to age groups, the incidence rate reaches 1 per 10,000 person-years for patients aged 80 to 84 years (11). Furthermore, retinal artery occlusion affects more men compared to women and vascular comorbidities are common in these patients (12,14,15).

2.1. THE EYE

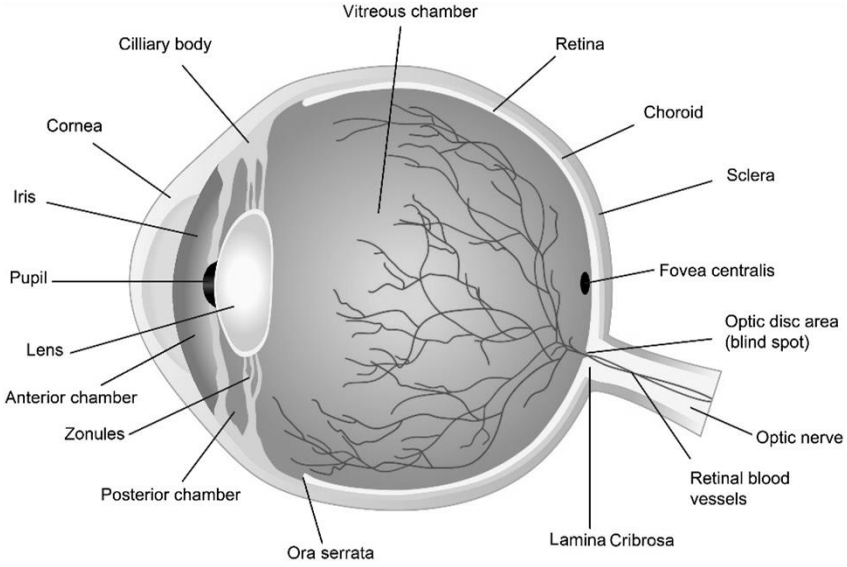
The eye is an almost spheric globe. The inside of the eye is separated into three parts: the anterior chamber, the posterior chamber, and the vitreous body (16,17).

The front surface of the eye and the inner eyelids are covered by the conjunctiva, a thin clear membrane that inserts at the limbus, from where the dehydrated corneal epithelium forms a clear cornea. Posteriorly the iris is found, which is the coloured part around the pupil that controls the amount of light entering the eye, by regulating the pupil size. The part between the cornea and the iris is the anterior chamber. The ciliary body, an extension of the iris, controls the shape of the lens through little fibres called zonules. The lens is behind the iris and will be clear in a healthy eye. The posterior chamber is between the back of the iris and the lens. The vitreous body is the space between the lens and the retina. The space is filled with vitreous humour, which help maintain the shape of the eye (16,17).

The wall of the eye globe comprises three layers, of which the inner is the retina, the outer is the sclera, and between them is the choroid (17). The retina is comprised of the neurosensory retina and the retinal pigment epithelium. The inner aspect of the posterior two-thirds of the vitreous body is lined with the retina, which is a multi-layered, semi-transparent neural tissue that converts light into nerve signals (16,18). The retina is one of the most metabolically active tissues of the body (19). The retina ends at the ora serrata, where the retina is 0.1 mm thick. At the posterior pole, the retina is 0.23 mm thick (16). When examining the retina, the macula is visible, which is an area with different pigmentation due to the presence of luteal pigment. The fovea is in the centre of the macula (16,20). The photoreceptors of the fovea constitute the central vision (17,20). Between the retina and the sclera is the choroid, which is a vascular layer of the eye, supplying the outer third of the retina (21). The retinal artery and retinal vein supply the rest of the retina, except the fovea, which is avascular (16). The optic nerve carries the visual message to the brain. At the optic nerve head is the

lamina cribrosa, which is a collagen meshwork structure that is placed between the intraocular pressure and the intracranial pressure (22,23) (Figure 1).

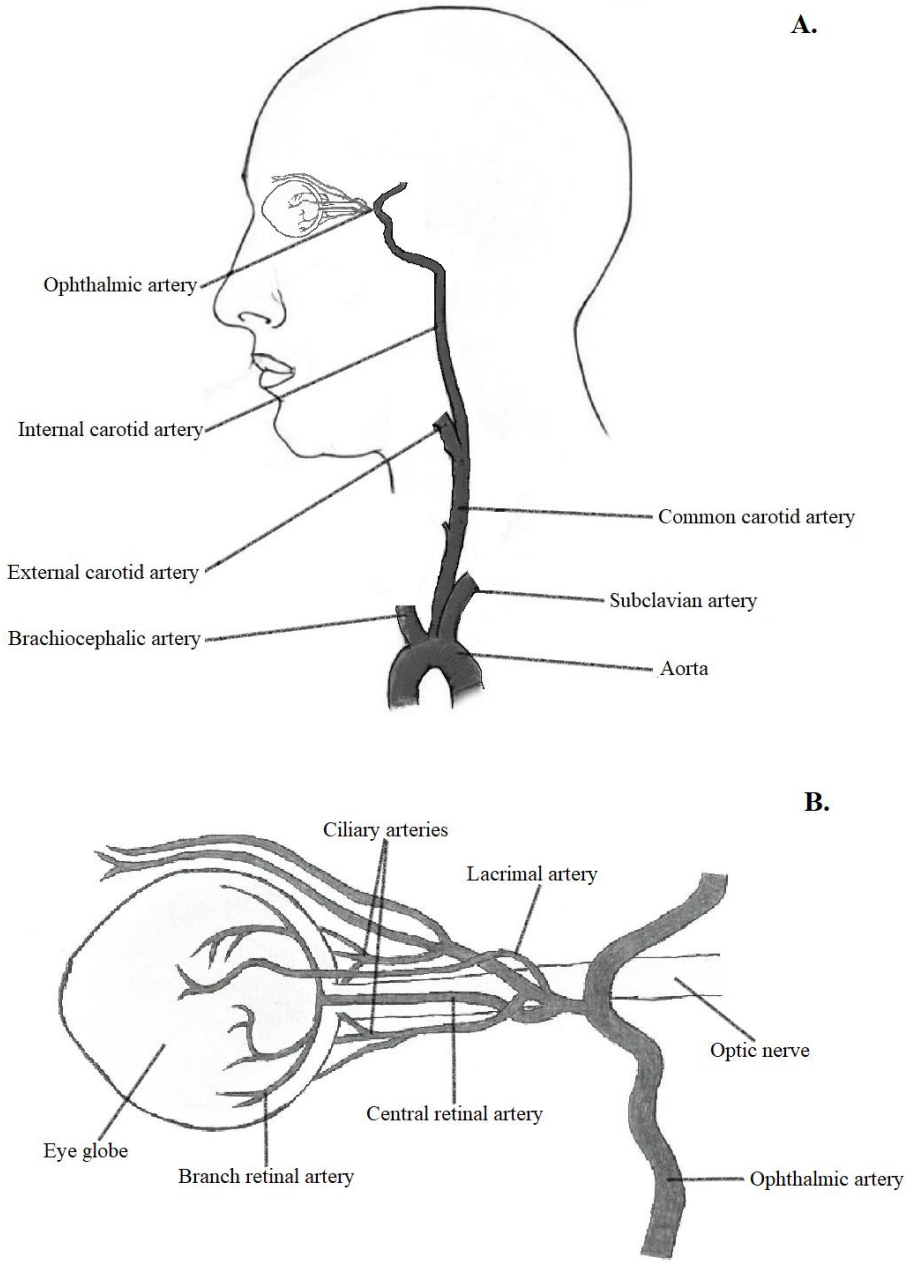
Figure 1. Anatomy of the human eye.



2.2. THE ARTERIES FROM THE HEART TO THE RETINA

The blood exits the heart through the aortic valve from the left ventricle. From here it enters the aorta. The cranial branches of the aorta ending in the retina include the common carotid arteries. On the right side, the innominate artery branches off the aorta and give rise to the common carotid artery, whereas on the left side the common carotid artery arises directly from the aorta. Around the mandible angle the common carotid arteries divide into the external and internal branches. The first branch of the internal carotid artery is the ophthalmic artery, which supply all structures of the eye. The ophthalmic artery runs through the optic canal on the medial side of the eye. The central retinal artery is the first branch of the ophthalmic artery. The central retinal artery penetrates the optic nerve and continue along the centre of the optic nerve. Adjoint with the optic nerve, the central retinal artery pierces the eyeball and branches off to form the branch retinal arteries (16,24–26). The choroid is a principal vasculature between the retina and the sclera, where the ciliary arteries are embedded. They supply the outer layers of the retina with nutrients (16,21,25,27). A schematic representation of the blood supply to the eyes is shown in Figure 2.

Figure 2. Schematic presentation of the retinal arterial blood supply



A. Blood supply from the aorta to the eye, B. Blood supply focused on the ocular arteries.

2.3. RETINAL ARTERY OCCLUSION

Retinal artery occlusions can be subcategorized according to their anatomical location and the symptoms they cause. The main subtypes include central retinal artery occlusion and branch retinal artery occlusion, where the central retinal artery occlusion will cause more pronounced visual impairments and blindness compared with limited visual impairments caused by branch retinal artery occlusions (2,9,28).

2.3.1. ETIOLOGY AND PATHOPHYSIOLOGY

Different pathogeneses have been described for retinal artery occlusion, including thromboembolism and vasculitis. These pathogeneses are shared by the main subtypes of retinal artery occlusion (2,29).

The main cause of retinal artery occlusion is thromboembolism caused by systemic atherosclerosis(2,14). The emboli may originate from the internal carotid artery, aortic arch, or heart (2,30,31). The most common embolic source is a plaque in the ipsilateral carotid artery (2). Cardiogenic embolism may cause retinal artery occlusion as well. This embolic source is more prevalent in younger patients under the age of 40 years and patients with a suggestive medical history (2,32,33). Another pathogenesis causing retinal artery occlusion is vasculitis, which may be triggered by inflammatory diseases or medicinal products (2). This pathogenesis should be considered when no visible embolus is present at the funduscopic examination. Previously described rare causes of retinal artery occlusion include infections, manipulation of the neck at a chiropractor, and procedures or treatments in connection with other diseases (34–39).

2.3.2. DIAGNOSIS AND ACUTE CLINICAL FEATURES

Diagnosing retinal artery occlusion and the determination of the subtype is based on the clinical features present at a funduscopic examination (40). Furthermore, a fluorescein angiography or an optical coherence tomography angiography may be conducted to identify slowed or absent filling of the retinal arteries (41).

The main clinical feature of retinal artery occlusion is an acute loss of vision. A central retinal artery occlusion causes a profound vision loss or monocular blindness, while a branch retinal artery occlusion causes a smaller visual impairment matching the area of the retina affected (42). A proportion of patients have a cilioretinal artery supplying the macular region, which may preserve a small part of the central vision (43).

Distinct clinical features are present at the funduscopic examination of retinal artery occlusion. For central retinal artery occlusion, general whitening due to ischemia is present. Additionally, a classic characteristic when the central vision is affected is a macular cherry red spot, where the pigmented epithelium of the retina and the choroidal vasculature become more visible through the more transparent ischemic

retina. For branch retinal artery occlusion, the affected part of the retina will become whitened due to ischemia. The retinal emboli and non-perfused vessels or ghost vessels may be visible in the funduscopic examination. A visible embolus is more frequent in branch retinal artery occlusion than in central retinal artery occlusion (31,44).

2.3.3. MANAGEMENT AND TREATMENT

The prognosis for visual recovery in patients with central retinal artery occlusion is poor. Improvement in visual acuity occurs in approximate 20% of patients with central retinal artery occlusion with no ciliary sparring, rarely with full restoration of vision (30,45). Therefore, an effective treatment would be valuable. However, no indication for an effective treatment has yet been found in randomized clinical trials (1). The use of different treatments has been studied in patients with retinal artery occlusion including ocular massage, carbogen inhalation, intraocular pressure reducing drugs, carbonic anhydrase inhibitors, and haemodilution. These treatments were either shown to be ineffective or in some cases even harmful (46–48).

Studies indicate that the maximum therapeutic window for patients with retinal artery occlusion is six hours with better preservation of vision with early treatment (47,49,50). Animal studies have shown that ischemia of the retina will result in permanent damage if the occlusion persist for more than four hours. Furthermore, full visual recovery was possible if blood flow was restored within 97 minutes (51,52).

Acute intravenous treatment with thrombolysis has been used to treat ischemic stroke to achieve revascularization, which was shown to reduce the risk of death and the dependence on others following the event (53–56). In patients with retinal artery occlusion, it has been suggested that thrombolysis may achieve revascularization before permanent damage to the retina occurs (57,58). Nevertheless, thrombolysis is a systemic treatment associated with both intracranial and systemic haemorrhages (55,59,60). More research is needed to determine whether the side effects are too severe compared to the potential beneficial effect of thrombolysis treatment in patients with retinal artery occlusion.

Additionally, the association between stroke and retinal artery occlusion has resulted in the recommendation of a prompt referral for stroke evaluation ideally within 24 hours following a retinal artery occlusion event (28,61–65). The evaluation involves a computed tomography, magnetic resonance imaging, or ultrasound scan of the neck or head to check for plaques in the arteries. Such plaques could have caused the retinal artery occlusion and may cause other emboli to dislodge and potentially cause a fatal stroke (61).

The long-term management of patients with retinal artery occlusion often include antithrombotic treatment to prevent recurrent cardiovascular events (30). In patients

with carotid artery stenosis, stenting or a carotid endarterectomy is performed to remove plaque from the artery and reduce the risk of stroke and recurrent events (66,67).

