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Retinal ischemia due to different stages of atherosclerosis - insights from a retrospective study on central retinal artery occlusion

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Abstract

Background Ischemic stroke (IS) and retinal ischemia (IR) share similar vascular risk factors, but differ in their risk for subsequent or recurrent stroke and therapeutic options. This study characterizes the cardiovascular risk profiles and magnitude of atherosclerosis of the carotid artery of patients with central retinal artery occlusion (CRAO) in relation to the presence of the retrobulbar "spot sign" on orbital color-coded sonography (OCCS).

Methods We performed a retrospective analysis on the detailed cardiovascular risk factors and neuroimaging data in patients with IR presenting between 2009 and 2023. Based on OCCS findings, CRAO were further divided into hyperechoic ("spot sign positive", ssCRAO) or hypoechoic CRAO (heCRAO). Statistical analyses were performed with Mann-Whitney-U and χ [2] testing. P-values were considered significant if < 0.05.

Results Overall, 112 patients were identified (heCRAO: *n* = 32; ssCRAO: *n* = 80). ssCRAO patients were significantly older (median 74 years vs. 66.5 years, Mann-Whitney-U: p-value < 0.001). Overall, 15/103 (14.6%) patients had concurrent acute ischemic stroke– 9 in the ipsilateral internal carotid territory, 2 in other territories and 4 disseminated. Further significant differences were found regarding the echogenicity of atherosclerosis (AS) in the two subgroups with (mainly) echorich AS being more common in the ssCRAO group (p-value < 0.001, *n* = 108) and the distribution of high-grade vs. low-grade stenoses of the ipsi- and contralateral carotid artery (p-value < 0.05, *n* = 99). 20 out of 112 patients had atrial fibrillation (aFib) with 17 of these being on ongoing oral anticoagulation.

Conclusion According to this study, atherosclerosis may be one of the most important risk factors for IR while a specific embolic source could not be demonstrated (i.e. acute plaque rupture). By contrast, current oral anticoagulation for aFib in CRAO patients was high, thus only an incidental finding and may be an incidental finding due to its prevalence in the elderly. Furthermore, we were able to distinguish two subgroups of IR that differ in risk

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factors and most likely also in etiology, therapy and prognosis. The study underlines the importance of OCCS to detect "spot signs" in IR with indications for both, acute thrombolysis and secondary prevention.

Keywords Retinal ischemia, Spot sign, Orbital color coded sonography, Atherosclerosis, Cholesterol emboli, Central retinal artery occlusion

Background

Retinal ischemia (IR) from non-arteritic central retinal artery occlusion (CRAO) still lacks effective treatment and prognosis remains poor [1, 2]. Yet, the retina and brain share the same arterial supply and the vascular risk factors for ischemic stroke (IS) and IR are similar [3]. Nevertheless, the progress seen in IS therapy, mainly intravenous thrombolysis (IVT) and mechanical thrombectomy, has not been achieved in IR [4]. Current treatment options for IR due to CRAO are limited to "conservative" procedures [5–7]. The potential advantage of systemic thrombolysis is currently being investigated in controlled studies while local intra-arterial therapies have been abandoned due to severe complications, lack of efficacy and late presentation of patients [1, 4, 6, 8–15].

Still, the specific etiopathology and embolic source is not well defined, which is critical for secondary prevention as well as for the prognosis after recanalizing therapies in the acute setting. A promising diagnostic tool is orbital color-coded sonography (OCCS) which can identify the presence or absence of the retrobulbar "spot sign" as a marker for CRAO. A positive "spot sign" may suggest either calcified or cholesterol emboli in CRAO and branch retinal artery occlusion, and these dominantly cholesterol emboli are "Hollenhorst plaques" [16, 17]. Frequently found upon fundoscopy, they are thought to originate from atherosclerotic plaques. In fact, a patho-histological work-up of carotid endarterectomy specimen of "symptomatic" high-grade internal carotid artery (ICA) stenoses from the Oxford Plaque and Athero-Express-Study revealed significantly more features of plaque vulnerability such as large lipid core, inflammation and overall plaque instability as well as less fibrous content and calcification in patients with IS to patients with IR [18]. Thus, organ size and emboli composition may also be responsible for differences between stroke and retinal ischemia that render a direct transfer of successful therapeutic strategies from IS to IR problematic. Also retinal arteries including the central retinal artery are essentially endarteries similar to the perforating arteries of the pons and basal ganglia. This implies higher susceptibility to ischemia, difficulties for penetration and distribution of thrombolytic agents and consequently shorter therapeutic windows and the possibility of plain hypoperfusion infarction. All these factors may need to be considered for future studies.

