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STUDENT REPORT

Characteristics of patients with retinal artery occlusion initiated with antithrombotic treatment: A pilot study

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Abstract

Objectives: Retinal artery occlusion (RAO) is an acute ophthalmological emergency widely considered to be the equivalent of a cerebral ischemic stroke. Currently, some patients with RAO are initiated in prophylactic antithrombotic treatment and others are not. This study evaluates characteristics of patients with RAO initiated with prophylactic antithrombotic treatment compared to patients whom receive no prophylactic treatment.

Method: This preliminary study included all potential patients with RAO identified from the 1st of January 2017 to the 30th of November 2020 in the North Denmark Region. Identification of this patient group was achieved using the International Classification of Diseases (ICD) and data was gathered through each patient's electronic medical record. Retrospectively the diagnoses of RAO were confirmed. Patients with RAO were grouped by their antithrombotic treatment status and compared in terms of basic characteristics, diagnostic follow-up, time from symptom onset to healthcare contact and time from symptom onset to antithrombotic treatment initiation. Chi squared tests or one-way analysis of variance were used to compare proportions or means between groups.

Results: Of the 98 patients with RAO included in this study, 46 were initiated with antithrombotic treatment, 7 received no treatment before or after RAO and 45 were already in antithrombotic treatment before RAO. Most patients were initiated with aspirin (N = 44) and some patients were subsequently prescribed clopidogrel (N = 17) as a mono- or dual antiplatelet therapy. The most prevalent comorbidities were hyperlipidaemia (69.4 %), hypertension (82.7 %) and carotid artery disease (27.6 %). The majority of patients received ultrasound of the carotid arteries (83.7 %) after RAO onset. Patients receiving no treatment were more likely not to have any diagnostic follow-up (n = 3/7)(p = 0.05) and were observed to contact healthcare much later after symptom onset.

Conclusion: The majority of patients with RAO received antithrombotic treatment and the standard medication initiated was aspirin. Some patients' antithrombotic treatment was altered to clopidogrel, especially if diagnosed with carotid artery disease. Patients receiving no antithrombotic treatment were observed to have waited a longer period after RAO symptoms before contacting healthcare. These patients were also less likely to receive diagnostic follow-up.

1 Introduction

Retinal artery occlusion (RAO) is a relatively rare ocular disease estimated to affect 1-2 people per 100.000 people[1][2] and causes severe monocular visual impairment with over 60 % of patients having a final visual acuity (VA) of counting fingers or less on the affected eye [3].

Patients with RAO typically present acute, painless, monocular vision loss due to processes that interrupts the blood flow to the retina, leading to irreversible ischemic damage [1][4]. RAO is traditionally categorized based on the type of artery occluded as either a central retinal artery occlusion (CRAO) or a branch retinal artery occlusion (BRAO)[1][5]. The CRAO and BRAO etiology

are further divided into arteritic or non-arteritic RAO of which the former is rare and is caused by giant cell arteritis[4][5]. Non-arteritic RAO accounts for approximately 95.5 % cases and can be either permanent or transient[3]. It is usually caused by an embolism from a thromboembolic source, the most common being symptomatic carotid artery disease [1][4][5]. Furthermore, RAO is strongly associated with arterial hypertension, diabetes mellitus, carotid artery disease, cardiac arrhythmia, transient ischaemic attacks (TIAs), cerebral vascular accidents and smoking [4][5][2]. These risk factors also predispose for ischemic stroke [6]. In addition, studies have shown that patients with RAO have a higher risk of developing ischemic stroke within the first year[7][8][9], with the highest risk being within seven days after RAO onset [2][10][11][12].

Currently, there is no evidence-based effective treatment protocol of patients with RAO [13][14][15]. A US based study involving a survey of 45 university hospitals found only 20 % had implemented a protocol [15]. As such, various treatment strategies have been suggested of which none have shown to be effective [1][14]. In the acute management of patients with RAO, intravenous thrombolysis and conservative treatment consisting of bulbus massage, anterior chamber paracentesis, intraocular pressure-lowering eye drops and laser thrombectomy have been used as possible treatments [1][13][14]. Furthermore, some patients with RAO are initiated in prophylactic antithrombotic treatment to prevent new ischemic events [7][8][16]. The rationale behind this treatment is that RAO can be considered the ocular equivalent of an ischemic cerebral stroke and therefore can benefit from following the same local treatment protocol. The choice of antithrombotic agent initiated largely depends on the patient's other risk factors [8][16]. However, there is currently little research regarding the effect of this treatment specifically for patients with RAO [7][14][16]. Current evidence suggests that the antithrombotic treatment has very little prophylactic effect for ischemic stroke [7][14][16].