Research in treatment and management of patients with retinal artery occlusion has mainly been conducted in patients with central retinal artery occlusion. However, since the pathophysiology include atherosclerotic emboli for both central and branch retinal artery occlusion, the research may be suitable for both subtypes. Nonetheless, this needs to be investigated before implementation in clinical settings.

2.4. CARDIOVASCULAR DISEASES AND RETINAL ARTERY OCCLUSION

Retinal artery occlusion has been associated with multiple cardiovascular diseases, including stroke, systemic arterial hypertension, diabetes, ischemic heart disease, renal disease, and hyperlipidaemia (2–6,68). One study found that 67% of patients with retinal artery occlusion had a cardiovascular disease in their medical history. Furthermore, they determined that 40% had clinically relevant carotid stenosis (69). Following a retinal artery occlusion event, the risk of cardiovascular diseases is increased as well (70).

An especially strong association has been described between retinal artery occlusion and stroke, they have even been described as equivalent diseases (2,71). The rate ratio of stroke has been found to be at least two times higher in patients with retinal artery occlusion compared to randomly selected controls. The risk is especially high during the first month following the retinal artery occlusion event but remain elevated afterwards (7). The strong association is supported by several shared characteristics between the two diseases. They are mainly thromboembolic events, components of the central nervous system, and they share the blood supply provided through the internal carotid arteries (2,8,72–76). Furthermore, the blood-retina barrier and the blood-brain barrier are structurally and functionally similar (77,78). However, there are essential differences between the two diseases, which underline the importance of investigating retinal artery occlusion and stroke individually. First, the choroid supply the outer retina with blood, ensuring an alternative blood supply for part of the retina in case of an occlusion (21). Second, the vitreous humour is a reservoir of nutrients and metabolites that the retina can receive by diffusion (79,80). This contribute to a longer retinal tolerance time for acute ischemia than for the brain (81). Finally, cerebral oedema often occurs in patients experiencing stroke, which may result in structural compression causing both ischemia and cerebral herniation since there is no room for expansion in the cranium (82,83). The retina on the other hand is a small structure compared to the eye globe with room for expansion, which reduces the risk of structural compression. These variations and special characteristics of the retina may provide other potential treatment options than for the brain.

CHAPTER 3. AIMS AND HYPOTHESES

The overall aim of this project was to investigate the interplay between retinal artery occlusion and other cardiovascular diseases. The following sections describes the specific aims and hypotheses for the included studies individually.

3.1. STUDY I

Aim: To examine clinical risk factors, including cardiovascular diseases, eye diseases, systemic diseases, and inflammatory diseases, associated with the development of retinal artery occlusion compared to healthy controls.

Hypothesis: Atherosclerosis is associated with the development of retinal artery occlusion, however a pathogenesis involving the physiology of the eye contributes to the pathophysiology of retinal artery occlusion as well. Risk factors for the development of retinal artery occlusion may help elucidate the pathogeneses resulting in retinal artery occlusion events.

3.2. STUDY II

Aim: To assess the risk of stroke in patients with retinal artery occlusion depending on the CHA_2DS_2-VASc score and the ESSEN Stroke Risk score. Additionally, the study aims to investigate the stroke predictive properties of both the risk scores in a retinal artery occlusion population.

Hypothesis: Both the CHA_2DS_2-VASc score, and the ESSEN Stroke Risk score predict the risk of stroke in patients with retinal artery occlusion. The predictive performance of the ESSEN Stroke Risk score is higher than for the CHA_2DS_2-VASc score.

3.3. STUDY III

Aim: To investigate whether retinal artery occlusion is associated with an increased risk of major adverse cardiovascular events in patients with diabetes and thereby assess the use of retinal artery occlusion as a predictor for macrovascular complications in patients with diabetes.

Hypothesis: The risk of major adverse cardiovascular events is increased in patients with diabetes and retinal artery occlusion compared to patients with diabetes and no diagnosis of retinal artery occlusion. Consequently, retinal artery occlusion could be a potential predictor of cardiovascular complications in patients with diabetes.

CHAPTER 4. METHODS

4.1. SETTING AND DESIGN

The studies included in this dissertation were all based on data from the Danish nationwide registries. The three studies differed in design. The first study was a case-control study, while the other two studies were cohort studies. In the case-control study the data was analysed retrospectively, whereas the data in the cohort studies was analysed prospectively.

4.2. DATA SOURCES

Denmark has a long tradition of collecting and registering information in national health registers. The Danish registers provide an exceptional resource for epidemiological research. All individuals with a permanent residence in Denmark receive a personal identification number at birth or upon immigration. All health data is linked to this personal identification number (84,85).

Many Danish registers have been introduced for administrative purposes. Danish legislation (Persondataloven) states that data from the registers may be used for statistical and scientific purposes (86). For this project, access to the register data was approved by Statistics Denmark. The Act on Processing of Personal Data states that full anonymity for all individual level data must be preserved, but informed consent is not needed to access data (84,87,88). Furthermore, no approval from an ethics committee is necessary for register-based research (84,87). To ensure full anonymity, the personal identification number is encrypted by Statistics Denmark before researchers access the data (89).

A short description of each of the three utilized registers for this project is present in the following sections.

4.2.1. THE DANISH CIVIL REGISTRATION SYSTEM

The fundament of the extraordinary Danish registers is the personal identification number or the Central Person Register number (CPR-number). All the personal information connected to the CPR-number is registered and updated daily in the Danish Civil Registration System. The registered information includes CPR-number, name (first, middle, and last), date of birth, sex, place of residence, migration status, place of birth, citizenship, kinship (CPR-number of parents, siblings (under maternal CPR-number), spouses, children), as well as information on vital status, which is continuously updated. The Danish Civil Registration System was established in 1968 and is considered to be of high quality. Several reasons ensure the quality of the

Danish Civil Registration System. First, for all citizens it is required by law to be registered in the Danish Civil Registration System and the citizens generally trust and accept the registration. Second, the Danish Civil Registration System was established for administrative purposes and is used frequently. When errors are encountered, they are corrected. Finally, each Danish resident has a certificate with their CPR-number and needs this when encountering the health care system (85,87,90).

4.2.2. THE DANISH NATIONAL PATIENT REGISTRY

The Danish National Patient Registry is a nationwide population-based registry, collecting data on all hospital admissions in Denmark. At the establishment in 1977 the information in the registry did not include contacts to emergency rooms, specialist outpatient clinics, and psychiatric wards. This information was included in 1995. Contacts with private hospitals were included in 2003. However, the proportion of admissions to private hospitals in Denmark is very small (91,92).

Data recorded in the Danish National Patient Registry includes administrative data, diagnoses, procedures, and examinations. Some of the characteristics included in the administrative data are, the CPR-number, admission hospital and department, duration of patient contact, and admission type. Data on diagnoses includes both primary diagnosis and secondary diagnoses. Since 1994, diagnoses in the Danish National Patient Registry have been classified according to the International Classification of Diseases version 10 (ICD-10). Until the end of 1993 ICD-8 was used. It is important to be aware of different definitions and changes in coding over time in the Danish National Patient Registry. Payment for public hospitals has been calculated based on recorded data since 2000, constituting a financial reason for recording information comprehensively in the registry (91,92).

4.2.3. THE DANISH NATIONAL PRESCRIPTION REGISTRY

A register on individual-level data on all prescription drugs sold in Danish pharmacies was established in 1994 for administrative purposes. Information in the Danish National Prescription Registry can be divided into four overall categories, including information on the drug user, the dispensing of the drug, the prescriber, and the pharmacy. The main information on the drug user is the CPR- number used to identify all prescriptions dispensed to this individual and for linkage with data from other registers. Registered dispending information include date, product information, price, dose information, and the Anatomical Therapeutic Chemical (ATC) code for the drug (88,89). World Health Organization defined the ATC classification system, which enable research in drug use and monitoring of both medicine use and side effects. Drugs are classified based on their active substance in five levels, including anatomical main group, therapeutic subgroup, pharmacological subgroup, chemical subgroup, and chemical substance (93). The coverage and validity of the Danish National Prescription Registry is considered high. Electronic dispensing systems at

Danish pharmacies ensure accurately registered data. Furthermore, several drugs are reimbursable for the drug user providing an economic purpose for recording the dispensing of the drug. Another reason for high-quality data is that the redemption of the prescriptions is recorded, ensuring that the drug is collected from the pharmacy (88,89).

4.3. UTILIZED REGISTER CODES

Obtaining the specific information wanted for each study requires selection of diagnoses and prescriptions that with high accuracy represent the diseases of interest. Some of the wanted information is a combination of several diagnoses, while other information is a specific disease with a specific diagnosis code. In some instances, there are no specific code for the patients of interest, in these cases a reasonable proxy can be used. A proxy is an alternative information in the registries, that would include the wanted patients with an accuracy corresponding to the true identifier (94). A proxy could be diagnoses, prescriptions, operations, and/or procedures.

4.4. STUDY POPULATION

The study population varied between the studies. Study I was a case-control study, where the case-population included all Danish patients with an incident diagnosis of retinal artery occlusion between January 1, 2000 and December 31, 2018. Each case was matched on birth year and sex with five random individuals from the background population with no diagnosis of retinal artery occlusion. The patients with retinal artery occlusion were extracted using ICD-10 codes from the Danish National Patient Registry. The control population was randomly chosen in the registries from individuals who matched the described criteria (95).

Study II was a cohort study, with a source population of Danish patients with an incident diagnosis of retinal artery occlusion between January 1, 1995 and December 31, 2018. The patients with retinal artery occlusion were extracted using ICD-10 codes from the Danish National Patient Registry (96).

Study III was a cohort study, where the study population comprised patients with diabetes. Patients with incident retinal artery occlusion occurring between January 1, 2000 and December 31, 2018 were identified in the population of patients with diabetes. Each patient with retinal artery occlusion was matched on birth year, sex, and duration since diabetes diagnosis with five random patients with diabetes but no diagnosis of retinal artery occlusion (97). The algorithm used to include patients with diabetes consisted of an ICD-10 code for a diabetes diagnosis in the Danish National Patient Registry and/or more than one ATC-code for glucose-lowering drugs in the Danish National Prescription Registry (98,99). Patients with retinal artery occlusion were identified using ICD-10 codes in the Danish National Patient Registry (97).

All three studies are summarized in Table 1.

Table 1. Summary of study information for each individual study.

Study I	Study II	Study III
Study design		
Retrospective case-control study	Prospective cohort study	Prospective cohort study
Study period		
January 1, 2000 – December 31, 2018	January 1, 1995 – December 31, 2018	January 1, 2000 – December 31, 2018
Study population		
Cases: Patients with incident retinal artery occlusion. Controls: Subjects from the general population matched on sex and birth year.	Patients with incident retinal artery occlusion.	Patients with diabetes and incident retinal artery occlusion. Control population matched on birth year, sex, and duration of diabetes, with no diagnosis of retinal artery occlusion.
Exclusion criteria		
Individuals who emigrated or immigrated up to five years before the index date. Individuals < 18 years old. Inconsistent demographic information.	Individuals who immigrated less than one year before their retinal artery occlusion diagnosis or emigrated and was not returned at index date. Individuals < 18 years old. Inconsistent demographic information. Individuals who died at index date.	Individuals who immigrated less than one year before their diabetes diagnosis or emigrated and was not returned at index date. Individuals < 18 years old. Inconsistent demographic information. Individuals who died at index date.

Table 1. Continued

Study I	Study II	Study III
Exposure(s)		
Acute myocardial infarction, arterial hypertension, atrial fibrillation, cataract, diabetes, glaucoma, heart failure, inflammation, ischemic heart disease, liver disease, peripheral artery disease, psoriasis, renal disease, sleep apnea, stroke, venous thromboembolism	CHA_2DS_2-VASc score ESSEN Stroke Risk score	Retinal artery occlusion
Outcome of interest		
Retinal artery occlusion	Stroke	Major adverse cardiovascular events (Myocardial infarction, Ischemic stroke, Cardiovascular death)
Follow-up time		
5-years (retrospectively)	1-year	1-year and 5-years

This table references information from all three included studies (95–97).

4.5. EXPOSURES AND OUTCOMES

In study I, the exposures comprised potential risk factors for retinal artery occlusion, including acute myocardial infarction, arterial hypertension, atrial fibrillation, cataract, diabetes, glaucoma, heart failure, inflammation, ischemic heart disease, liver disease, peripheral artery disease, psoriasis, renal disease, sleep apnea, stroke, and venous thromboembolism. Retinal artery occlusion was the outcome of interest (95). In study II, the investigated exposures were existing risk scores. We selected the CHA_2DS_2-VASc score and the ESSEN Stroke Risk score that both were stroke risk scores. Correlating with stroke being the outcome of interest in study II (96). Retinal artery occlusion was the exposure in study III and major adverse cardiovascular events were the outcome of interest (97). Most of the included exposures and outcomes were extracted from the registries using ICD-10 codes in the Danish National Patient Registry and ATC-codes in the Danish National Prescription Registry.

4.5.1. RISK STRATIFICATION TOOLS

Risk stratification tools can separate a specified group of patients into risk groups according to their individual risk. Risk score schemes are one possible risk stratification tool. The prognosis associated with a disease may be of interest for both the patient and the physician when counselling the patient. Furthermore, risk stratification can assist in treatment decisions and allocation of patients for different treatments or managements (100,101).