In summary, due to differences in emboli size and composition, different responses to current medical, endovascular and surgical intervention for acute treatment and secondary prevention treatment, IR differs considerably from IS and thus, the Trial of Org 10,172 in Acute Stroke Treatment (TOAST) criteria might not be transferred directly from IS to IR [19]. The aim of this study was to identify specific cardiovascular risk factors, extracranial carotid atherosclerosis (AS) and possible causes for the emboli leading to IR in two distinct subgroups based on OCCS and fundoscopy: spot-sign positive CRAO (ssCRAO) and spot-sign negative (= hypoechogenic) CRAO (heCRAO).

Methods

This longitudinal, retrospective study was approved by the Ethical Review Board of the University of Regensburg (reference: 19-1542-104). Discharge letters were screened for patients who suffered CRAO. Patients with arteritic CRAO and amaurosis fugax as well as patients with branch retinal artery occlusion were excluded.

The following data were extracted from the medical record: age, sex, antihypertensive medication, diabetes mellitus, hypercholesterinemia, history of smoking, peripheral artery disease, presence of persistent or intermittent atrial fibrillation (AF), cardiac abnormalities including aortic and mitral valve pathologies and patent foramen ovale, previous stenting of coronary arteries and history of myocardial infarction, anti-thrombotic and anti-platelet medication as well as oral anticoagulation at presentation. Furthermore, the patients were evaluated for peripheral emboli and further vascular events.

Any available neuroimaging by cerebral computed tomography (cCT) and cerebral magnetic resonance imaging (cMRI) was re-evaluated for the presence of acute and previous cerebral ischemia, including the vascular territory and signs of small vessel disease according to Fazekas [20].

In addition, atherosclerosis was analyzed in detail using the ultrasound image data base as IR patients were routinely scanned as part of the diagnostic work up in the stroke unit (ClinWinData, Erlangen, Germany). Neurosonographic investigations were performed according to stroke unit standard including the central retinal artery in case of CRAO by technicians and neurological residents under supervision of the attending stroke neurologists experienced in neurovascular ultrasound. The echogenicity of atherosclerotic carotid plaques (internal and common carotid arteries) was re-classified and confirmed by a DEGUM certified neurosonologist (FS)

according to the Mannheim criteria using the ultrasound image archive. Any ICA stenoses were classified according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria including purely B-mode graduation in < 40% stenosis as flow acceleration is lacking [21, 22]. Further analyzed parameters included the stenosis and diameter of the common carotid artery and the diameters of both vertebral arteries.

All patients were routinely examined with fundoscopy in the ophthalmology department and by OCCS in the neurology department as part of the standard work-up according to previously published criteria and safety guidelines [23]. In brief, the distal part of the optic nerve was identified and scanned for the characteristic "spot sign" within 3 mm from the lamina cribrosa. CRAO was additionally confirmed by absence of arterial flow in the distal optic nerve (Fig. 1).

Statistical comparison was performed with Mann-Whitney-U (two group comparisons) and Chi-squared tests (χ [2] comparison of contingency tables).

Results

Overall, 112 patients treated between 2009 and 2023 were identified. The majority of patients (71%, 80 of 112 patients) had spot-sign CRAO, the heCRAO represented the smallest subgroup with 32 patients (29%). There was a significant difference in age distribution between males and females overall (mean age females = 74yrs., $n = 43$ vs. mean age males 70yrs., $n = 69$; p-value < 0.02, Mann-Whitney-U testing). Females were not significantly older on average in the ssCRAO subgroup (76yrs., $n = 33$ vs. 72 yrs., $n = 47$), but not in the heCRAO subgroup (67yrs., $n = 10$ vs. 67yrs., $n = 22$). With respect to the occurrence of ssCRAO versus heCRAO, patients with ssCRAO were significantly older (median 74yrs. vs. 66.5yrs.,

Mann-Whitney-U: p-value < 0.00129). Male patients were slightly overrepresented in the whole collective (69/112 patients = 61.6%) as well as in both subgroups (47/80 patients = 58.8% in ssCRAO, 22/32 patients = 68.8% in heCRAO). Boxplots of the ages split by event and single patients classified by sex, age and ocular event are shown in Fig. 2.

Overall, CT and MRI analysis in 15/103 (= 14.6%) patients showed concurrent acute ischemic events at the time of CRAO, 9 of which located in the ipsilateral middle or anterior cerebral arteries (MCA and ACA), 2 in other vascular cerebral territories and 4 disseminated above the ipsilateral ICA territory. Information on anticoagulation and antiplatelet drugs was available for 14 of 15 patients, and only 4 patients were without any. Overall, 75 of 95 patients were without old cerebral infarcts, and in 20 patients with old ischemic lesions (= 21.1%), 10 were located in the ipsilateral ACA/MCA territory, 5 in other territories and 5 disseminated.

Information on the echogenicity of atherosclerosis was available for 108 patients from the patients records based (and stroke unit standards) with confirmation by a DEGUM certified neurosonographeur (FS). χ2 revealed significant differences between the two subgroups (p-value < 0.001). In our cohort, (mainly) echorich AS is overrepresented in the ssCRAO group whereas mixed or (mainly) echopoor AS is dominant in the heCRAO group. The distribution of AS and ocular event is shown in Fig. 3, one time grouped by the type of AS and the other time grouped by ocular event.