Due to the scarce research related to treatments of patients with RAO and their effectiveness, there is no consensus on any particular prophylactic treatment protocol to avoid RAO at the contralateral side or other ischemic events such as stroke [13][15]. As such, it is currently not clear which patients are initiated in prophylactic treatment and which are considered to require no prophylactic treatment. There may be inconsistencies in the time taken for a patient to contact healthcare, the departments they are examined in, and the diagnostic tools used. These factors may affect the decision of initiating antithrombotic treatment for patients with RAO.

Hence, this preliminary study will evaluate characteristics of patients with RAO initiated with prophylactic antithrombotic treatment compared to patients that receive no prophylactic treatment. These characteristics include time to first contact to healthcare, time of referral to the Department of Ophthalmology and diagnostic follow up.

2 Method

2.1 Study design and data management

This retrospective cohort study was based on patients diagnosed with RAO at Aalborg University Hospital in the North Denmark Region. Data was acquired through medical journals. In Denmark, all residents will at birth be assigned with a unique, permanent civil registration number, which is linked to the electronic medical record (EMR) nationwide. The EMR contains information about the patient's state of health, all initiated treatments and

any previous treatments the patient has received. Healthcare professionals are obligated to register any medical decisions and treatments in the patient's EMR. This study gathered data on a patient level by accessing their EMR. Data was extracted twice from each patient journal by two separate researchers. The two entries were later compared by the same researchers and merged into one dataset to ensure the data extracted was accurate. The data was not anonymized and therefore required ethical approval. Data was managed using the electronic data capture software REDCap version 10.6.26, 2021 Vanderbilt University [17].

2.2 Ethical approval

Research involving sensitive bioinformatics data must be approved by the National Committee on Health Research Ethics in Denmark. This study was approved on the 16th of July 2021, case 2109081. In addition to this, the study was also accepted and approved by the data-responsible institute (Region Nordjylland) on the 1st of September 2021, ID-number 2021-156.

2.3 Participants

Potential patients with RAO were identified using the International Classification of Diseases, the 10th revision (ICD-10)[18]. Participants with the following ICD-10 codes were included: transient retinal artery occlusion (H34.0), central retinal artery occlusion (H34.1), other retinal artery occlusion (H34.2) and retinal vascular occlusion, unspecified (H34.9). Patients with subcategories within these codes were also included. These codes were selected to include all possible RAO cases and exclude other diseases.

To ensure the correct diagnosis was given, every diagnosis of RAO was confirmed by retrospectively evaluating fundus photography, optical coherence tomography, and the medical history. In cases of missing fundus photos, the diagnosis was also accepted if two separate ophthalmologists confirmed the diagnosis in the medical history. Patients with incorrect diagnosis code were excluded from the study (Figure 1). Other exclusion criteria were prior retinal vein occlusion to RAO, unspecified date of RAO onset and arteritis temporalis at RAO onset.

The data collected included date of birth, gender, type of RAO, dates of onset of RAO, dates of first contact to healthcare and the Department of Ophthalmology. Furthermore, diagnostic tools such as electrocardiography (ECG), carotid ultrasonography, magnetic resonance imaging of the cerebrum (MRI-cerebrum), and computed tomography scan or angiography of the cerebrum (CT-cerebrum or CT-angiography) were included if performed within thirty days of RAO onset. All patients were assumed to have taken fundoscopic imaging and optical coherence tomography as part of the routine diagnostic process when seen at the department of ophthalmology, hence, these diagnostic investigations were not included in the data extraction.

2.4 Antithrombotic treatment

Antithrombotic treatment status was defined based upon the EMR or date of antithrombotic drug prescription. Based on this information, patients receiving treatment before onset of RAO, patients initiated in treatment due to RAO as well as patients receiving no treatment either before or after RAO were identified. These patients were separated into the following groups: 'Treatment initiated', 'Treatment before RAO' and 'Untreated', meaning no treatment before and after RAO.