4.5.1.1 CHA_2DS_2-VASc score

The CHA_2DS_2-VASc score was considered an exposure in study II. The CHA_2DS_2-VASc score was developed for stroke and thromboembolic risk stratification in patients with atrial fibrillation to identify patients not in need of anticoagulation treatment (102–104). However, the utility of the score has been validated in other populations, including patients with stroke, myocardial infarction, and coronary artery disease (105–108). The CHA_2DS_2-VASc score is a clinically based risk score, where each variable adds to the total score. The maximum score is 9 points (102,103). The composition of the clinical variables and their scores are summarized in Table 2.

Table 2. Components of the CHA_2DS_2-VASc score.

Disease	Score
Congestive heart failure/Left ventricular dysfunction	1
Hypertension	1
Age ≥ 75 years	2
Diabetes	1
Stroke/Transient ischemic attack	2
Vascular disease*	1
Age 65-74 years	1
Sex (Female)	1
Maximum score	**9**

**Including myocardial infarction and peripheral artery disease.*

Overview of the score associated with each risk factor included in the CHA_2DS_2-VASc score (102,104).

4.5.1.2 ESSEN Stroke Risk score

The ESSEN Stroke Risk score was the other risk score used in study II. The ESSEN Stroke Risk score was specifically developed for risk stratification of recurrent stroke within one year in patients with stroke (109–111). Similar to the CHA_2DS_2-VASc score, the ESSEN Stroke Risk score is a point-based risk score and several of the included variables are comparable between the two scores (109,110). The included variables are mainly clinical variables with one exception, which is smoking. The included variables and their score are summarized in Table 3. Information about smoking habits was not available in this project, therefore we chose diagnoses of lung cancer or chronic obstructive pulmonary disease as a proxy for smoking.

Table 3. Components of the ESSEN Stroke Risk score.

Disease	Score
Age 65-75 years	1
Age > 75 years	2
Hypertension	1
Diabetes	1
Myocardial infarction	1
Peripheral artery disease	1
Smoking*	1
Ischemic stroke/transient ischemic attack	1
Other cardiovascular events	1
Maximum score	**9**

**Lung cancer and chronic obstructive pulmonary disease used as proxies.*

Overview of the score associated with each risk factor included in the ESSEN Stroke Risk score (109,110,112).

4.5.2. MAJOR ADVERSE CARDIOVASCULAR EVENTS

Major adverse cardiovascular events were the outcome of interest in study III (97). The composite outcome of major adverse cardiovascular events is frequently used in randomized controlled trials and observational studies. Major adverse cardiovascular events may be defined differently between studies (113). In this study major adverse cardiovascular events were comprised of non-fatal myocardial infarction, non-fatal stroke, and death, which define the three-point major adverse cardiovascular events (114). This three-point composite endpoint was recommended by both the United

States Food and Drug Administration and the European Medicines Agency when evaluating cardiovascular safety of diabetic agents (113,115,116). It would have been preferable to include cardiovascular death instead of death in general, but this information was not available in this project. We assessed that the number of deaths due to other reasons besides cardiovascular events would be equally distributed between patients with retinal artery occlusion and patients without. Hence, death due to any cause was applicable in the composite outcome in the study.

4.6. STATISTICS

Descriptive statistics were identified in all studies using proportions and frequencies for categorical measures and means and standard deviations for continuous measures.

In study II and III we calculated the incidence rate of the outcome of interest as the ratio between the number of events occurring during the specific time frame and the total observation time in the specified time interval. The incidence rate is a measure of the occurrence of new cases of the outcome of interest during follow-up (117). Furthermore, we calculated the cumulative incidence in study II and III to identify the probability of the outcome of interest occurring during a specified time interval. The Kaplan-Meier estimator was used when death was included in the outcome, the Aalen-Johansen estimator was used when death was a competing risk (96,97,117).

A general description of the methods used in each study will be presented in the following sections.

4.6.1. REGRESSION MODELS

Numerous regression models exist and when choosing the model, we considered what kind of data was used, the study rationale, the study design, and whether competing risk was present. This resulted in the use of different regression models throughout the project, including the conditional logistic regression model, the Cox proportional hazard regression model, and the Fine and Gray regression model.

4.6.1.1 Conditional logistic regression

Study I was designed as a matched case-control study (95). Matching is done to adjust for confounding, control unmeasured confounding, and improve study efficacy since smaller populations are needed to achieve the same precision. Matching should only be done on risk factors that would introduce confounding, otherwise there is a risk of overmatching (117–119).

Conditional logistic regression is the standard model for matched case-control data. In matched case-control studies, an unconditional logistic regression model may overestimate the effect of the included variables. Conditional logistic regression is an

extension of logistic regression, where both stratification and matching are considered, and it is possible to adjust for confounders. This model is especially good for studies with a rare disease as the outcome variable (118–120). A conditional logistic regression model was used in study I. Retinal artery occlusion was our dichotomous outcome variable, and the independent variables were all the diseases we investigated as risk factors for retinal artery occlusion. We matched the controls on birth year and sex, which are known risk factors for retinal artery occlusion. Furthermore, the model was adjusted for potential confounders (95).

In conditional logistic regression the population is stratified according to the matching variables that are associated with the outcome. In each stratum the cases and controls are selected. The probability is calculated relative to each strata, which is different from the regular logistic regression (120).

4.6.1.2 Cox proportional hazard regression model

The Cox proportional hazard regression model is the most common regression technique to use when researching time-to-event data (121). The Cox proportional hazard regression model was used in both study II and study III (96,97).

The Cox model is semiparametric and estimates the hazard rate ratio, which is a comparison of the hazard rates between the investigated strata. The hazard rate is interpreted as the probability that the outcome of interest will occur in the next time interval, given that it did not occur in the prior time intervals (122,123). An assumption of the model is that the hazards are proportional over time and thereby the measure of association is constant over time (121–124). This assumption was assessed to be acceptable in both studies.

4.6.1.3 Fine and Gray regression model

In study II, we used a Fine and Gray regression model (96), which is an alternative to a Cox proportional hazard regression model for survival data, where the risk ratio is estimated and competing risk is considered in the analysis. Competing risk is an event that occurs instead of the outcome of interest, which prevents the occurrence of the outcome (125,126). Competing events should not be confused with right-censoring events, where the observation of potential future events is prevented but the subject remains at risk. Comparable with the Cox proportional hazard regression model, the Fine and Gray regression model is semiparametric, and effects are expected to be proportional over time (126). In our survival analysis in study II, we performed both a Cox proportional hazard regression model and a Fine and Gray regression model. We compared the estimated effect measures between the two regression models, which would indicate whether the hazard rate ratio was comparable with the subdistributional hazard rate ratio. Comparable effect measures would indicate a comparable rate ratio and risk ratio (96).

4.6.2. PREDICTION PERFORMANCE

Prediction performance of a model can be tested and validated by investigating the calibration and discrimination of the model. The calibration is a measure of the difference between the predicted risk and the observed risk, while the discrimination is a measure of the model's ability to rank individuals based on whether they have the event of interest or not (127–129). In study II, we measured the prediction performance of models using contemporary stroke risk scores in patients with retinal artery occlusion (96). The following prediction measures were estimated.

4.6.2.1 C-statistics

C-statistics evaluates the discrimination of a model and is a measure for the goodness of fit of a regression model with a dichotomous outcome. C-statistics is equal to the area under the Receiver Operating Characteristic (ROC) curve (128–131). The ROC curve plots the sensitivity against one minus the specificity, which is equal to the rate of true positives against the rate of false positives (132,133). C-statistics measures the probability that the model assigns the higher risk of event to the strata that has the event when comparing with a random subject that do not develop the endpoint (129,130). The C-statistics is a rank statistic, which entails that miscalibration of the predicted risk is not considered. Therefore, other measures of prediction performance must be used to fully assess the predictive accuracy of a model (128–130). The presence of death as a competing risk in our study made the interpretation of the C-statistics more complicated. With no competing risk, controls are alive and event-free. When competing risk is present, controls can either be defined as event-free and alive or defined as event-free and alive or dead, resulting in different interpretations (134,135). At the specified time, we defined controls as alive and event-free.

4.6.2.2 Brier score and index of prediction accuracy

The Brier score and the index of prediction accuracy both reflect the calibration and discrimination of a model. The Brier score is calculated as the average squared differences between the predicted risks and outcomes. The lower the Brier score, the better performance of the model. A useless model predicting 50% for all subjects have a benchmark Brier score of 25%, therefore all potentially useful prediction models should have a Brier score below 25%. In our study, we estimated the Brier score for both the prediction models being investigated and for a null model. The null model in study II predicted the prevalence of the outcome for all subjects in the test dataset without any predictors included and was used in the calculation of the index of prediction accuracy. The Brier score of a prediction model should always be compared with the Brier score of the null model to assess the predictive abilities (127,128,136).

The index of prediction accuracy is one minus the ratio between the Brier score for the model under investigation and the Brier score for the null model. In addition to

measuring calibration and discrimination, the index of prediction accuracy can distinguish a useless model from a harmful model. A useless model will have an index of prediction accuracy of zero, whereas a harmful model will have a negative index of prediction accuracy (127,136).

4.6.3. SUBGROUP ANALYSES AND SENSITIVITY ANALYSES

Primary analyses can be supplemented by subgroup analyses and sensitivity analyses. Subgroup analyses are used to assess potential variation in effect across specified groups. Sensitivity analyses assess the robustness of the identified results by alterations in assumptions, methods, models, or variables (137).

In study I, we stratified the population according to age, sex, and retinal artery occlusion subtype. Conditional logistic regression was used to identify the effect for each stratum and using a Wald test the interaction between the strata was identified. These subgroup analyses were conducted to identify the effect between retinal artery occlusion and the investigated risk factors in each stratum and test whether statistically significant differences were present between the studied strata (95).

Subgroup analyses were performed in study III to investigate whether and how much each individual outcome contributed to the overall effect estimated in the main analysis. We estimated the effect for each individual outcome of major adverse cardiovascular events, including myocardial infarction, stroke, and death (97).

In study III, we performed two sensitivity analyses. The first sensitivity analysis investigated confounding introduced by previous cardiovascular events to ensure the predictive abilities of retinal artery occlusion found in the study were not facilitated by other arterial thromboembolic events. All patients with a previous diagnosis of an arterial thromboembolic disease were excluded. The arterial thromboembolic diseases included heart failure, ischemic heart disease, myocardial infarction, peripheral artery disease, and stroke. The second sensitivity analysis investigated confounding introduced by other diseases. All patients with a hospital contact during the three months prior to their retinal artery occlusion event were excluded (97).

In study III, we performed a post-hoc landmark analysis to consider the risk of major adverse cardiovascular events following the initial phase after a retinal artery occlusion event, where the incidence of major adverse cardiovascular events increases markedly. This analysis investigated whether a long-term (1 year – 5 years) risk of major adverse cardiovascular events was associated with retinal artery occlusion. In this analysis, all patients with a major adverse cardiovascular event between 1 and 5 years after their retinal artery occlusion event were included (97).

Cox proportional hazard regression models were used in all the supplemental analyses conducted in study III for the populations specified above (97).

CHAPTER 5. STUDIES

In the following sections the three studies included in this dissertation will be summarised. The complete studies have been attached as appendices.

5.1. STUDY I

Study I has been published in *International Journal of Ophthalmology* and was authored by Marie Ørskov, Henrik Vorum, Torben Bjerregaard Larsen, Gregory Y.H. Lip, Toke Bek, and Flemming Skjøth (95).

5.1.1. AIM

In study I, we wanted to investigate ophthalmic, cardiovascular, systemic, and inflammatory risk factors for retinal artery occlusion, to help elucidate potential pathogeneses for the development of the disease. We hypothesized that especially cardiovascular diseases would increase the risk of retinal artery occlusion.

5.1.2. METHODS

Study I was a matched case-control study. The case population consisted of all incident retinal artery occlusion patients from January 1, 2000 to December 31, 2018 in the Danish national registries. Each case was matched on sex and birth year with five random controls from the database without a diagnosis of retinal artery occlusion (95).

Exposures were selected from existing literature for retinal artery occlusion, and closely associated diseases, including ischemic stroke and retinal vein occlusion (2–6,11,138–144). Four categories of exposures were selected, and we included events up to 5 years prior to the index date. The first group consisted of cardiovascular diseases, including acute myocardial infarction, arterial hypertension, atrial fibrillation, diabetes, heart failure, ischemic heart disease, peripheral artery disease, stroke, and venous thromboembolism. The second group consisted of systemic diseases, including liver disease, renal disease, and sleep apnea. The third group consisted of inflammatory diseases, including psoriasis and inflammation. The last group consisted of eye diseases, where we included cataract and glaucoma (95).