Occurrence of atrial fibrillation, either permanent or intermittend and a major cause of severe cerebral stroke, did not differ statistically significant between the subgroups but revealed a non-significant trend towards less AF in heCRAO compared to the other two subgroups (2

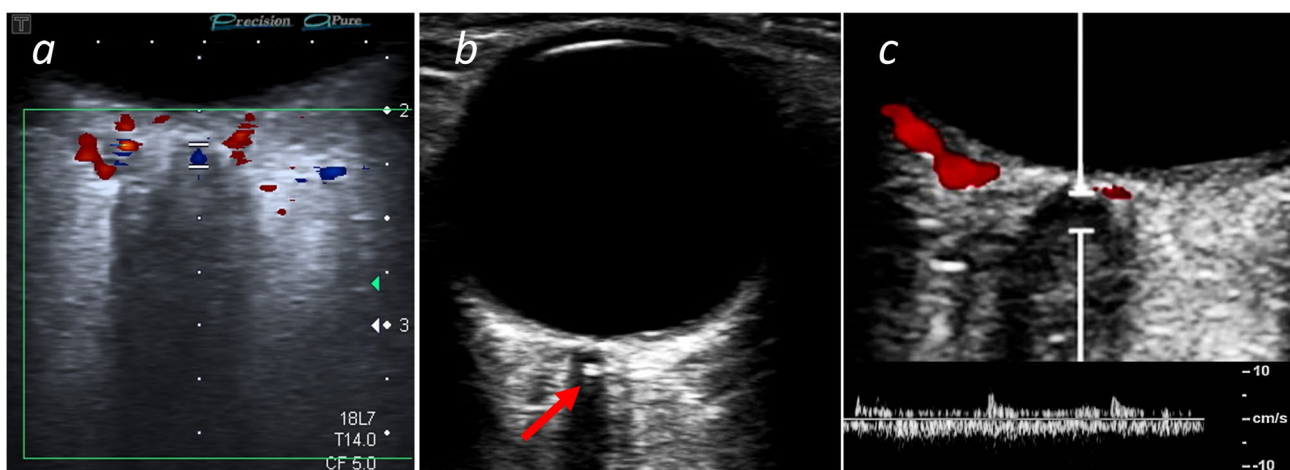**Fig. 1** hypoechoic CRAO/heCRAO without spot sign (**figure a**) and spot sign positive CRAO/ssCRAO (red arrow, **figure b**) can be differentiated by OCCS. A positive spot sign predicts poor prognosis as well as poor response to intravenous thrombolysis and excludes an arteritic CRAO while proving an embolic cause. **Figure c** shows the corresponding flow profile with slow resistance flow profile in the central retinal artery (lower)
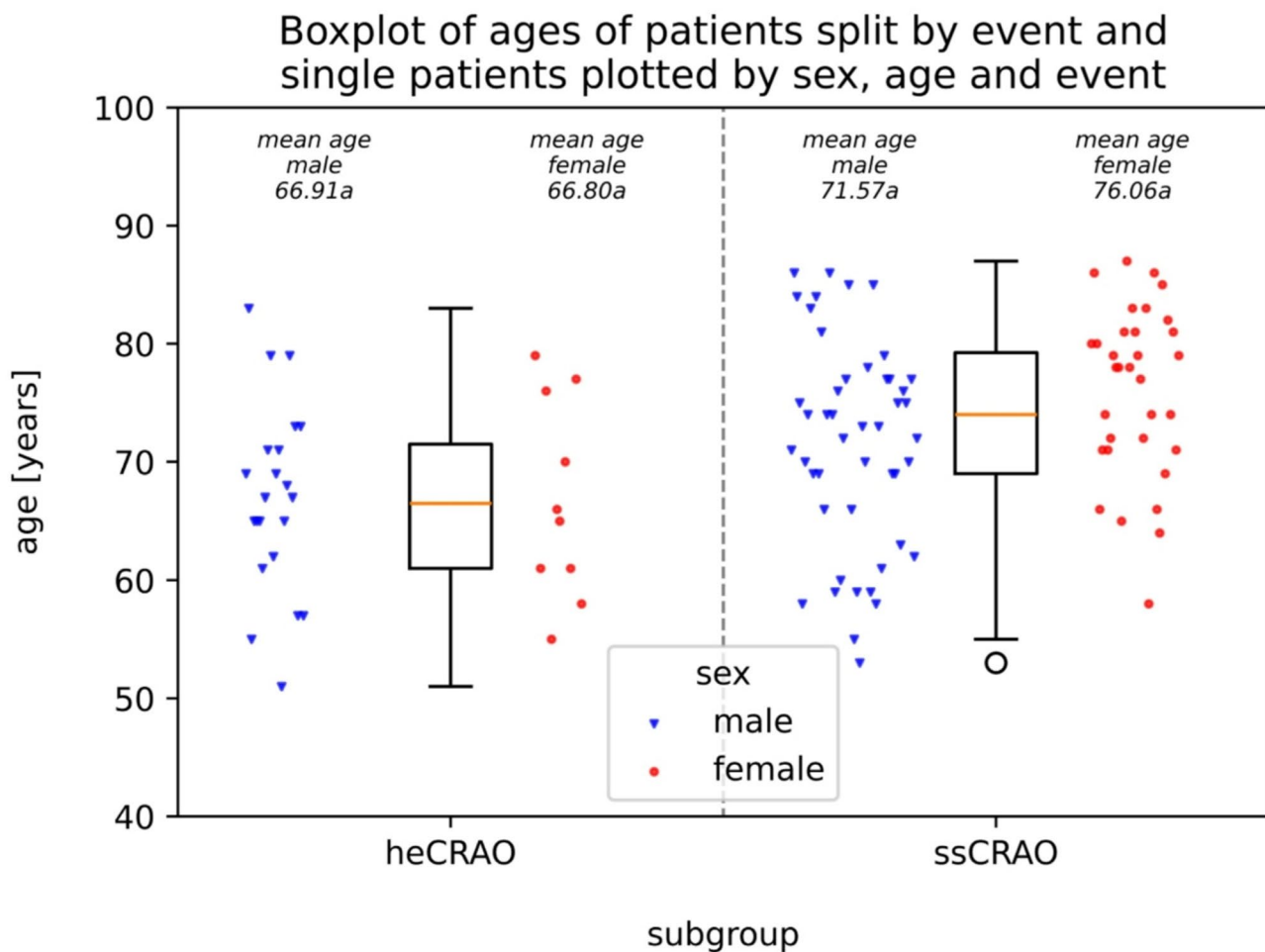
Fig. 2 This figure shows boxplots of the ages of the patients (regardless of their sex) grouped by ocular event. The dots show every single patient for each group with blue triangles representing male and red circles representing female patients. Overall, there was a significant difference between the two subgroups regarding the ages and females showed a significantly different age distribution in the whole cohort compared to males