Patients were defined as being on antithrombotic treat-

ment before onset of RAO if an antithrombotic drug had an active prescription in the EMR with a prescription date before onset of RAO. Similarly, patients were defined to be initiated on antithrombotic treatment after onset of RAO, if the treatment was initiated within three months after RAO. For all relevant prescriptions, the date of prescription, dosage and prescribing department was noted. Antithrombotic treatment was subdivided into the following groups: 'Aspirin', 'Clopidogrel', 'Anticoagulant' and 'Antiplatelet'. Anticoagulant medicine includes warfarin, phenprocoumon, dabigatran, edoxaban, rivaroxaban, apixaban whilst antiplatelet includes ticagrelor and prasugrel.

2.5 Comorbidities

To account for patient characteristics and the decision of initiating antithrombotic treatment the following comorbidities were included: hyperlipidaemia, diabetes mellitus, hypertension, cerebrovascular accident, carotid artery disease, ischemic heart disease and atrial fibrillation. Of these comorbidities, apart from cerebrovascular accident, ischemic heart disease and atrial fibrillation, patients were assumed to have had the condition at the time of RAO onset if diagnosed within one month after RAO onset. Hyperlipidaemia, diabetes mellitus, hypertension were defined if diagnosed at hospital or ordination of respectively antihyperlipidemic drug, glucose lowering drug or antihypertensive drug. Smoking status and familiar disposition of ischemic stroke were also included.

2.6 Statistical analysis

Baseline characteristics were registered for all the included patients with RAO and defined at RAO onset and analysed using descriptive statistics (number, percentage, mean ± standard deviation and median with interquartile range (IQR)). Descriptive analysis was carried out by splitting patients with RAO into groups based on their use of antithrombotic treatment according to the objective of this paper; 'Treatment initiated', 'Treatment before RAO' and 'Untreated'. Furthermore, the 'Treatment initiated' group was divided into four separate groups based on the primary antithrombotic treatment: 'Aspirin', 'Clopidogrel', 'Anticoagulant agent' or 'Antiplatelet agent'. Likewise, the 'Treatment before RAO' group was subdivided into two separate subgroups: 'Unchanged', meaning their antithrombotic treatment was unaltered, and 'Changed after RAO', meaning the antithrombotic treatment was changed after diagnosis of RAO. This allowed patients with characteristics requiring a more effective antithrombotic treatment to be clearly distinguished.

These groups were compared in terms of time until contact to the healthcare system, time from RAO onset to antithrombotic treatment initiated and diagnostic tools utilized. The time until contact to healthcare was divided into the following groups: 'within 24H', '24-48H', '3-7 days', '7-14 days', '15-30 days', '31-90' and '>90 days'.

Time taken for patients to be examined in the various departments was compared in two perspectives. Firstly, the time elapsed for the patient to be examined at the department of ophthalmology following a referral was compared. The time until healthcare contact was divided into the following groups: 'Within 24H', 'Between 24-48H', '3-7 days' and '>7 days'. Secondly, the time taken for a patient to be examined at a department, referred to by the department of ophthalmology, was compared with an addition of a 'N/A' group accounting for patients not being referred further. These times were divided into the similar groups as the aforementioned. Furthermore, Chi squared tests or one-way analysis of variance (ANOVA) were used to com-

pare proportions or means between groups with alpha set to 0.05.

All statistical data analyses were carried out using STATA (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC).

3 Results

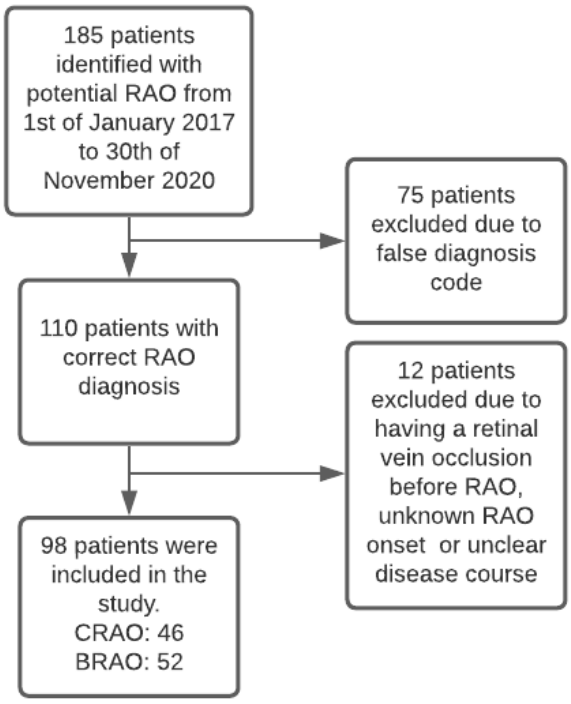

Figure 1: Flowchart of patients with RAO from 1st of January to 30th of November 2020.