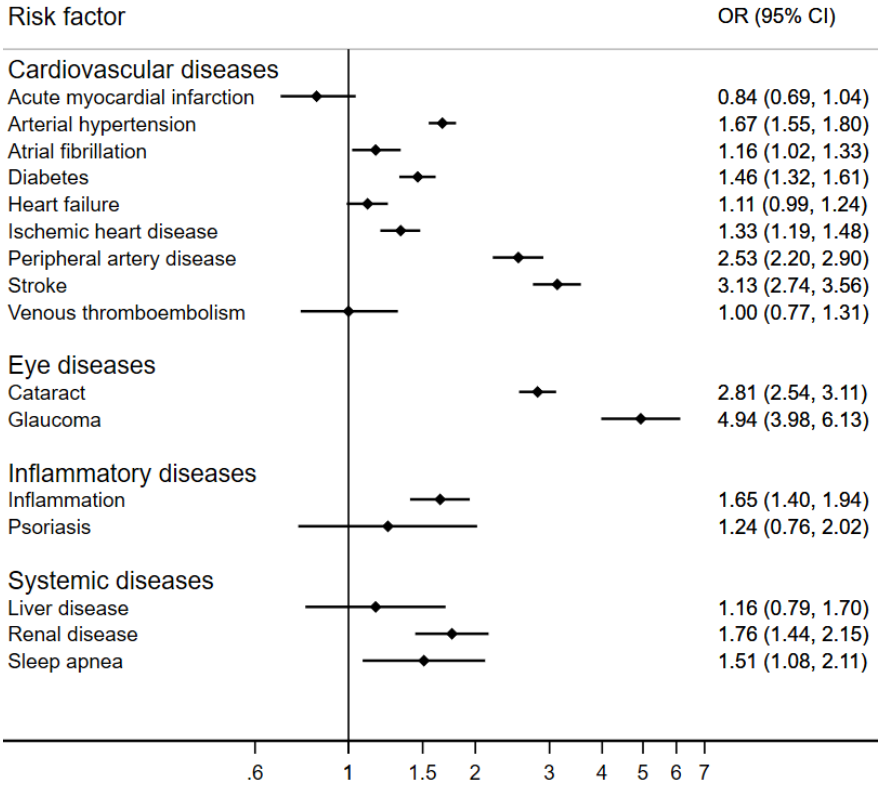
The effect of each exposure was investigated using conditional logistic regression, estimating the odds ratio and the 95% confidence interval (95% CI). The model was adjusted for sex, birth year, cataract, glaucoma, renal disease, and all the included cardiovascular diseases except venous thromboembolism. Subgroup analyses were

conducted stratifying the population according to sex, age, and retinal artery occlusion subtype.

5.1.3. MAIN RESULTS

A total of 31,872 individuals were included in study I, including 5312 incident retinal artery occlusion cases and 26,560 matched controls. As expected, all investigated exposures were more prevalent in the patients with retinal artery occlusion compared with the controls.

Figure 3: Adjusted odds ratios for investigated risk factors.



Abbreviations: OR, odds ratio

This figure was adapted from Table 1 in study I: Ørskov M, Vorum H, Larsen TB, Lip GYH, Bek T, Skjøth F. Clinical risk factors for retinal artery occlusions: a nationwide case-control study. International Ophthalmology. 2022 Aug;42(8):2483–91.(95)

Multiple risk factors found to be associated with the development of retinal artery occlusion supported the well-established pathogenesis, systemic atherosclerosis, as a pathogenesis for retinal artery occlusion (2). Furthermore, a strong association was found between retinal artery occlusion and glaucoma. This association suggests that increased intraocular pressure may increase the risk of retinal artery occlusion, possibly by changes in the pressure gradients both over the lamina cribrosa between the inside and the outside of the eye and over the vascular wall inside the eye. The hazard rate ratio of the associated cardiovascular diseases ranged from 1.16 (95% CI: 1.02-1.33) for atrial fibrillation to 3.13 (95% CI: 2.74-3.56) for stroke. Additionally, we found a strong association between peripheral artery disease and retinal artery occlusion with a hazard rate ratio of 2.53 (95% CI: 2.20-2.90). Moreover, the effect measures for arterial hypertension, ischemic heart disease, and diabetes were statistically significant. Strong effect measures for the ophthalmic diseases were identified, with hazard rate ratios of 2.81 (95% CI: 2.54-3.11) for cataract and 4.94 (95% CI: 3.98-6.13) for glaucoma. Furthermore, statistically significant effect measures were identified for renal disease, sleep apnea, and inflammation (Figure 3) (95).

Only minor differences were identified in the stratified analyses on sex and retinal artery occlusion subtype, suggesting risk factors are relatively consistent for both sexes and the investigated retinal artery occlusion subtypes. However, in the age stratified analysis, the younger age group showed larger effect measures especially for the cardiovascular diseases and the ophthalmic diseases.

5.1.4. CONCLUSION

This study provided a thorough summary of risk factors associated with the development of retinal artery occlusion. Cardiovascular diseases supported systemic atherosclerosis as the main pathogenesis for retinal artery occlusion. Furthermore, a strong association between retinal artery occlusion and glaucoma suggested that the intraocular pressure and thereby changes in the pressure gradients of the eye may contribute to the development of retinal artery occlusion as well.

5.2. STUDY II

Study II has been published in *TH Open* and was authored by Marie Ørskov, Henrik Vorum, Torben Bjerregaard Larsen, and Flemming Skjøth (96).

5.2.1. AIM

We wanted to evaluate the CHA_2DS_2-VASc score and the ESSEN Stroke Risk score as prediction models for stroke in patients with retinal artery occlusion. We expected that the risk scores would accurately predict the risk of stroke and thereby be suitable prediction models for stroke risk stratification in patients with retinal artery occlusion.

5.2.2. METHODS

Study II was a cohort study and included all patients from the Danish national registries with incident retinal artery occlusion between January 1, 1995 and December 31, 2018 (96). The population was risk stratified at the index date according to the point level of the CHA_2DS_2-VASc score and the ESSEN Stroke Risk score. A limited number of patients had a point level of four or above. They were collapsed into one stratum for each risk score. All patients were followed until the outcome of interest stroke, the competing event death, or censoring because of emigration or administrative end of follow-up on 31 December, 2018 (96).

Both the risk and rate were investigated for stroke in patients with retinal artery occlusion during a follow-up period of one year. The rate was investigated by estimating the incidence rate and the effect using a Cox proportional hazard model. A likelihood ratio test was performed to assess the goodness of fit of the model. The risk was investigated by identifying the cumulative incidence and estimating the effect using a Fine and Gray model. Furthermore, the predictive abilities of the included risk scores were investigated using C-statistics, Brier score, and the index of prediction accuracy.

5.2.3. MAIN RESULTS

The population included in study II consisted of 7906 patients with retinal artery occlusion. They were stratified according to the point level on the stroke risk scores investigated. It is recommended that these patients are scanned quickly following their retinal artery occlusion event, however, only 5.9% of the included patients received a scanning of their head or neck within 48 hours. The proportion of patients initiating platelet aggregation inhibitor treatment increased during the follow-up period. At baseline, 40.7% of the patients were under treatment. After 1 year, 65.9% (95% CI: 64.8%-66.9%) was estimated to be under treatment (96).

The rate and the risk increased for each point level of both the risk scores (Table 4). The cumulative incidence of stroke showed an increasing risk of stroke for increasing point levels on the included risk scores during the one-year follow-up period, with a markedly increase the first month after the retinal artery occlusion event (Figure 4).

A score of 0 was used as reference in the conducted survival analyses. For the CHA_2DS_2-VASc score, the estimated hazard rate ratios were 1.56 (95% CI: 0.99-2.44), 1.71 (95% CI: 1.11-2.65), 1.72 (95% CI: 1.12-2.65), and 3.48 (95% CI: 2.33-5.20) for a score of 1, 2, 3, and 4 or above, respectively. For the ESSEN Stroke Risk score the estimated hazard rate ratios were 1.47 (95% CI: 1.04-2.06), 1.82 (95% CI: 1.30-2.56), 2.47 (95% CI: 1.74-3.48), and 3.85 (95% CI: 2.76-5.38) for a score of 1, 2, 3, and 4 or above, respectively (Table 4). The ESSEN Stroke Risk score separated the patients more accurately according to their stroke risk compared with the

CHA_2DS_2-VASc score. The estimated effect measures of the Fine and Gray model were comparable to the effect measures of the Cox model (Table 5). A maximum likelihood test showed statistically significant differences between the effect of the point levels for both the investigated risk scores ($p<0.05$). This suggested that the risk of stroke increased as the point levels on the included risk scores increased for patients with retinal artery occlusion. Therefore, we assessed the predictive abilities of the CHA_2DS_2-VASc score and the ESSEN Stroke Risk score (96).

To assess the discrimination of the risk scores as predictive tools, the C-statistics was estimated for both scores. The C-statistics was 61% (95% CI: 58%-63%) for the CHA_2DS_2-VASc score and 62% (95% CI: 59%-64%) for the ESSEN Stroke Risk score. The Brier score and the index of prediction accuracy assessed both the discrimination and calibration of the models. The Brier score was estimated for both risk scores and for the null model. Similar Brier scores were obtained for both the included risk scores and the null model, with a rounded score of 2.7% for each model. These Brier scores resulted in an index of prediction accuracy of 0.00 for both risk scores (96) (Table 6).

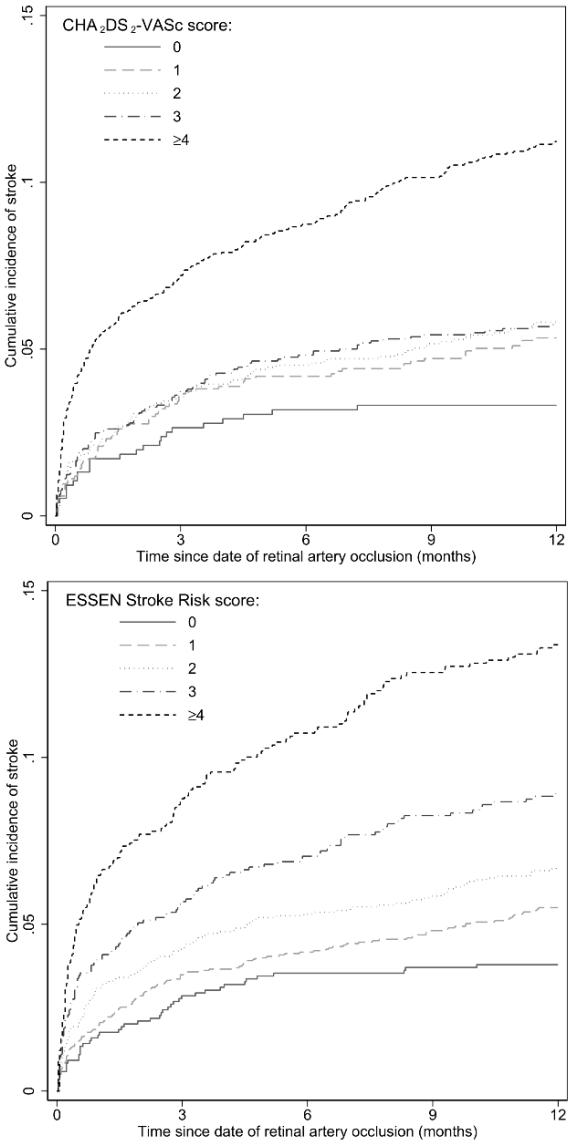
Table 4. Stroke in patients with retinal artery occlusion.

Score	**Rate /100 PY (95%CI)**	**Risk % (95% CI)**	**Effect HR (95% CI)**
CHA_2DS_2-VASc score			
0	3.62 (2.46-5.31)	3.4 (2.3-4.9)	Reference
1	5.66 (4.49-7.15)	5.3 (4.2-6.6)	1.56 (0.99-2.44)
2	6.29 (5.13-7.72)	5.8 (4.7-7.0)	1.71 (1.11-2.65)
3	6.35 (5.21-7.75)	5.8 (4.7-7.0)	1.72 (1.12-2.65)
≥4	13.25 (11.78-14.89)	11.2 (10.0-12.5)	3.48 (2.33-5.20)
ESSEN Stroke Risk score			
0	3.97 (2.97-5.32)	3.8 (2.8-5.0)	Reference
1	5.89 (4.96-6.99)	5.5 (4.6-6.5)	1.47 (1.04-2.06)
2	7.43 (6.24-8.84)	6.7 (5.6-7.9)	1.82 (1.30-2.56)
3	10.18 (8.46-12.25)	8.9 (7.4-10.6)	2.47 (1.74-3.48)
≥4	16.43 (14.01-19.27)	13.4 (11.5-15.4)	3.85 (2.76-5.38)

Abbreviations: PY, person-years; CI, confidence interval; HR, Hazard rate ratio.

This table was adapted from Table 3 in study II: Ørskov M, Vorum H, Larsen TB, Skjøth F. Evaluation of risk scores as predictive tools for stroke in patients with retinal artery occlusion: A Danish nationwide cohort study. TH Open. 2022;6(4):e429–36 (96).

Figure 4. Cumulative incidence of stroke events during the 1-year follow-up stratified according to level on the CHA_2DS_2-VASc score and the ESSEN Stroke Risk score, respectively.



This figure is reused from study II: Ørskov M, Vorum H, Larsen TB, Skjøth F. Evaluation of risk scores as predictive tools for stroke in patients with retinal artery occlusion: A Danish nationwide cohort study. TH Open. 2022;6(4):e429–36 (96).

Table 5. Stroke in patients with retinal artery occlusion.

Score	Risk SHR (95% CI)
CHA_2DS_2-VASc score	
0	Reference
1	1.55 (0.99-2.43)
2	1.69 (1.10-2.62)
3	1.69 (1.10-2.61)
≥4	3.38 (2.26-5.05)
ESSEN Stroke Risk score	
0	Reference
1	1.45 (1.04-2.04)
2	1.79 (1.27-2.52)
3	2.41 (1.70-3.41)
≥4	3.71 (2.66-5.18)

Abbreviations: PY, person-years; CI, confidence interval; SHR, subdistributional hazard rate ratio.

This table was adapted from supplemental Table S2 in study II: Ørskov M, Vorum H, Larsen TB, Skjøth F. Evaluation of risk scores as predictive tools for stroke in patients with retinal artery occlusion: A Danish nationwide cohort study. TH Open. 2022;6(4):e429–36 (96).

Table 6. Predictive performance of the CHA_2DS_2-VASc score and the ESSEN Stroke Risk score as stroke risk stratification models in patients with retinal artery occlusion.