out of 32 patients in heCRAO vs. 18 out of 80 patients in ssCRAO and BRAO, χ [2]: p-value ≈ 0.08). Out of the 20 patients with AF, information on medical treatment was available for 19 patients, 17 of them were treated with oral anticoagulants (with or without antiplatelet drugs) and two patients received antiplatelet drugs only. Out of the patients with AF, information about concurrent IS was available for 19/20 patients. Two of them suffered acute IS within the ipsilateral MCA/ACA territory despite oral anticoagulation. No acute events were found in other territories in all patients with AF.

Considering old ischemic events, this information was available for 18 patients with atrial fibrillation. The majority (10/18 = 55,6%) had no old cerebral infarcts while 4 patients had old events in the same ACA/MCA territory and 4 in other territories.

High grade ICA stenosis has a higher risk for cerebral infarcts, and information on both ICA was avalaible for 99 patients. The vast majority of patients had no or low grade ICA stenosis (defined as 50% according

to NASCET, and TOAST) with ipsilateral ICA stenosis < 50% present in 88 of 99 patients (88%). Thus, an ICA stenosis larger than > 50% NASCET was observed in 11 patients and only 2 of 99 patients had an > 50% stenosis in the contralateral ICA. We observed signicant differences between hight- and low-grade stenosis as shown in Fig. 4 (p-value in chi square on contingency table < 0.22 with ≥ 50% stenosis according to NASCET).