3.1 Patient selection

From the 1st of January 2017 to the 30th of November 2020, a total of 185 patients were identified with potential RAO in the North Denmark Region. 75 patients were excluded due to incorrect diagnosis code, and 12 patients were excluded due to prior retinal vein occlusion diagnosis or unclear medical history. Hence, 98 patients were included in this study (Figure 1).

Among the three primary groups, 'Treatment initiated', 'Treatment before RAO' and 'Untreated', most patients were initiated with antithrombotic treatment after RAO (n = 46, 46.9 %), closely followed by the group receiving antithrombotic treatment before RAO (n = 45, 45.9 %) and patients being untreated before and after RAO (n = 7, 7.1 %). Of the 'Treatment initiated', 27 patients received aspirin as the primary treatment and 19 received clopidogrel as their primary treatment. Furthermore, 17 of the patients who received clopidogrel, received aspirin either as monotherapy or in combination with clopidogrel as dual antiplatelet therapy for a period, varying from three weeks up to three months. No patients were initiated with either anticoagulant treatment or any other antiplatelet treatment. Of the patients in 'Treatment before RAO', 16 patients had their antithrombotic treatment altered after RAO onset of which 15 were changed to clopidogrel and one changed to rivaroxaban.

3.2 Basic characteristics

The basic characteristics of the included patients are presented in Table 2. Of the 98 patients with RAO, 34 were female and 64 were men. Mean age was 70.7 ± 11.3 years and mean BMI was 27.8 ± 6.0. No significant differences regarding age (p = 0.08) and BMI (p = 0.47) were found within the groups. 24.5 % of the patients were smokers at time of diagnosis, 40.8 % were former smokers and 30.6 % had never smoked. In terms of comorbidities, hyperlipidaemia (n = 68, 69.4 %), hypertension (n = 81, 82.7 %) and carotid artery disease (n = 27, 27.6 %) were amongst the most recurring conditions in general. Hyperlipidaemia had a lower prevalence amongst 'Aspirin' and

'Untreated' ($p \leq 0.01$), and carotid artery disease was significantly more prevalent ($p \leq 0.01$) for 'Clopidogrel' and 'Changed after RAO'.

3.3 Contact and treatment

Patients independent of group showed a median of one day (IQR, 4.3 - 0.0) from RAO onset to healthcare contact (Table 2). No significant differences ($p = 0.19$) were found between the groups. In continuation of this, Chi-square test showed a significant difference ($p < 0.01$) in the defined time groups. The median from RAO onset to treatment initiated was three days (IQR, 10.0 - 1.0) with no significant differences ($p = 0.24$) within the groups. 'Aspirin' patients differed by a median of two days in regard to time to healthcare contact and treatment initiated after RAO onset.

3.4 Diagnostic follow-up

The majority of patients received ultrasound of the carotid arteries (n = 82, 83.7 %) (Table 2). The patients receiving no treatment were more likely not to have any diagnostic follow-up (n = 3/7)($p = 0.05$). Patients in the groups 'Clopidogrel' and 'Changed after RAO' received more thorough diagnostic follow-up including ECG ($p < 0.01$), MRI cerebrum ($p < 0.01$) and CT cerebrum/CT-angiography (Table 2).

Table 1: Basic characteristics for patients with RAO grouped by antithrombotic treatment status. ⋆: 39/98 missing data values. †: 4/98 missing data values.