	C-statistics % (LB-UB)	Brier score % (LB-UB)	Index of prediction accuracy score
Null model		2.716 (2.375-3.052)	
CHA_2DS_2-VASc score	61 (58-63)	2.715 (2.375-3.051)	0.0002 (-0.0009-0.0021)
ESSEN Stroke Risk score	62 (59-64)	2.713 (2.372-3.044)	0.0007 (-0.0004-0.0030)

Abbreviations: LB, lower bound; UB, upper bound.

This table is reused from study II: Ørskov M, Vorum H, Larsen TB, Skjøth F. Evaluation of risk scores as predictive tools for stroke in patients with retinal artery occlusion: A Danish nationwide cohort study. TH Open. 2022;6(4):e429–36 (96).

5.2.4. CONCLUSION

In conclusion, risk stratification according to the CHA_2DS_2-VASc score and the ESSEN Stroke Risk score were both associated with an increased risk of stroke in patients with retinal artery occlusion. However, the estimated predictive abilities suggested that the discrimination of both the risk scores was poor.

5.3. STUDY III

Study III has been published in *The American Journal of Medicine* and was authored by Marie Ørskov, Henrik Vorum, Torben Bjerregaard Larsen, Michael Larsen, and Flemming Skjøth (97).

5.3.1. AIM

In study III, we wanted to investigate the general risk of major adverse cardiovascular events in patients with diabetes, with or without retinal artery occlusion. We hypothesized that a retinal artery occlusion event in a patient with diabetes would be associated with an increased general risk of macrovascular diseases. Thereby, suggesting that retinal artery occlusion may be a predictor of macrovascular complications in patients with diabetes.

5.3.2. METHODS

We conducted a nationwide register-based cohort study. The base population included all patients with diabetes. From this population we selected all patients with incident retinal artery occlusion between January 1, 2000 and December 31, 2018. At-risk set sampling was used to match each patient with diabetes and retinal artery occlusion, on birth year, sex, and time since diabetes diagnosis, with five random patients with diabetes, but no retinal artery occlusion event. Major adverse cardiovascular events are a composite endpoint consisting of myocardial infarction, stroke, and death, which was the outcome in this study (97).

We investigated the rate and the risk of major adverse cardiovascular events in patients with diabetes, with or without retinal artery occlusion both at 1-year follow-up and 5-years follow-up. The rate was assessed by identifying the incidence rate of major adverse cardiovascular events in the two groups and by estimating the hazard rate ratio with a Cox proportional hazard model. The cumulative incidence assessed the risk of major adverse cardiovascular events and was calculated using the Kaplan-Meier estimator (97).

To ensure the results were robust, sensitivity analyses were conducted. Furthermore, a supplemental analysis and a post-hoc analysis were performed to ensure each

individual outcome influenced the result and that an increased risk remained after the initial acute phase following the retinal artery occlusion event.

5.3.3. MAIN RESULTS

The included population consisted of 992 patients with diabetes and retinal artery occlusion and 4960 matched patients with diabetes and no retinal artery occlusion diagnosis. The mean time from a diabetes diagnosis to a retinal artery occlusion diagnosis was 7.9 (SD 5.7) years (97).

The incidence rate of major adverse cardiovascular events in patients with diabetes and retinal artery occlusion was 20.97 (95% CI: 18.11-24.29) per 100 person-years at 1-year follow-up, after 5-years follow-up the incidence rate was 15.24 (95% CI: 13.89-16.72) per 100 person-years. The incidence rates for the patients with diabetes and no retinal artery occlusion were lower, at 6.25 (95% CI: 5.57-7.00) and 6.83 (95% CI: 6.45-7.22) after 1-year and 5-years of follow-up, respectively. (97) (Table 7).

During the first months of follow-up the cumulative incidence increased markedly for the retinal artery occlusion population. The difference between the two populations was substantial throughout the follow-up period of five years (Figure 5). The cumulative incidences for patients with diabetes with or without retinal artery occlusion were after 1 year 18.2% (95% CI: 15.9%-20.7%) and 6.1% (95% CI: 5.4%-6.8%), respectively. These increased over the 5-years follow-up to 51.2% (95% CI: 47.9%-54.7%) and 29.4% (95% CI: 28.0%-30.8%), respectively (97) (Table 7).

When comparing the patients with diabetes, with or without retinal artery occlusion, the estimated effect measure was 3.36 (95%CI: 2.79-4.05) after 1-year follow-up and 2.27 (95% CI: 2.04-2.53) after 5-years follow-up. All the analyses supported that the risk of major adverse cardiovascular events was increased in patients with diabetes and retinal artery occlusion compared with patients with diabetes, but no retinal artery occlusion (97) (Table 7).

The sensitivity analyses ensured that the measured effect was not confounded by prior arterial thromboembolic diseases or other diseases we did not consider. In the post-hoc landmark analysis we ensured that the estimated effect was statistically significant between 1 and 5 years after the index date and not just an acute increased effect during the first period following the retinal artery occlusion event (Table 7). Additionally, a supplemental analysis showed that each endpoint in major adverse cardiovascular events, including myocardial infarction, stroke, and death, contributed to the estimated effect. However, the effect for myocardial infarction was statistically insignificant after one year of follow-up (97) (Table 8).

Table 7. Major adverse cardiovascular events in patients with diabetes, with or without retinal artery occlusion.

Group	Incidence, /100 PY (95% CI)	Risk, % (95% CI)	Effect, HR (95% CI)
Main analysis			
1-year follow-up			
RAO	20.97 (18.11-24.29)	18.2 (15.9-20.7)	3.36 (2.79-4.05)
No RAO	6.25 (5.57-7.00)	6.1 (5.4-6.8)	Reference
5-year follow-up			
RAO	15.24 (13.89-16.72)	51.2 (47.9-54.7)	2.27 (2.04-2.53)
No RAO	6.83 (6.45-7.22)	29.4 (28.0-30.8)	Reference
Restricted to patients with no prior arterial cardiovascular disease			
1-year follow-up			
RAO	11.88 (8.96-15.77)	10.9 (8.3-14.2)	3.01 (2.11-4.29)
No RAO	3.93 (3.17-4.87)	3.8 (3.1-4.7)	Reference
5-year follow-up			
RAO	9.71 (8.27-11.40)	38.2 (33.5-43.3)	2.24 (1.85-2.71)
No RAO	4.34 (3.92-4.80)	19.9 (18.2-21.8)	Reference
Restricted to patients with no hospital contact within 3 months prior to index date			
1-year follow-up			
RAO	18.33 (15.42-21.80)	16.2 (13.8-18.9)	3.36 (2.69-4.18)
No RAO	5.44 (4.75-6.24)	5.3 (4.7-6.1)	Reference
5-year follow-up			
RAO	13.75 (12.36-15.29)	48.3 (44.6-52.2)	2.20 (1.94-2.49)
No RAO	6.31 (5.92-6.73)	27.6 (26.1-29.1)	Reference
Post-hoc landmark analysis among patients with no major adverse cardiovascular event at 1 year after a RAO diagnosis			
5-year follow-up			
RAO	12.91 (11.46-14.55)	43.9 (40.3-47.7)	1.90 (1.66-2.18)
No RAO	6.91 (6.46-7.40)	26.9 (25.5-28.4)	Reference

Abbreviations: RAO, retinal artery occlusion; PY, person-years; CI, confidence interval; HR, Hazard rate ratio.

This table was adapted from Table 2 in study III: Ørskov M, Vorum H, Larsen TB, Larsen M, Skjøth F. Retinal artery occlusion as an early indicator of macrovascular complications in diabetes. American Journal of Medicine. 2022 Sep;(Epub ahead of print) (97).

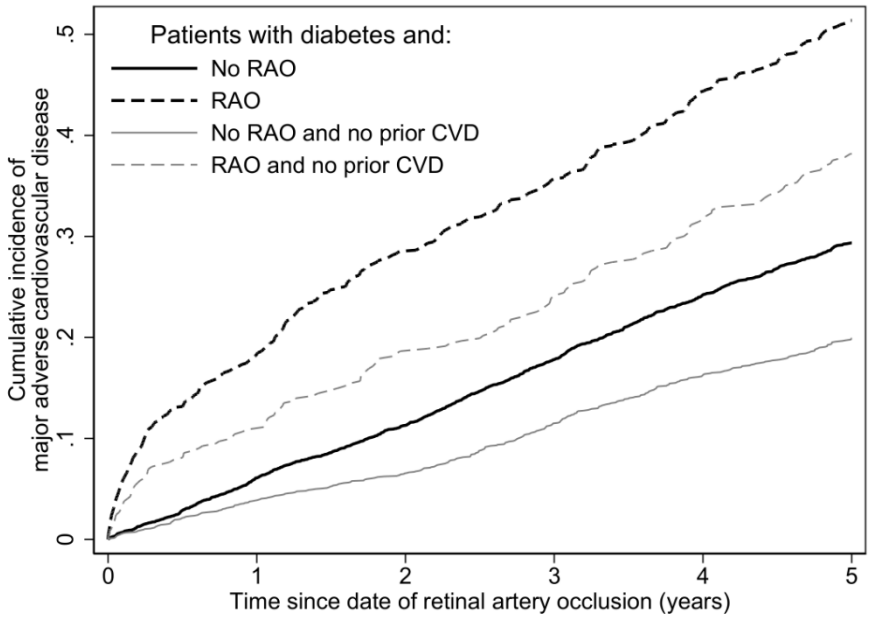
Table 8. Stratified analysis of major adverse cardiovascular events in patients with diabetes, with or without retinal artery occlusion.

Group	Incidence, /100 PY (95% CI)	Risk, % (95% CI)	Effect, HR (95% CI)
Stroke			
1-year follow-up			
RAO	10.04 (8.13-12.40)	9.0 (7.3-10.9)	5.48 (4.06-7.39)
No RAO	1.82 (1.47-2.25)	1.8 (1.5-2.2)	Reference
5-year follow-up			
RAO	4.97 (4.23-5.82)	19.3 (16.5-22.2)	3.17 (2.60-3.86)
No RAO	1.56 (1.39-1.75)	7.4 (6.5-8.2)	Reference
Myocardial infarction			
1-year follow-up			
RAO	1.66 (1.00-2.75)	1.6 (0.9-2.6)	1.48 (0.84-2.63)
No RAO	1.12 (0.85-1.46)	1.1 (0.8-1.4)	Reference
5-year follow-up			
RAO	2.19 (1.74-2.77)	10.1 (7.9-12.5)	2.09 (1.59-2.74)
No RAO	1.07 (0.93-1.23)	5.2 (4.5-5.9)	Reference
Death			
1-year follow-up			
RAO	10.52 (8.61-12.85)	9.9 (8.1-11.9)	2.88 (2.25-3.70)
No RAO	3.69 (3.18-4.28)	3.6 (3.1-4.2)	Reference
5-year follow-up			
RAO	9.72 (8.72-10.83)	38.5 (35.2-42.0)	1.98 (1.75-2.25)
No RAO	5.06 (4.75-5.40)	23.0 (21.7-24.4)	Reference

Abbreviations: RAO, retinal artery occlusion; PY, person-years; CI, confidence interval; HR, Hazard rate ratio.

This table was adapted from Table 3 in study III: Ørskov M, Vorum H, Larsen TB, Larsen M, Skjøth F. Retinal artery occlusion as an early indicator of macrovascular complications in diabetes. American Journal of Medicine. 2022 Sep;(Epub ahead of print (97).

Figure 5. Cumulative incidence of major adverse cardiovascular events during the 5 year follow-up.



Abbreviations: RAO, retinal artery occlusion; CVD, arterial cardiovascular diseases.

The black lines represent the main analysis. The grey lines represent the sensitivity analysis restricted to patients with no prior arterial cardiovascular diseases. Both the dotted lines represent the patients with diabetes and retinal artery occlusion. Both solid lines represent the patients with diabetes and no retinal artery occlusion.

This figure is reused from study III: Ørskov M, Vorum H, Larsen TB, Larsen M, Skjøth F. Retinal artery occlusion as an early indicator of macrovascular complications in diabetes. American Journal of Medicine. 2022 Sep;(Epub ahead of print)(97).

5.3.4. CONCLUSION

In this study we found an increased risk of major adverse cardiovascular events in patients with diabetes and retinal artery occlusion compared to patients with diabetes but no retinal artery occlusion. There is no reason to assume that the results are not applicable for all macrovascular complications in patients with diabetes and maybe in other populations as well. This suggests that retinal artery occlusion may be used as a predictor of macrovascular complications in patients with diabetes and when a retinal artery occlusion is identified it should instigate a thorough examination or risk estimation for cardiovascular diseases or signs of systemic atherosclerosis.

CHAPTER 6. DISCUSSION

In the following sections each of the included studies is discussed separately to specify their individual contributions.

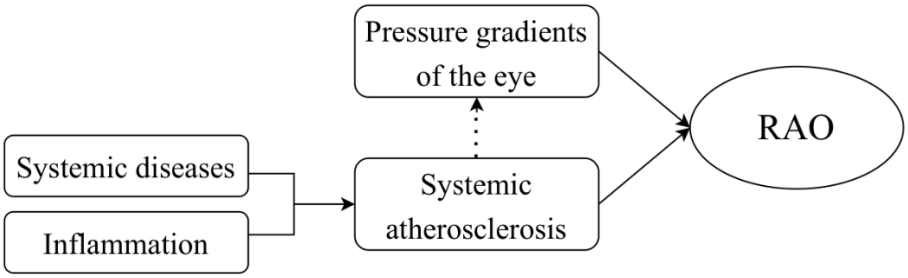
This project was conducted to outline and investigate elements of the clinical course for retinal artery occlusion with a focus on the interplay between retinal artery occlusion and cardiovascular diseases. Retinal artery occlusion is an important disease to understand because it is associated with extensive negative clinical impact. Patients with retinal artery occlusion are at increased risk of potentially fatal cardiovascular diseases. Furthermore, these patients may lose their vision and no effective treatment or definite clinical guidelines have been determined.