In this retrospective study we also analyzed the presumed etiology of IR by the treating physician during the hospital stay in 105/112 cases by analyzing the discharge letter, mainly according to the TOAST criteria. 55 cases were classified as cryptogenic, 12 were attributed to AF and 34 were classified as large-artery atherosclerosis. 4 patients had other determined causes for their IR (floating structure on aortic valve, ruptured aortic plaque, calcification of bicuspid aortic valve, thrombus from mitral valve). No significant differences for a variety of variables except mean age were found between the two subgroups heCRAO and ssCRAO, see Table 1.
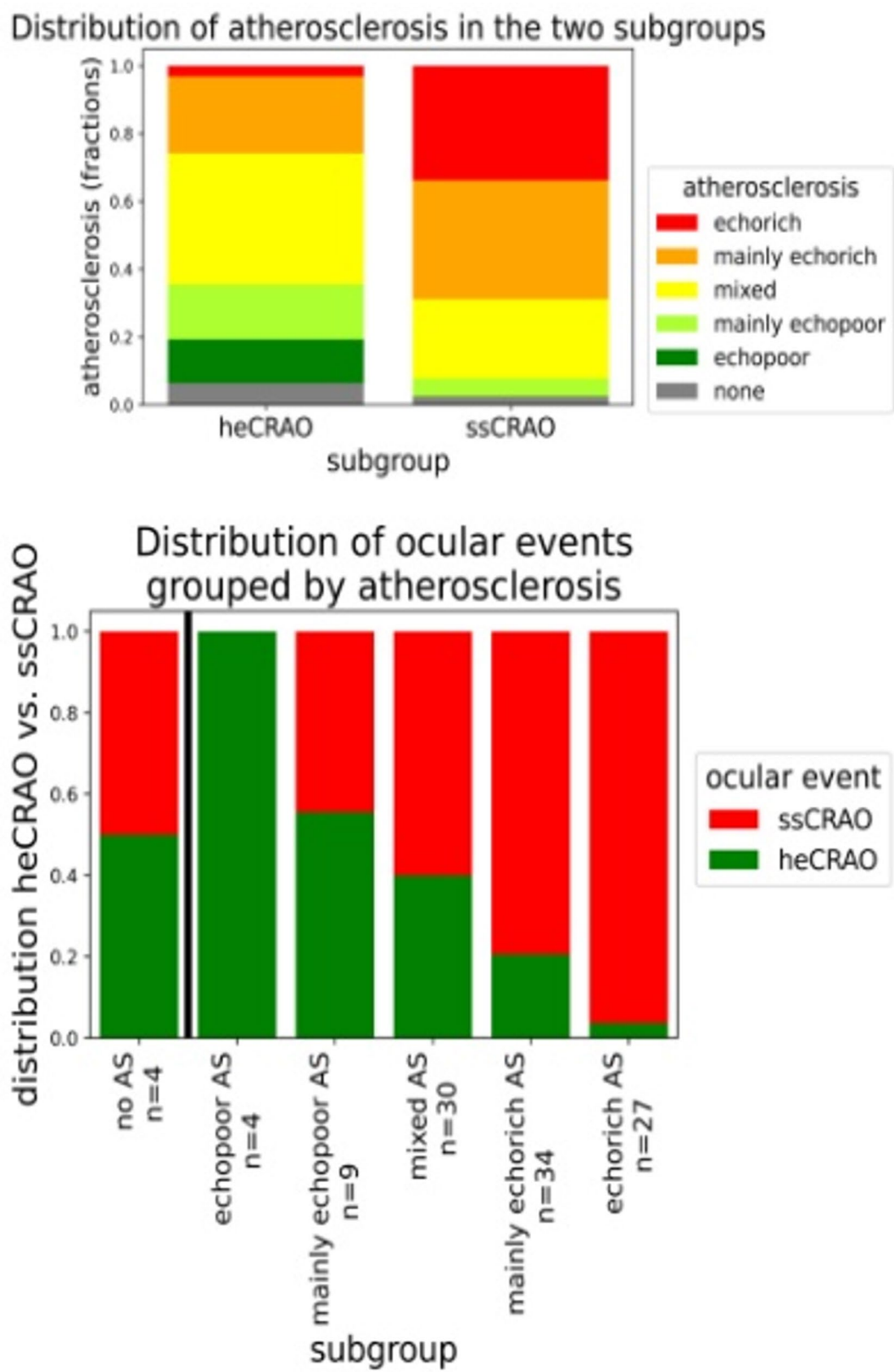
Fig. 3 Detailed analysis of distribution of atherosclerosis and ocular events, grouped by ocular event (upper) and by atherosclerosis (lower). AS = atherosclerosis
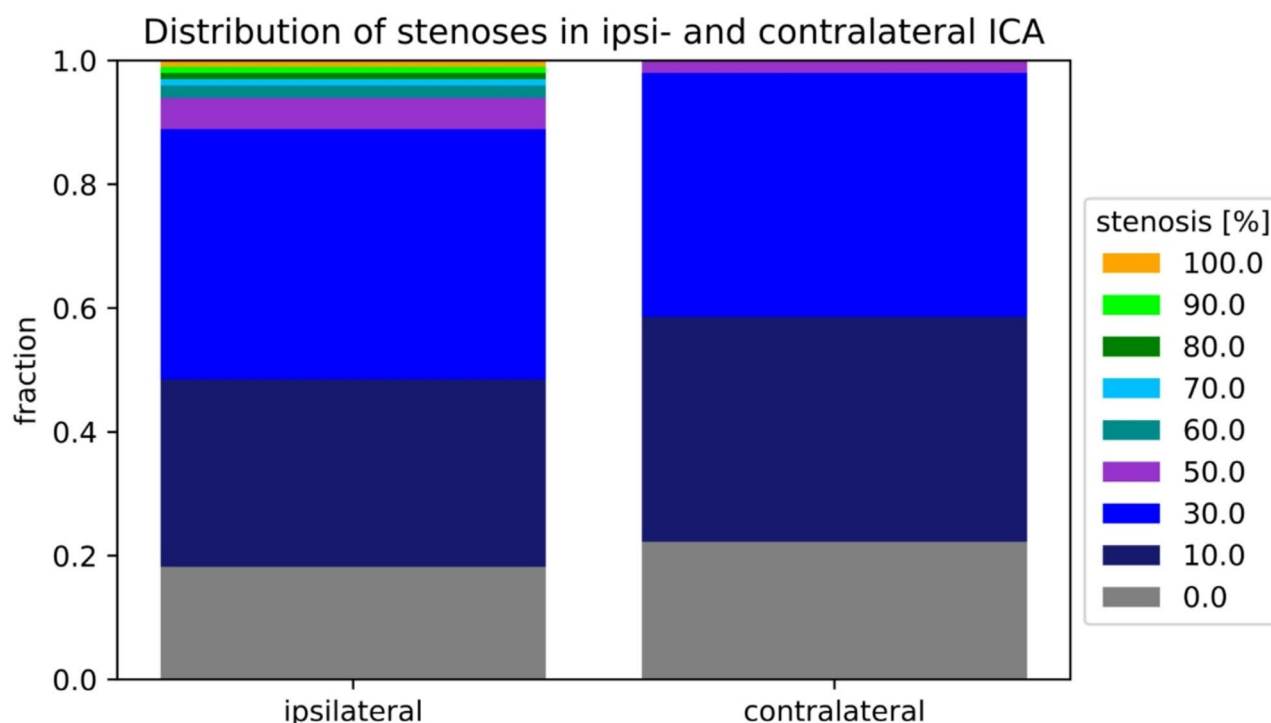
Fig. 4 Comparison of the distribution of ICA stenoses ipsi- and contralateral. Significant differences are present when comparing high-grade (at least 50%) vs.no or low-grade stenoses in both groups. Overall, the vast majority of patients had stenoses of less than 50%