Characteristics	Treatment initiated		Treatment before RAO				P-value
	Aspirin (n = 27)	Clopidogrel (n = 19)	Untreated (n = 7)	Unchanged (n = 29)	Changed after RAO (n = 16)	Total (n = 98)	
RAO type, n (%)							
CRAO	11 (40.7)	11 (57.9)	2 (28.6)	14 (48.3)	8 (50.0)	46 (46.9)	
BRAO	16 (59.3)	8 (42.1)	5 (71.4)	15 (51.7)	8 (50.0)	52 (53.1)	0.67
Female gender, n (%)	11 (40.7)	6 (31.6)	5 (71.4)	5 (17.2)	7 (43.8)	34 (34.7)	0.06
Age at RAO onset, mean (sd)	67.0 (13.3)	70.5 (8.7)	65.1 (19.9)	74.0 (8.5)	73.8 (8.2)	70.7 (11.3)	0.08
BMI, mean (sd)⋆	29.1 (8.8)	27.7 (4.2)	23.8 (2.2)	26.9 (4.7)	29.5 (7.3)	27.8 (6.0)	0.47
Tobacco, n (%)†							
Former smoker	4 (14.8)	8 (42.1)	1 (14.3)	16 (55.2)	11 (68.8)	40 (40.8)	
Current smoker	8 (29.6)	6 (31.6)	2 (28.6)	5 (17.2)	3 (18.8)	24 (24.5)	
Never	11 (40.7)	5 (26.3)	4 (57.1)	8 (27.6)	2 (12.5)	30 (30.6)	≤0.01
Comorbidities							
Hyperlipidemia, n (%)	11 (40.7)	15 (78.9)	3 (42.9)	25 (86.2)	14 (87.5)	68 (69.4)	<0.01
Diabetes Mellitus, n (%)	2 (7.4)	2 (10.5)	1 (14.3)	6 (20.7)	3 (18.8)	14 (14.3)	0.65
Hypertension, n (%)	19 (70.4)	13 (68.4)	5 (71.4)	29 (100.0)	15 (93.8)	81 (82.7)	≤0.01
Cerebrovascular accidents, n (%)	4 (14.8)	2 (10.5)	2 (28.6)	12 (41.4)	3 (18.8)	23 (23.5)	0.08
Carotid artery disease, n (%)	2 (7.4)	8 (42.1)	0 (0.0)	6 (20.7)	11 (68.8)	27 (27.6)	<0.01
Ischemic heart disease, n (%)	0 (0.0)	1 (5.3)	1 (14.3)	12 (41.4)	7 (43.8)	21 (21.4)	<0.01
Atrial fibrillation, n (%)	0 (0.0)	0 (0.0)	1 (14.3)	11 (37.9)	2 (12.5)	14 (14.3)	<0.01
Disposition, n (%)	3 (11.1)	2 (10.5)	3 (42.9)	9 (31.0)	7 (43.8)	24 (24.5)	0.04

Table 2: Time from RAO onset to healthcare contact as well as time from RAO to treatment initiation both grouped by antithrombotic treatment status. Diagnostic tools utilized is included.