We investigated risk factors associated with the development of retinal artery occlusion and the pathogenesis supported by these risk factors. Understanding the pathogenesis of a disease may be valuable in the development of an effective treatment for the disease. In addition, we aimed to identify the patients with retinal artery occlusion at immediate risk of subsequent stroke events. A risk assessment model, which could stratify the patients according to risk of stroke at their retinal artery occlusion event would be an effective tool for the physician. Finally, we assessed retinal artery occlusion as a predictive tool of complications in patients with diabetes. The negative clinical impact is considerable for retinal artery occlusion, but the event is not fatal. Identifying one of the first signs of systemic atherosclerosis would be valuable for patients at increased risk of atherosclerotic events, which would enable early intensified treatment, thereby, reducing the risk of subsequent cardiovascular events and cardiovascular death. Thus, we investigated whether retinal artery occlusion was a potential predictor of macrovascular diseases. Combined, these three studies cover most of the clinical course for retinal artery occlusion, from causes to complications. Detailed information about a disease is important before effective management and treatment can be developed.

6.1. RISK FACTORS FOR RETINAL ARTERY OCCLUSION

Study I resulted in an overview of risk factors associated with retinal artery occlusion. Different risk factors were investigated, including cardiovascular diseases, ophthalmic diseases, inflammatory diseases, and systemic diseases. The investigated risk factors supported the established pathogenesis, systemic atherosclerosis, for retinal artery occlusion. Furthermore, the associated risk factors suggested that changes in the pressure gradients over the lamina cribrosa between the intraocular environment and the intracranial environment and the transmural pressure over the vascular wall may be associated with the development of retinal artery occlusion (Figure 6) (95).

Figure 6. Possible pathophysiology for retinal artery occlusion.



Abbreviations: RAO, retinal artery occlusion.

This figure shows a possible pathophysiology for retinal artery occlusion based on associated risk factors in study I.

This figure is a re-creation of figure 1 from study I: Ørskov M, Vorum H, Larsen TB, Lip GYH, Bek T, Skjøth F. Clinical risk factors for retinal artery occlusions: a nationwide case-control study. International Ophthalmology. 2022 Aug;42(8):2483–91 (95).

Atherosclerotic plaques originating from the carotid artery and the heart have been described as the main pathogenesis causing retinal artery occlusion (2). Different cardiovascular diseases are associated with plaques originating from the systemic arteries and the heart. Several of the investigated cardiovascular diseases with a considerable measure of effect were associated with systemic atherosclerosis (145,146), which support systemic atherosclerotic plaques as the main cause of retinal artery occlusion.

The strongest association of the cardiovascular diseases was identified between stroke and retinal artery occlusion (Figure 3). Stroke is a major risk factor of arterial thromboembolism and has previously been associated with retinal artery occlusion (2,73,147). The primary cause of stroke is embolization caused by systemic atherosclerosis, which correlates with the pathogenesis causing retinal artery occlusion (2,73).

We assessed that the strong associations between diabetes and both cardiovascular diseases and atherosclerosis facilitated the association found between retinal artery occlusion and diabetes. Therefore, we categorized diabetes as a cardiovascular disease. However, diabetes could have been classified as an endocrinological disease.

A weak association was identified between atrial fibrillation and retinal artery occlusion and no statistically significant association was identified between heart failure or acute myocardial infarction and retinal artery occlusion (Figure 3). Atrial fibrillation is the most common cardiac arrythmia. A turbulent blood flow through the atria may lead to thrombus formation. The thrombus is able to dislodge from the atrial

wall and embolize to the brain, resulting in a cardioembolic stroke (146,148,149). Heart failure and acute myocardial infarction have been described as risk factors for cardiogenic embolization as well (150). Based on the weak or lacking associations between retinal artery occlusion and atrial fibrillation, heart failure, and acute myocardial infarction, embolization originating from the heart may not be the primary cause of retinal artery occlusion in general. However, it has previously been suggested that cardiac diseases may mainly be associated with retinal artery occlusion in younger patients (32,33). Our population did not qualify as a younger population with a mean age of 68.4 years. Therefore, a specific population of younger patients with retinal artery occlusion is needed to further investigate the association between retinal artery occlusion and cardiac diseases.

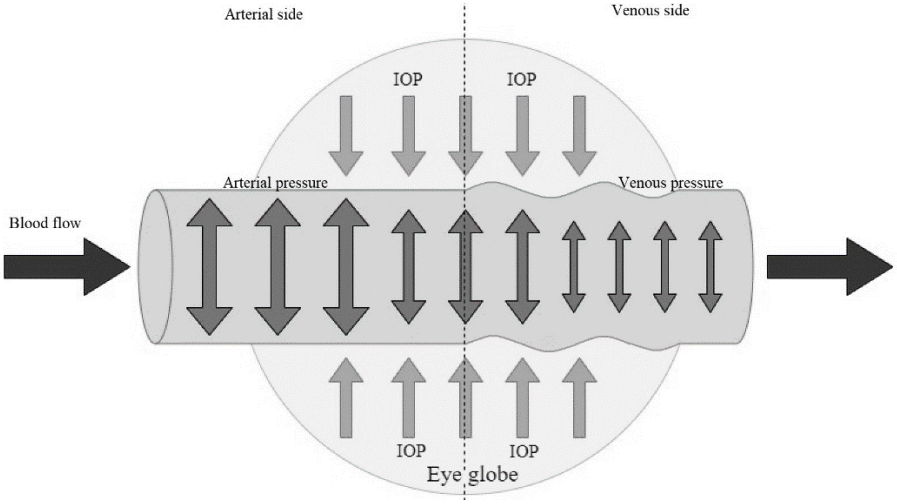
No association was found between venous thromboembolism and retinal artery occlusion (Figure 3). The main cause of venous thromboembolism can be illustrated by Virchow's triad, which include stasis, endothelial injury, and hypercoagulability (151). A venous thromboembolism is a thrombosis in the venous cardiovascular system, whereas atherosclerosis affects the arterial system. The lacking association between venous thromboembolism and retinal artery occlusion indicates that thrombus formation in the venous system does not affect the risk of retinal artery occlusion.

The investigated systemic and inflammatory diseases, associated with retinal artery occlusion, supported systemic atherosclerosis as the main cause of retinal artery occlusion as well. They have been found to be associated with cardiovascular diseases and atherosclerosis in previous studies (152–154). Liver disease and psoriasis were investigated and were found not to be associated with retinal artery occlusion. They both had a limited number of affected patients, which resulted in wide confidence intervals that reached equivalence. They were investigated since they had previously been found to be associated with atherosclerosis (155–157). A larger population of patients with liver disease and psoriasis or with retinal artery occlusion is needed for further investigation of the association between these diseases.

Inflammation was a composite exposure constituted of different inflammatory diseases with a low prevalence for each individual disease. However, it would be interesting to examine the different inflammatory diseases separately since the effect may vary, which would require a larger population.

Glaucoma and cataract were associated with the development of retinal artery occlusion (Figure 3), which may be explained by their shared association with age (11). The incidence of retinal artery occlusion increases with age. Similarly, the incidence of cataract and glaucoma increases substantially with age (158–161).

Figure 7. Schematic representation of the eye as a starling resistor.



Abbreviations: IOP, intraocular pressure.

The blood flows through the retinal arteries where the pressure inside the vessel exceeds the intraocular pressure outside the vessel, keeping the vessel dilated. When the blood reaches the venous side, the pressure inside the vessel is approximately the same as outside the vessel, if the intraocular pressure exceeds the venous pressure, the vein may collapse.

The association with glaucoma may suggest another possible pathogenesis mainly described in respect to retinal vein occlusion (25,162). Glaucoma is associated with increased intraocular pressure, as an imbalance in the composition of the fluid in the eye causes the intraocular pressure to increase (163). Glaucoma was associated with retinal artery occlusion, which may indicate that changes in the pressure gradients between the intraocular environment and the extraocular environment and the transmural pressure over the vascular wall may increase the risk of retinal artery occlusion. The mechanism has been described for the retinal veins, where the intraocular pressure provides a hydrostatic environment in the eye. The eye acts like a Starling resistor around the thin and flexible retinal vein walls. Increased intraocular pressure will reduce the transmural pressure, which may cause stasis or even pulse-synchronous stops in the blood flow (Figure 7). Fluctuations of the transmural pressure around zero and an intraocular pressure exceeding the intraluminal pressure inside the retinal vein both increase the susceptibility for initiation of thrombosis formation (25,162). The retinal arterioles will not collapse similarly to the retinal veins since they are thicker and the intraluminal pressure is higher (162). However, large changes in the pressure gradients of the eye or prolonged changes in the haemodynamics may affect the retinal arteries and increase the susceptibility for retinal artery occlusion. Nonetheless, this pathogenesis has been found to be stronger associated with the development of retinal vein occlusion compared to retinal artery

occlusion (164). Arterial hypertension may influence the intraocular pressure and thereby establish a connection between systemic atherosclerosis and the pressure gradients in the eye (165,166). However, the relationship between arterial hypertension and intraocular pressure is complex and further research is needed to understand the association between systemic atherosclerosis and the pressure gradients in the eye.

Instead of using glaucoma as a proxy for intraocular pressure, it would have been desirable to include intraocular pressure specifically. However, no diagnosis code exists for intraocular pressure in the utilized registers. The only way to include intraocular pressure would be to review the individual journals of the patients, where the intraocular pressure usually is measured and noted during ophthalmologic examinations in connection with most eye diseases. However, this would rarely correspond with the time when the intraocular pressure increased initially or caused symptoms in the patient and thereby eliminate the time aspect of the relation between the diseases.

We conducted additional studies to investigate the similarities and differences in risk factors between retinal artery occlusion and the two closely associated diseases, stroke and retinal vein occlusion (164,167). These studies supported the findings in this study. We compared the risk profiles between retinal artery occlusion and stroke. We found that cardiogenic embolization was stronger associated with the development of stroke than the development of retinal artery occlusion (167), which supports that mechanisms originating from the heart are not the main cause of retinal artery occlusion. The differences that exist between similar diseases are especially important in the management of the patients. However, we also identified several shared risk factors between the two diseases with emphasis on diseases associated with systemic atherosclerosis (167). In addition, we conducted a review identifying risk factors for retinal vein occlusion, where both cardiovascular diseases and eye diseases were comparable with the risk factors identified in this study for retinal artery occlusion (168). Therefore, we wanted to compare the association of the identified risk factors between retinal artery occlusion and retinal vein occlusion. We found that cardiovascular diseases were stronger associated with retinal artery occlusion than retinal vein occlusion, suggesting a stronger association between retinal artery occlusion and systemic atherosclerosis. Compared to retinal artery occlusion, we found a stronger association between the ophthalmic diseases and retinal vein occlusion (164). This supported a larger impact on the vulnerable veins when the pressure gradients change between the inside and the outside of the eye and over the vascular wall inside the eye.

Patients with systemic atherosclerosis may benefit from being scanned for carotid stenosis and receive a carotid endarterectomy if stenosis is present, which additionally may reduce the risk of retinal artery occlusion. Furthermore, future studies could

investigate if any antithrombotic treatment is effective in the prevention of retinal artery occlusion in patients with systemic atherosclerosis.

6.2. IDENTIFYING PATIENTS WITH RETINAL ARTERY OCCLUSION AT HIGH RISK OF STROKE

In study II we found an increasing risk of stroke dependent on increasing point levels of both the CHA_2DS_2-VASc score and the ESSEN Stroke Risk score in patients with retinal artery occlusion. Furthermore, we found that the discriminative abilities of the risk assessment models were insufficient due to the low prevalence of stroke in the strata.

As mentioned earlier, there are no guidelines for the management of retinal artery occlusion. However, an instant referral to a stroke clinic for evaluation is recommended after a retinal artery occlusion event due to the high risk of stroke in patients with retinal artery occlusion (28,61–65). The evaluation at a stroke clinic entails brain imaging of the neck or head to examine the carotid arteries for stenosis. Unfortunately, our data showed that only approximately 6% of the retinal artery occlusion population was scanned within 48 hours following their retinal artery occlusion event. This may indicate that the physicians need a tool for risk estimation for stroke. A useful risk assessment model would enable accurate separation of high-risk patients and low-risk patients, which could possibly be used to implement different management schemes for patients according to their individual risk. Thereby, patients at high-risk could be evaluated for stroke immediately following their retinal artery occlusion.

The structure of the two risk assessment models is similar, where presence of risk factors corresponds to an addition of points to the score. Furthermore, both the models have stroke as their endpoint, which was the reason for the inclusion of these specific risk scores (169–171). The included risk scores were originally developed for other purposes, but we wanted to investigate whether the use of these scores could be extended beyond these purposes. The CHA_2DS_2-VASc score was originally designed for risk stratification of stroke in patients with atrial fibrillation (169). The pathogenesis for atrial fibrillation and retinal artery occlusion may vary since atrial fibrillation mainly cause cardiogenic embolization (145,146), whereas retinal artery occlusion is stronger associated with systemic atherosclerosis and thereby atherosclerotic embolization (2,95,172). This could explain the less specific separation of patients according to risk when using the CHA_2DS_2-VASc score compared to the ESSEN Stroke Risk score. The ESSEN Stroke Risk score was developed for risk stratification of recurrence in patients who already experienced a stroke event (171). Previously, retinal artery occlusion has been described as an equivalent of stroke and the two diseases are very closely associated (71,167), which support the more segregated division of patients according to risk when using the ESSEN Stroke Risk score compared to the CHA_2DS_2-VASc score.