Discussion

In this study we differentiated CRAOs based on the pre- or absence of the hyperechoic "spot sign" in OCCS with the aim to define the most likely embolic source in order to optimize prevention and perhaps therapy [24–26]. Atherosclerosis appears to account for the majority of emboli to the retina and central retinal artery although a "specific source" such as plaque rupture could not be demonstrated. The presence of AF and the degree of carotid stenosis may be only indicative for the presence of cerebrovascular risk factors in the elderly population.

AF without anticoagulation is a strong risk factor for IS and therefore also discussed as possible etiology in IR [25]but is more common in brain than in ocular events probably due to larger emboli size [26]. Most of the patients in our cohort with AF were already on oral anticoagulation and the majority had co-existing atherosclerosis casting doubt on the causality of AF for IR. In clinical practice CRAO in these patients is discussed as failure or undertreatment of OAC leading either to change in OAC regimen (i.e. factor X inhibition to direct thrombin inhibition) or addition of antiplatelet drugs, often with increased risk of bleeding complications. However, a current observational study is currently ongoing whether or not AF is an independent risk factor for IR and on the preventive value of anticoagulation [27]. However, if the current data holds true patients with AF and IR may rather benefit from an intensification of blood

pressure control and cholesterol lowering, amongst others, aiming to stabilize atherosclerosis.

The differentiation between ssCRAO and heCRAO exhibited differences in the age distributions and the correlating atherosclerotic risk profile. Adding data to the current discussion on atherosclerosis and sex differences, we found affected female patients to be older than affected males in the overall cohort and patients with ssCRAO being older than patients with heCRAO [28]. Based on our current and previous data, we propose the (cholesterol) emboli syndrome in atherosclerosis as pathophysiological hypothesis for a large number of CRAO, and ssCRAO can persist over years and even after IVT [29, 30]. The type of atherosclerosis seems to correlate with the clinical phenotype (ssCRAO– echorich atherosclerosis vs. heCRAO– echopoor atherosclerosis) and echorich, advanced atherosclerosis with clinically relevant stenosis is not a necessary requirement for embolic IR due to atherosclerosis. Figure 5 depicts our hypothesis on the etiology of those two ocular events. Small, echopoor emboli entering the brain might not cause (clinically relevant) ischemia given the collateral cortical network opposed to endarteries in the retina, and may be more amendable to endogenous endothelium-initiated plasminogen activator.