	Treatment initiated			Treatment before RAO			
Days between onset of RAO and first contact to healthcare	Aspirin (n = 27)	Clopidogrel (n = 19)	Untreated (n = 7)	Unchanged (n = 29)	Changed after RAO (n = 16)	Total (n = 98)	P-value
Days, median (IQR)	1.0 (4.0 - 0.0)	1.0 (3.0 - 0.0)	25.0 (212.0 - 0.0)	1.0 (5.0 - 0.0)	1.0 (1.8 - 0.0)	1.0 (4.3 - 0.0)	0.19
Grouped by days, n (%)							
Within 24H	15 (55.6)	12 (63.2)	2 (28.6)	19 (65.5)	12 (75.0)	60 (61.2)	
24-48H	3 (11.1)	2 (10.5)	0 (0.0)	2 (6.9)	1 (6.3)	8 (8.2)	
3-7 Days	6 (22.2)	2 (10.5)	0 (0.0)	4 (13.8)	1 (6.3)	13 (13.3)	
8-14 Days	1 (3.7)	3 (15.8)	1 (14.3)	4 (13.8)	0 (0.0)	9 (9.2)	
15-30 Days	1 (3.7)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	2 (2.0)	
31-90 Days	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (12.5)	3 (3.1)	
>90 Days	0 (0.0)	0 (0.0)	3 (42.9)	0 (0.0)	0 (0.0)	3 (3.1)	<0.01
Time from onset of RAO to antithrombotic treatment initiated							
Days, median (IQR)	3.0 (8.0 - 0.0)	1.0 (10.0 - 1.0)	-	-	4.5 (10.8 - 2.0)	3.0 (10.0 - 1.0)	0.24
Grouped by days, n (%)							
Within 24H	10 (37.0)	10 (52.6)	-	-	3 (18.8)	16 (25.8)	
24-48H	2 (7.4)	2 (10.5)	-	-	2 (12.5)	4 (6.5)	
3-7 Days	8 (29.6)	0 (0.0)	-	-	4 (25.0)	15 (24.2)	
8-14 Days	2 (7.4)	6 (31.6)	-	-	4 (25.0)	14 (22.6)	
15-30 Days	1 (3.7)	1 (5.3)	-	-	1 (6.3)	6 (9.7)	
31-90 Days	1 (3.7)	0 (0.0)	-	-	2 (12.5)	4 (6.5)	
>90 Days	3 (11.1)	0 (0.0)	-	-	0 (0.0)	3 (4.8)	0.09
Diagnostics follow-up							
ECG, n (%)	8 (29.6)	14 (73.7)	2 (28.6)	11 (37.9)	13 (81.3)	48 (49.0)	<0.01
Ultrasound of the carotid arteries, n (%)	22 (81.5)	18 (94.7)	4 (57.1)	23 (79.3)	15 (93.8)	82 (83.7)	0.14
MRI cerebrum, n (%)	2 (7.4)	10 (52.6)	0 (0.0)	7 (24.1)	6 (37.5)	25 (25.5)	<0.01
CT cerebrum and CT-angiography, n (%)	3 (11.1)	6 (31.6)	0 (0.0)	5 (17.2)	6 (37.5)	20 (20.4)	0.10
None, n (%)	4 (14.8)	0 (0.0)	3 (42.9)	4 (13.8)	1 (6.3)	12 (12.2)	0.05

Table 3: Est. time until seen at Dept. of Ophthalmology after referral and est. time until seen at referred department from Dept. of Opthalmology. Both subtables are grouped by the department in action.

Est. time elapsed until seen at dept. of ophthalmology after referral	General Practise (n = 17)	Private Ophthalmologist (n = 49)	On-call doctor (n = 19)	Dept. Of Neurology (n = 7)	Emergency Department (n = 4)	Other (n = 2)	Total (n = 98)	P-value
Within 24H, n (%)	17 (100.0)	20 (40.8)	19 (100.0)	4 (57.1)	4 (100.0)	1 (50.0)	65 (66.3)	
Within 24H-48H, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
3 - 7 days, n (%)	0 (0.0)	3 (6.1)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	4 (4.1)	
>7 days, n (%)	0 (0.0)	26 (53.1)	0 (0.0)	2 (28.6)	0 (0.0)	1 (50.0)	29 (29.6)	<0.01

Est. time elapsed until seen at referred dept. from dept. of ophthalmology	Neurology (n = 70)	Cardiology (n = 4)	None (n = 20)	Other (n = 4)	Total (n = 98)	P-value
Within 24H, n (%)	17 (24.3)	0 (0.0)	0 (0.0)	1 (25.0)	18 (18.6)	
Between 24-48H, n (%)	7 (10.0)	0 (0.0)	0 (0.0)	3 (75.0)	10 (10.3)	
3-7 days, n (%)	26 (37.1)	0 (0.0)	0 (0.0)	0 (0.0)	26 (26.8)	
>7 days, n (%)	19 (27.1)	3 (75.0)	0 (0.0)	0 (0.0)	22 (22.7)	
N/A, n (%)	1 (1.4)	1 (25.0)	19 (100.0)	0 (0.0)	21 (21.6)	<0.01

3.5 Referral

As shown in Table 3, most patients were seen at the Dept. of Ophthalmology within 24 hours of symptom onset (n = 65/98), however a larger portion of patients (n = 26/49) referred from the private ophthalmologist was seen after seven days from when the referral was made. After being seen at the Dept. of Ophthalmology, the majority of patients (n = 70/98) were referred to the Dept. of Neurology and some patients (n = 19/98) never received a referral. Of the patients referred to the Dept. of Neurology, most were seen between the 3-7 days (n = 26/70), however, Table 3 shows random variation within this group.