Based on the groups formed by the point levels of the risk scores, the ESSEN Stroke Risk score showed a better distinction between the patients compared to the CHA_2DS_2-VASc score, where the middle scores showed similar rates and risks (Table 4). However, they both divided the patients into groups with increasing risk of stroke with increasing point levels of the scores. The increase in risk for the CHA_2DS_2-VASc score and the ESSEN Stroke Risk score was noticeable and suggest a clinically relevant separation of patients. Furthermore, the difference was statistically significantly different between the individual groups according to the likelihood ratio test performed for each risk assessment model. The estimates of the Fine and Gray regression model were comparable with the effect estimates of the Cox proportional hazard model, which suggest that the hazard rate ratio can be interpreted as the risk ratio.

Since stroke risk stratification according to the risk scores was clinically relevant, the predictive abilities of the risk assessment models were investigated. A good prediction model needs good discrimination to precisely separate patients who will develop disease from patients who will not develop disease. The standard measure of discrimination is the C-statistics (129–131). Additionally, a good prediction model should have a good calibration. The calibration is a measure of the comparability between the predicted risks and the observed risks across the range of a risk assessment model (127). The Brier score is able to assess both the discrimination and the calibration (127,173). The investigated risk stratification models did not specify a specific risk for each point level of the risk scores, which entail that the Brier score mainly was a measure of the discrimination. Furthermore, the index of prediction accuracy was estimated, which compared the Brier score of each of the risk assessment models and the null model (127,136). A comparison with the null model ensured that the estimated predictive abilities were provided by the risk assessment models and not by other factors present before introducing the risk scores in the respective models. Both the C-statistics and the Brier score showed estimates better than random concordance for both risk assessment models as prediction models for stroke in patients with retinal artery occlusion, which aligned with the estimated rates and risks in the previous analyses. However, the index of prediction accuracy was approximately zero (Table 6), which indicates that there was no difference in predictive abilities between the null model and the investigated risk assessment models.

The index of prediction accuracy seems inconsistent with the other estimated measures in this study. However, this is due to the comparison made with the null model. All the other analyses performed showed an increased risk of stroke with increasing point levels of the risk assessment models in patients with retinal artery occlusion. The impediment is that the risk assessment models predict increasing risk of stroke but lack the ability to predict low risk of stroke. This indicates that the risk assessment models cannot discriminate between the patients who develop stroke and

the patients who do not develop stroke. Thereby, the point levels of the scores increase regardless of the development of stroke subsequently.

When dealing with a disease with a large negative clinical impact, such as stroke, a high sensitivity of a prediction model is especially important. Sensitivity is a measure of the discrimination and a high sensitivity will result in a low number of false negatives (129,174). It is desirable to identify all the patients who will develop stroke, which is possible to the detriment of also evaluating more patients who will not develop stroke. The C-statistics summarize the discrimination in one single number, where the sensitivity is one of the included measures, which would be more clinically relevant (129,174). The Brier score does not consider sensitivity or specificity, which limits the interpretation of the clinical relevance of the scores obtained (174,175).

We wanted to investigate whether the patients experiencing a stroke within the first period following the retinal artery occlusion event were grouped together by either of the risk scores. The time course following the index date was estimated using the cumulative incidence plot. We found a markedly increase in stroke risk during the first period for all point levels of both the investigated risk scores (Figure 4). Thereby, the population with an acute subsequent stroke event within the first month following the retinal artery occlusion were not grouped together in one stratum but separated in the different risk strata by both the investigated risk scores.

There are different ways to assess a risk assessment model. We investigated the static risk score at the patient's date of retinal artery occlusion. However, risk is not static. Another way of investigating the risk assessment models would be to include the dynamic nature of risk when identifying the risk score (176). This could happen by using the change in the status of the included risk factors in the risk assessment models during the last year prior to a patient's index date as the risk score.

6.3. RETINAL ARTERY OCCLUSION AS A PREDICTOR OF MACROVASCULAR COMPLICATIONS

The results of study III supported retinal artery occlusion as a potential predictor of cardiovascular events in patients with diabetes. The results showed a more pronounced increase in risk during the first period following the retinal artery occlusion event, but with a substantial risk during the full follow-up period of five years. A risk of this magnitude supports initiation of patient monitoring for cardiovascular diseases and continued monitoring for at least five years, which enable early instigation of treatment.

Reliable predictors of subsequent events and complications following a disease are important for the identification of high-risk patients and for the development of ideal management according to the risk for subsequent events. Other predictors have been identified for major diabetic complications, including biological markers and

complication status (177–181). Diabetes is associated with multiple complications and cardiovascular diseases contribute substantially to the morbidity and mortality of these patients (182,183). Therefore, a predictor of especially cardiovascular events would be beneficial for a better prognosis for patients with diabetes. The main cause of retinal artery occlusion is systemic atherosclerosis (2,95). Therefore, retinal artery occlusion is a potential predictor of atherosclerotic cardiovascular events.

The ideal predictor of atherosclerotic cardiovascular events would be the initial atherosclerotic event. However, an atherosclerotic plaque gradually progresses and become more susceptible to ruptures over time. The initial ruptures may be smaller and cause clinically asymptomatic embolism (184). We wanted to investigate retinal artery occlusion as a predictor of the atherosclerotic cardiovascular events because the eye is a sensory organ. Thereby, even the smaller occlusions of the branch retinal arterioles may be symptomatic and cause visual impairment in a part of the visual field. Furthermore, the retinal arterioles can be directly visualized using ophthalmoscopy (185), which enable visualization of the state of the arterioles and may reveal visible emboli causing the occlusion (186).

The increased risk of subsequent cardiovascular events in patients with retinal artery occlusion identified in this study underlines the need for international clinical guidelines, especially to avoid additional cardiovascular events. Therefore, both ophthalmologists and cardiologists should be included in the management of patients with retinal artery occlusion to ensure a specialized response for both vision preservation and systemic atherosclerosis. However, there are no definite clinical guidelines for patients with retinal artery occlusion and no effective treatment have been verified in randomized clinical trials (1,187). Therefore, the management of patients with retinal artery occlusion may vary between countries or even departments. For a consistent management for patients with retinal artery occlusion to make sense an effective treatment or management scheme must be identified. The efficacy of some interventions, used in patients with stroke, have been investigated in patients with retinal artery occlusion. Thrombolysis is a therapy that dissolve blood clots and improve blood flow. Thrombolytic therapy is used as an acute treatment of ischemic strokes, administered within four and a half hours of symptom initiation (54–56,188). Thrombolytic treatment have been associated with a better visual acuity outcome in the treated patients with central retinal artery occlusion compared to the untreated patients (57). As mentioned previously, both ischemic strokes and retinal artery occlusions are often caused by emboli originating from the carotid artery. A carotid endarterectomy reduces the risk of recurrent emboli by removing the unstable plaques in the common and internal carotid artery, thereby, improving the blood flow (67,189). Furthermore, carotid endarterectomy was determined to reduce the risk of subsequent stroke in patients with retinal artery occlusion (190). Additionally, antithrombotic treatment is generally administered patients with retinal artery occlusion where atherosclerosis is the cause of the occlusion (30). Randomized

controlled clinical trials are needed to develop definite international guidelines for treatment and management of patients with retinal artery occlusion.

Sensitivity analyses were conducted to test the robustness of the results. The first sensitivity analysis restricted the population to patients with no prior atherosclerotic cardiovascular event. In this analysis, retinal artery occlusion was the first atherosclerotic event in the patients. The second sensitivity analysis restricted the population to patients with no contact to a hospital up to 3 months before their retinal artery occlusion. In this analysis, we tried to exclude any patients with diseases that could introduce confounding but had not been considered. Both sensitivity analyses excluded patients who were not healthy before their retinal artery occlusion event. Considerable associations were identified for both sensitivity analyses (Table 7), which suggest that other diseases or surveillance by the healthcare system did not introduce significant bias and ensured that the retinal artery occlusion event was the event triggering the elevated risk of stroke. In addition, we conducted a post hoc landmark analysis where the start of follow-up was set at one year after the patients' retinal artery occlusion event (Table 7). This analysis was conducted because we saw an initial markedly increase in the risk of major adverse cardiovascular events following the retinal artery occlusion (Figure 5). The patients with retinal artery occlusion experience an event that influence their risk, whereas the controls are given an arbitrary index date with no event. It is important to investigate if this difference between the two groups influenced the results. A statistically significant effect was identified in this analysis, which supported that the observed effect was not limited to an initial increase, but a persistent increase in patients with retinal artery occlusion over the full follow-up period. Combined, the sensitivity analyses showed that the results were robust and did not depend on previous diseases or the change in case subjects compared to control subjects.

The composite endpoint major adverse cardiovascular events were used as the outcome of this study. Thereby, the main cardiovascular diseases; stroke, myocardial infarction, and cardiovascular death were investigated. We conducted an analysis to ensure that each individual disease in the composite endpoint contributed to the observed effect. Stroke yielded the largest effect measures (Table 8), which were expected due to the close association between retinal artery occlusion and stroke (71,167). Death yielded a large effect measure as well (Table 8), which could be facilitated by fatal stroke events. However, we did not have information on cause of death and had to include all causes of death. We expect the large association observed to be due to cardiovascular events, especially stroke. Only a limited number of myocardial infarction events were observed during the follow-up period, which resulted in a wide confidence interval reaching equivalence at one year of follow-up (Table 8). Myocardial infarction is associated with both atherosclerotic embolization and cardiogenic embolization (146,148,191). The combination of a limited number of events and various pathogeneses may explain the statistically insignificant confidence interval during the first year of follow-up. However, the effect measure was

statistically significant at five years of follow-up and the mean effect measure at one year of follow-up indicated an increased risk of myocardial infarction in patients with retinal artery occlusion. Other cardiovascular diseases would be relevant to investigate as well to ensure predictive abilities for all diseases associated with systemic atherosclerosis.

We included patients with diabetes, a vulnerable population with a higher incidence of retinal artery occlusion than the general population. However, nothing refrains the general conclusions from this study from being applicable to patients without diabetes. Therefore, it would be relevant to conduct similar studies in other populations to verify this theory in other settings.

6.4. REFLECTIONS ON FUTURE MANAGEMENT FOR PATIENTS WITH RETINAL ARTERY OCCLUSION

Currently, a patient experiencing a retinal artery occlusion should receive an ophthalmologic examination to ensure that it is in fact a retinal artery occlusion and eliminate other systemic diseases as the cause of the symptoms. Furthermore, the patients should be checked by brain imaging of the head or neck. The brain imaging ensures that the occlusion is located in the eye and not the visual cortex of the brain. Additionally, it examines the carotid arteries for stenosis. In case of stenosis, a carotid endarterectomy should be performed to restore continuous blood flow and reduce the risk of subsequent stroke. From there, no evidence-based management is available, which is unfortunate since animal studies indicate that the retina, as opposed to the brain, can recover fully if revascularization occurs within 97 minutes following the occlusion (51,52).

6.4.1. ACUTE TREATMENT OF RETINAL ARTERY OCCLUSION

No treatment has been found to be effective for retinal artery occlusion in randomized clinical trials (1). When determining the most effective treatment for a disease the cause should be considered. In study I, embolization caused by systemic atherosclerosis was supported as the main cause for retinal artery occlusion (95). Two meta-analyses have indicated that intravenous thrombolysis may be effective in patients with retinal artery occlusion (57,58). Furthermore, a multicentre phase 3 randomized clinical trial will be initiated to investigate the effect of thrombolysis administered within 4.5 hours in patients with central retinal artery occlusion (192). Several aspects should be considered when using thrombolysis in patients with retinal artery occlusion. First, retinal artery occlusion is not a fatal event. Therefore, less risk should be taken when treating the disease and the risk of haemorrhages should be considered in patients treated with thrombolysis. Second, the time aspect is very important if restoring of vision should be a possibility. Finally, the structure of the emboli should be considered since cholesterol or calcium emboli are not lysable (193). Mechanical thrombectomy may be an effective alternative for non-lysable emboli and

patients not eligible for thrombolysis (194). However, this should be investigated in a randomized controlled clinical trial to determine the effect of the treatment.

6.4.2. LONG-TERM MANGEMENT OF PATIENTS WITH RETINAL ARTERY OCCLUSION

Guidelines for prevention or reduction of complications should probably be worked out for patients with retinal artery occlusion. Studies, including our own, have found a significant risk of cardiovascular complications in patients with retinal artery occlusion. These patients may benefit from being informed of this risk and advised to go for regular check-ups at their physician for cardiovascular risk assessment. The risk of stroke is especially of concern in these patients. Presently, a referral to specialized stroke evaluation following a retinal artery occlusion event is recommended (28,61–65). However, there is no recommendation of follow-up. We found an increased risk of stroke following retinal artery occlusion. Patients may benefit from regular re-evaluations of their stroke risk and when necessary, instigation of early intensified treatment to prevent stroke. Additionally, our results suggested that retinal artery occlusion may be a predictor of macrovascular events up to five years after their event in patients with diabetes. This could be investigated in patients with other previous cardiovascular diseases or diseases associated with cardiovascular diseases. If retinal artery occlusion is a general predictor of macrovascular diseases in patients with previous cardiovascular diseases or diseases associated with cardiovascular diseases, regular check-ups to evaluate risk factors and instigate early intensified treatment according to the observed risk assessment could be beneficial.