Given the age distribution and high rate of atherosclerosis we did not find an equivalent number of patients with embolism due to large-artery atherosclerosis as

Table 1 Detailed analysis of variables grouped by ocular event. Total refers to the number of patients in the group for which information on this variable was available. CCA: common carotid artery, ICA: internal carotid artery, OAC: oral anticoagulation. * significant p-value < 0.00029 (Mann-Whitney-U testing)

	Hypoechogenic (echo poor) CRAO Patients with available information, $n = 32$		Spot-sign (echo-rich) CRAO Patients with available information, $n = 80$	
age: mean ± std	66.88 ± 7.97*	32	73.42 ± 8.43*	80
male sex	68.75% (22)	32	58.75% (47)	80
echogenicity atherosclerosis:		total: 31		total: 77
no AS	6.5% (2)		2,6% (2)	
echopoor	12.9% (4)		0% (0)	
mainly echopoor	16.1% (5)		5,2% (4)	
mixed	38.8% (12)		23,4% (18)	
mainly echorich	22.6% (7)		35,1% (27)	
echorich	3.2% (1)		33,8% (26)	
stenosis of ipsilateral ICA: mean(%) ± std	23.75 ± 24.06	32	22.99 ± 17.70	77
stenosis of ipsilateral ICA:		**total: 32**		**total: 77**
none	7		12	
10–40%	19		58	
50%	3		3	
60%	0		3	
70%	1		0	
80%	1		0	
90%	1		0	
100%	0		1	
stenosis of ICA contralateral: mean(%) ± std	13.45 ± 13.70	29	17.71 ± 12.76	70
hypercholesterinemia		total: 32		total: 79
no	15,7% (5)		21,5% (17)	
yes	50% (16)		24,1% (19)	
treated	34,4% (11)		54,4% (43)	
hypertension		total: 32		total: 79
no	15,7% (5)		11,4% (9)	
yes	37,5% (12)		21,5% (17)	
treated	46,9% (15)		67,1% (53)	
diabetes mellitus	16,7% (5)	30	26,9% (21)	78
nicotin		total: 21	63,5% (33)	total: 52
no	38,1% (8)		28,8% (15)	
yes	42,9% (9)		7,7% (4)	
former usage	19,0% (4)			
peripheral artery disease	0% (0)	31	10.1% (8)	79
acute cerebral ischemia		total: 31		total: 72
same territory	19,4% (6)		4,2% (3)	
other territory	0% (0)		2,8% (2)	
different territories	3,2% (1)		4,2% (3)	
none	77,4% (24)		88,9% (64)	
OAC or antiplatelet drugs (AD)		total: 32		total: 72
none	59,4% (19)		34,7% (25)	
AD	31,3% (10)		37,5% (27)	
OAC	3,1% (1)		23,6% (17)	
both	6,3% (2)		41,7% (3)	
atrial fibrillation	6.3% (2)	32	22.5% (18)	80
patent foramen ovale	0% (0)	31	2,5% (2)	80
presumed etiology at discharge		total: 32		total: 80
cryptogenic	59,4% (19)		45% (36)	
atrial fibrillation	3,1% (1)		13,8% (11)	
atherosclerotic	37,5% (12)		27,5% (22)	

Table 1 (continued)

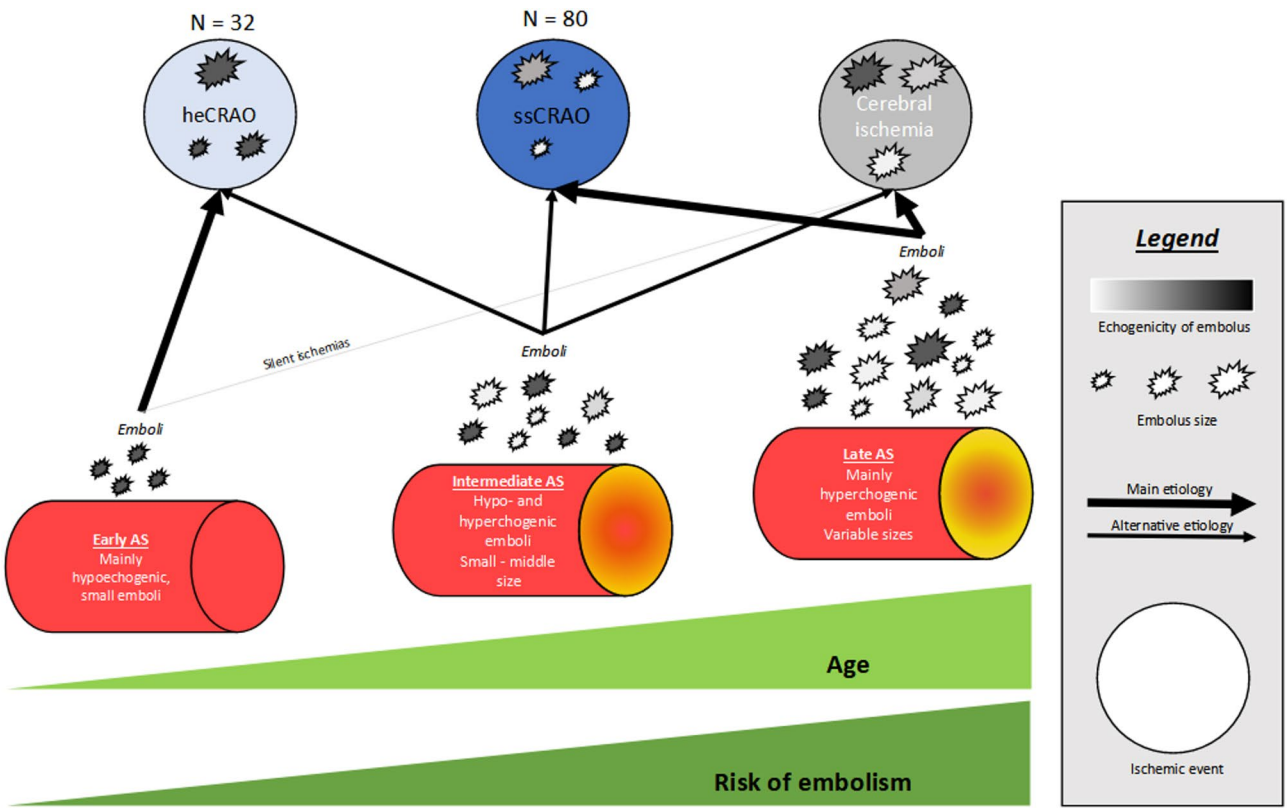|	Hypoechogenic (echo poor) CRAO Patients with available information, $n = 32$	Spot-sign (echo-rich) CRAO Patients with available information, $n = 80$
other	0% (0)	5% (4)
not defined	0% (0)	8,8% (7)