4 Discussion

This preliminary retrospective cohort study evaluated data from 98 RAO patients extracted through EMRs. The objective was to evaluate the characteristics of patients with RAO initiated with antithrombotic treatment compared with the patients not receiving this treatment.

This study has shown a general tendency for patients with RAO to be initiated in antithrombotic treatment since only 13.2 % of patients not in any prior antithrombotic treatment remained untreated. Regarding patients initiated with antithrombotic treatment, aspirin was the primary choice of prophylactic treatment. Overall, the patients who did not receive antithrombotic treatment had delayed contact to healthcare and were observed to get diagnostic follow-up less frequently.

4.1 Strengths and limitations

A strength of this study is that the diagnosis of RAO of all included patients were validated. False data and data entry was minimized by the design with double-data entry and subsequent merging. Patients were evaluated individually by assessing and extracting information from their EMR. This made it possible to get exact dates of RAO onset as opposed to registry studies, where the symptom onset is assumed to be the date the patient is assigned an ICD-code following confirmed diagnosis.

Data which is not available through data registers such as BMI, smoking status and disposition of ischemic stroke could be collected. In addition, data collection was carried out using a custom made questionnaire with set definition and rules to ensure consistency in the format and data collected.

Certain limitations were present for the current study. The study included 98 patients making an inappreciable sample size which is not ideal for statistical analysis. Only seven patients turned out to be untreated making comparison with this group difficult since any potential data outliers would have great influence. Lastly, The data was conducted from a single hospital weakening the overall generalisability, since different hospitals nationwide may differ in the handling of patients with RAO.

4.2 Choice of antithrombotic drugs used in treatment and diagnostic follow-ups implemented

Of the included patients in this study, 54.1 % did not receive any thrombotic treatment prior to RAO onset and of these patients 13.2 % did not receive antithrombotic treatment after RAO. Two register-based studies, from respectively Denmark and Taiwan by Vestergaard et al. and Kang et al., found that half of patients with RAO and CRAO received antithrombotic treatment prior to RAO [7][8]. However, comparing the percentage of untreated groups with these studies is not suitable since both of their

'Untreated groups' are based on drug claims. Hence, this is the first study to, our knowledge, comparing characteristics of patients initiated with antithrombotic treatment with those untreated.

This study found that aspirin was the primary choice of drug, if antithrombotic treatment was initiated. Of those receiving clopidogrel, 17 patients were firstly initiated with aspirin. Every patient receiving aspirin had a dosage of 75 mg. Noticeably, both 'Aspirin' (59.3 %) and 'Clopidogrel' (63.2 %) inconsistently received bolus of 300 mg aspirin. The primary differences within the 'Aspirin' and 'Clopidogrel' was the latter having a higher prevalence of carotid artery disease (42.1 %, $p < 0.01$) and hyperlipidaemia (78.9 %, $p < 0.01$). Similarly, the "Changed after RAO", which primarily consisted of patients changed to clopidogrel treatment (n = 15/16), had a higher prevalence of carotid artery disease (68.8 %, $p < 0.01$). Furthermore, 'Clopidogrel' and 'Changed after RAO' also received a more thorough diagnostic follow-up consisting of ECG, ultrasound and/or MRI. Hence, it could suggest that the initiation with clopidogrel is due to carotid artery disease.

4.3 Timeframe from symptom onset until antithrombotic treatment

Although no significant difference was found, untreated patients had a greater tendency to contact healthcare long after symptom onset with a median of 25 days (IQR, 212.0 - 0.0). This variable stands out for the untreated patients which may influence the decision of not initiating the treatment. Furthermore, most patients contacted healthcare within 24 hours (61.2 %), 48 hours (8.2 %) and 3 - 7 days (13,3 %) with a median of 1 day. However, contradicting findings were seen in a study by Hayreh et al. 2005, in which 24.5 % of patients presented within the first 24 hours [3]. Moreover, the study found 48.4 % patients contacted healthcare within the first 7 days[3] whilst the current study found 82.7 % contacted healthcare in the same time interval. This suggests that possible variance exists between the population groups of the different studies at different healthcare systems.