The general risk of stroke is too low to justify anticoagulation treatment for all patients. Therefore, we wanted to identify a stroke risk stratification model for patients with retinal artery occlusion. However, the risk stratification models we investigated did not show sufficient predictive abilities to be implemented in clinical practice. Future studies could investigate whether a modified risk stratification model may be more ideal as a prediction model. A possibility is to create a more detailed model using big data and machine learning techniques, which may result in a more detailed and precise risk estimate.

The results of study III support the need for an effective treatment that prevent or reduce the risk of subsequent cardiovascular events in patients with retinal artery occlusion. Antiplatelet treatment has been found to reduce the risk of occlusive vascular events. However, they did not specifically investigate patients with retinal artery occlusion but stated that the results could be extrapolated to other high-risk patient groups (195). Future studies could confirm this statement in patients with retinal artery occlusion to determine the effectiveness of different antithrombotic treatments in these patients.

6.5. METHODOLOGICAL CONSIDERATIONS

Epidemiological studies aim to estimate measures of interest that are accurate and precise. However, errors of different types may occur. Systematic errors lead to loss of accuracy, whereas random errors lead to loss of precision. The accuracy of the results is also referred to as the validity. All epidemiological studies are evaluated on both their internal and external validity. Potential violations of the internal validity include selection bias, information bias, and confounding. The external validity concerns the generalizability of the results. Internal validity is a prerequisite for external validity (117).

6.5.1. SELECTION BIAS

Selection bias is introduced when there are systematic differences between exposure and outcome for the study participants and the subjects theoretically eligible for the study (117,196). Informative censoring may introduce selection bias, when loss to follow-up and competing risks result in differential loss (197). Therefore, selection bias may occur in all types of observational studies, introduced at the conception of the study or during the study process.

Study I was a case-control study and the main selection bias in case-control studies is control selection bias, where the control group is not representative of the population from which the cases were drawn (197). Danish registries have a practically complete population coverage from which both cases and controls were drawn for study I. This unselective population ensures minimal potential control selection bias.

In cohort studies, the outcome of interest should not have occurred at the time of entry, therefore selection of the cohort is not associated with the outcome. Study II and III were both cohort studies and thereby susceptible for selection bias introduced by informative censoring. A major strength of the Danish registries is their virtually complete follow-up, resulting in a negligible potential selection bias introduced by informative censoring due to loss to follow-up (197–199).

Competing risk may introduce selection bias. In study III, the outcome of interest was a composite endpoint including a potential competing risk, which was death. A composite endpoint including the competing risk eliminate the potential selection bias, which could have been introduced (200). In study II, the outcome of interest was stroke and death was a competing risk. A composite endpoint including death would result in a different interpretation of the results, which did not correlate with the aim of our study. Therefore, the competing risk of death was a potential source of selection bias. The effect will be overestimated if competing risks are ignored, making it very important to consider when analysing data (201). We performed a Fine and Gray analysis considering death as a competing event and found that the rate ratio was comparable with the risk ratio.

6.5.2. INFORMATION BIAS

Information bias is introduced during data collection and results in subjects being placed in the wrong exposure or outcome strata. Different types of information bias are relevant dependent on the study design, including surveillance bias, recall bias, reporting bias, and interview bias (117,202–204). All types of information bias can result in either differential misclassification or non-differential misclassification. Differential misclassification is when inaccurate information is different in the strata being compared. The bias introduced is unpredictable because the results might be overestimated, underestimated, or move towards equivalence. Non-differential misclassification equally affects all strata being compared and the bias will result in conservative estimates moving towards the null hypothesis. Misclassification is a concern in the study population, exposure, and outcome (117,203,204).

There is a general risk of misclassification in study I and III because retinal artery occlusion events may be asymptomatic, undiagnosed, or diagnosed at a private ophthalmologist and therefore not be registered in the national registries (205). Thereby, patients with retinal artery occlusion could be classified as controls or non-exposed, which would introduce differential bias since this misclassification would only affect one of the groups. The differential bias would result in an underestimation of the true effect.

One type of information bias is surveillance bias, where one group is monitored more closely than the other (202). There is a risk of surveillance bias in study I, where patients with retinal artery occlusion were compared with random controls from the background population. Patients with a previous diagnosis may be monitored more closely, have regular check-ups, or in general be more aware of their health. Especially a previous eye disease may lead to surveillance bias, since these patients may receive eye examinations, where retinal artery occlusion could be identified even as asymptomatic events. However, this would be a non-differential information bias because it would involve all subjects with a previous diagnosis both cases and controls and the measure of effect would approach equivalence.

In study II, we evaluated the inclusion of each element of the included risk scores, to ensure the most accurate definition. Nonetheless, using diagnoses codes limit the accuracy of the inclusion and an individual assessment by a physician may potentially have resulted in a different score in some cases. Therefore, we cannot reject the possibility of misclassification. However, the misclassification would be non-differential, which would move the effect towards equivalence.

In studies using registry data, the accuracy of the registration of the diseases are important and a potential source of misclassification (198). Several validation studies investigating the positive prediction value of information in the Danish National Patient Registry exist. These studies investigate the positive prediction value, but the

negative prediction value, specificity, and sensitivity are rarely identified. The negative prediction value is a measure of the proportion of eligible patients that were not included and finding these patients in very large registries is difficult (117).

The main diagnosis utilized in all the studies in this project was retinal artery occlusion. We have validated the diagnosis codes for the disease to make sure the validity was suitable for use in research. We calculated a positive prediction value of 79.4% for retinal artery occlusion, which suggested no significant misclassification (206).

Stroke was included as exposure or outcome in all three studies. The positive prediction value for ischemic stroke in the Danish National Patient Registry is approximately 90% (207–209), which is high. However, the positive prediction value for unspecified stroke (which was included in the stroke definition as well) is only approximately 65% (209,210). Hence, uncertainty is present when defining stroke. This uncertainty should be considered carefully when estimating event rates. The uncertainty is non-differential, and the measure of effect would move towards equivalence.

In study III, major adverse cardiovascular events were the outcome of interest, which included stroke, myocardial infarction, and death. Information bias concerning stroke was described above. The positive prediction value for myocardial infarction has been reported to be 97.0%-98.0% (207,208), which is high and acceptable for research. Information regarding death was obtained in the Danish Civil Registration System. No studies have validated the information in this registry. However, information in this registry is assumed to be of high quality and to have great coverage meaning there is no suspicion of significant misclassification.

The positive prediction value for information in the Danish National Patient Registry varies from below 15% to 100% (92). The positive prediction values reported for diagnoses used in this project were acceptable for research use, varying between 87%-100% (207,208,210). A lower positive prediction value of 76% was identified for heart failure (207), which we assessed to be acceptable for research purposes. We could not assess the validity for all diagnoses used in this project and potential misclassification may be present for the diagnoses with no reported positive prediction value, which included ischemic heart disease, inflammation, sleep apnea, cataract, and glaucoma. The diseases with no reported positive prediction values may introduce information bias. However, the misclassification would affect all the subjects included in the study and therefore be non-differential, moving the measure of effect towards equivalence.

To avoid underestimation of some diseases, pharmacological information on specific medical drugs were used to identify patients with the disease in question. This was especially important when identifying patients with hypertension, where we used

either a diagnosis of hypertension or at least two prescriptions of anti-hypertensive medicaments. This algorithm was validated, and the specificity and sensitivity were reported to be 94.7% and 80.0%, respectively (102). This suggests that no significant misclassification was associated with the classification of hypertension. Similarly, patients with diabetes were identified by either a diagnosis of diabetes or the collection of at least two prescriptions for glucose lowering drugs. This algorithm has not been validated, but it was inspired by the algorithm used in the Danish Diabetes Registry.

6.5.3. CONFOUNDING

Confounding is bias imposed by factor, other than the exposure of interest, that is associated with both the exposure and the outcome (117,200). Confounding is a systematic error that should be considered in all studies of causality. A confounder is defined as a factor associated with both the outcome and exposure of interest that potentially may introduce bias. Furthermore, a confounder is not an intermediate causal link between the exposure and outcome of interest (117,200,211–213). A crude statistical model does not consider any external exposure and thereby depict results as they appear in the world. Confounding present in an analysis can be accounted for by conducting an adjusted statistical analysis.

In study II and III no adjustment was made in the survival analyses. Both studies investigated predictive abilities. If implemented in clinical practice it is important that predictive tools reflect the real world and not a theoretical world where different factors affecting the results are adjusted for. Therefore, we used a crude model, where confounding was possible, to avoid misrepresenting what the world looks like.

In study I, we adjusted for sex, age, and the included risk factors assessed to introduce confounding based on the existing literature. The adjusting was made to elucidate the individual direct effect of each investigated risk factor. We were not interested in an effect confounded by other factors, which could provide the entire estimated effect. Adjusting for intermediate variables can introduce overadjustment bias, which should be considered when interpreting the adjusted model (117,212).

Complete elimination of confounding is impossible. The remaining confounding, which we did not or could not adjust for, is the residual confounding. This is represented by the factors we did not consider as confounders, including factors that were not measured, factors that were measured incompletely, and factors that were unavailable in the utilized registries (117). The task of elucidating a causal association is a difficult task and potential fallacies should be considered when interpreting results both from a crude and an adjusted model.

6.5.4. GENERALIZABILITY

Generalizability or the external validity refers to the representativeness of the study population when extrapolating the results to the target population (117,214). The virtually complete coverage of the Danish registries is an advantage for the generalizability of the results, since the study sample and the target population are essentially the same (198). Therefore, the results from the studies should be representative for the Danish population. However, the results may not necessarily be representative for other populations that are more ethnically diverse, have another ethnicity dominating the population, or have an entirely different healthcare system.

6.5.5. RANDOM ERROR

Random error is unexplained variation in data. Increasing the study size will increase the precision of an estimate and thereby reduce random error (117). In the studies of this thesis, the study sizes were relatively large, resulting in comparatively precise results.

CHAPTER 7. CONCLUSIONS AND PERSPECTIVES

7.1. MAIN CONCLUSIONS

This PhD thesis is based on studies where we investigated the interplay between retinal artery occlusion and cardiovascular diseases. We examined the clinical course of retinal artery occlusion attempting to outline important elements that should be considered in the management of these patients.

First, we examined risk factors associated with the development of retinal artery occlusion. These risk factors supported two possible pathogeneses for retinal artery occlusion, including systemic atherosclerosis and changes in the pressure gradients over the lamina cribrosa between the intraocular environment and the intracranial environment and over the vascular wall inside the eye.

Second, we found that contemporary scores for stroke risk stratification were applicable in a retinal artery occlusion population. The ESSEN Stroke Risk score showed a better separation of the included patients compared to the CHA_2DS_2-VASc score. Further, we examined their predictive performance and found that the discrimination of the risk assessment models was poor.

Finally, we found that patients with diabetes and retinal artery occlusion had a significantly increased risk of macrovascular complications compared to patients with diabetes and no diagnosis of retinal artery occlusion. The risk increased noticeably during the first period following the retinal artery occlusion event and remained elevated for at least five years. Based on these results, patients with diabetes who are diagnosed with retinal artery occlusion would benefit from the immediate and continuously monitoring for macrovascular diseases to evaluate risk factors and instigate early intensified treatment when necessary.

7.2. PERSPECTIVES

Our studies highlight some of the challenges regarding the complex interplay between retinal artery occlusion and cardiovascular diseases. A need for a better understanding of retinal artery occlusion remains before definite international clinical guidelines can be produced and implemented. Besides the reflections mentioned through the discussion, other questions remain to be answered.

The structure of the emboli has been investigated by fundoscopy and three main types have been identified, including cholesterol, calcific, and platelet-fibrin (215).

However, the reliability of these differentiations has been found to be poor (216). Therefore, future studies could investigate the structure of the emboli to determine the composition, which would be beneficial in the determination of treatment regime for affected patients. In particular, the composition of retinal artery occlusions may suggest whether the emboli are lysable and thrombolysis is a possible treatment or non-lysable and other treatments should be considered.

We focused on a subset of cardiovascular diseases relevant in relation to retinal artery occlusion. Our study on risk factors showed a strong association between peripheral artery occlusion and retinal artery occlusion. The interplay between these two diseases would be relevant to investigate further and more specifically in future studies. Additionally, our results found an association close to equivalence between atrial fibrillation and retinal artery occlusion, which may indicate that there are clinical differences between cardiac embolization and atherosclerotic embolization. The knowledge of the interplay between cardiogenic embolization and retinal artery occlusion is limited and would be interesting to further investigate.

The stratified analyses in study I identified some differences between males and females, retinal artery occlusion subtypes, and age groups. Minor differences were identified between males and females and the retinal artery occlusion subtypes. However, several differences were found between the investigated age groups (95). These differences may indicate variations in pathogenesis, which may support different managements for the subgroups. Additional studies investigating subgroups of patients with retinal artery occlusion would be relevant to consider.

In a highly specialized healthcare system as the Danish, the focus is often on the exact problem with which a patient is referred. Further understanding the interplay between ophthalmic diseases and cardiovascular diseases could help the health care system adapt to a more multidisciplinary approach. This would require additional research in the associations between ophthalmic diseases and cardiovascular diseases, including other ophthalmic diseases besides retinal artery occlusion.

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APPENDICES

Appendix A

Study I: Ørskov M, Vorum H, Larsen TB, Lip GYH, Bek T, Skjøth F. Clinical risk factors for retinal artery occlusions: a nationwide case-control study. International Ophthalmology. 2022 Aug;42(8):2483–91.

Appendix B

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