In previous studies, patients diagnosed with RAO have shown to be at high risk of developing stroke, especially within the first seven days after symptom onset [2][10][11][12]. To prevent this outcome, patients with RAO are encouraged to be initiated in antithrombotic treatment as quickly as possible[19]. However, this study found that the time taken until initiation of antithrombotic treatment varies greatly with only 25.8 % of patients initiated within 24 hours, 6.5 % initiated 24-48 hours and 23.9 % initiated between 3-7 days. Remarkably, 21.7 % of patients were initiated between 8-14 days and 21.7 % initiated after 15 days. Hence, 43.4 % of patients are not initiated with antithrombotic treatment within the period where risk of stroke is greatest. This may be due to the time taken for the patient to be seen at the referred department, as the current study found 53.1 % of the patients referred to the Dept. of Ophthalmology, from a private ophthalmologist, were seen after seven days.

4.4 Comorbidities of patients with RAO initiated in antithrombotic treatment

In terms of comorbidities, this study found hypertension and hyperlipidaemia to be the most prevalent amongst the patients with RAO. Of the patients initiated in antithrombotic treatment, 56.7 % had hyperlipidaemia and 69.6 % had hypertension [see Table 1]. These were also the most prevalent conditions of the patients in antithrombotic treatment before RAO with 97.8 % having hy-

pertension and 86.7 % having hyperlipidaemia. Hence, these findings are in accordance with the already well defined knowledge on comorbidities of patients with RAO [2][8][19].

4.5 Positive predictive values of ICD-10 codes and RAO

There are possible limitations connected with the use of ICD-10 codes. A study from 2017 by Horsky et al., based on study scenarios and physicians giving relevant ICD-10 codes, found great variability in the precision of giving the appropriate ICD-10 code [20]. They found the diagnosis accuracy of primary diagnoses to vary from 48 % to 91 % [20]. Similarly, a Danish validation study from Sundbøll et al., validating the positive predictive value (PPV) of cardiovascular diseases, found an equal range from 64 % to 100 % PPV from ICD-10 codes [21]. In continuation of this, this study found the PPV of each ICD-codes and RAO to be: H34.0 (transient retinal artery occlusion) 0.0 %, H34.1 (Occlusio arteriae centralis retinae) 82.4 %, H34.2 (Other retinal artery occlusion) 76.9 % and H34.9 (Retinal vascular occlusion, unspecified) 35.1 %. Only H34.1 and H34.2 had PPVs above 75 %. Between H34.1 and H34.2, the majority (80.9 %) of patients given an incorrect code suffered from retinal vein occlusions. Hence, the discrepancy of the diagnosis of RAO within the included ICD-codes, this study found H34.1 and H34.2 to be the most viable codes when extracting data regarding RAO. However, further investigation is needed to clarify this potential issue.

4.6 Future studies

This preliminary study mainly implemented descriptive analysis due to the study design and small sample size. Future studies would benefit from including a larger population to allow better statistical analysis to find any correlation between the investigated characteristics and the decision to initiate antithrombotic treatment. The current study originally aimed to also investigate the outcome of the patients with RAO, in terms of ischemic stroke, but only five outcomes were observed in the investigated population, hence statistical analysis was not feasible. The prophylactic antithrombotic treatment for future outcomes in patients with RAO is not fully elucidated, future studies should include outcomes, such as stroke, to investigate whether the prophylactic antithrombotic treatment helps to avoid these complications from developing within the initial high-risk period.

The accuracy of the ICD-10 codes given to patients with RAO was highlighted in this study. Future studies would arguably benefit from using a similar study design, extracting data from EMRs or considering the PPVs of RAO within the ICD-10 codes found in this study.

5 Conclusion

This preliminary cohort study found that the majority of patients with RAO received antithrombotic treatment with the standard medication initiated being aspirin. Furthermore, nearly all patients received an ultrasound of the carotid arteries and were more likely to receive clopidogrel in case of carotid artery disease. Patients never receiving antithrombotic treatment were observed to seek medical attention long after symptom onset and were less likely to receive diagnostic follow-up. However, the effect of antithrombotic treatment in patients with RAO as a prophylactic treatment against the outcomes of stroke is still up for debate, hence, further research is required.

6 Acknowledgement

The authors would like to express their gratitude to supervisors Nanna Vestergaard and Tobias Nissen for great and valuable guidance and useful critique during the writing process of this research paper. Additionally, a special thanks to statistician Niels Bruun for helpful suggestions on statistical analysis and support in STATA.

7 Conflict of interest

None of the authors have conflicts of interests to disclose related to this study.

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