Fig. 5 Hypothesis on the etiology of different ocular events. Atherosclerosis seems to be the main risk factor even in early stages of AS

defined by the TOAST criteria which defines large-artery atherosclerosis as stenosis of brain supplying arteries higher than 50% [31]. In IS, the fraction of patients with large-artery atherosclerosis ranges from 15 to 70% [32–35]. Mead et al. speculate on pathogenetic differences in IR versus IS and found that severe ipsilateral carotid disease was less common in IS than in IR whereas atrial fibrillation was more common in ischemic stroke than in retinal ischemia [26]. This would be in-line with our cohort, although patients had significantly more high-grade stenoses in the ipsilateral ICA compared to the contralateral side, but the vast majority of patients had stenoses of less than 50%. We may hypothesized that stenoses less than 50% in the ipsilateral ICA might cause CRAO (by embolism), and could be considered "vulnerable" as recently reviewed in the context of embolic stroke of undetermined source (ESUS) [36].

In studies on symptomatic ICA stenosis, however, both transient and permanent ocular ischemia qualified as "symptomatic" but may present different types

of emboli. Platelet-fibrin emboli that arise from plaque rupture and exposure of the thrombogenic subendothelial matrix have higher potential for endogenous thrombolysis with recanalization while cholesterol containing emboli or calcified plaque components are more likely to result in permanent occlusion or hypoperfusion [30]. Despite similar vascular risk profiles, differences between IS and IR are also apparent in studies on symptomatic ICA stenosis. In these patients, the risk for subsequent IS after IR lies around 50% compared to that of another IS after IS [37–39]. In the North American Symptomatic Carotid Endarterectomy Trial (NASCET) the ipsilateral stroke risk in patients after transient and permanent IR significantly resembles that of asymptomatic high grade internal carotid artery stenosis. Both types of IR are in the medical treatment arm of NASCET, casting doubt on surgical carotid endarterectomy in these patients regarding the benefit-risk ratio with comparably low risk reduction [37–39]. However, it must be noted that transient

ocular symptoms such as amaurosis fugax dominate the population with respect to IR.

The percentage of concurrent acute ischemic stroke in our study population ranges within numbers given by other groups (Kim et al.: age-dependent 8–30% [33], Lee et al.: 12,1% [40], Hoyer et al.: 32,5% [41], Fallico et al.: 30% in CRAO [42]). While other studies used MRI, we mainly relied on clinical symptoms and cCT thus potentially underestimating the real number of concurrent stroke. Furthermore, we observed more, especially older cerebral infarction within same vessel territory of the affected eye, adding to the theory of atherosclerotic embolism being a more frequent cause for IR than atrial fibrillation. Laczynski et al. showed that the risk of subsequent stroke in patients with CRAO was lower than previously reported and comparable to that of all at-risk adults [43].

Given the current insufficient therapeutic options and often exceeded time frame for recanalization/ thrombolytic therapies in IR, primary prevention for IR is of highest importance. While a large body of evidence on overlapping risk factors exist in these patients, the embolic source and secondary stroke prevention is performed according to the TOAST criteria excluding (of course) microangiopathy. Also, recognition of cholesterol emboli and other atherosclerotic plaque components in acute cerebrovascular disease opposed to platelet-fibrin thrombi may have important prognostic implications for thrombolytic therapies in cerebral and retinal stroke and secondary prevention. However, presence of ssCROA should not hinder IV thrombolysis and i.e. the REVISION trial should add prognostic markers for IVT given the substudy on the presence or absence of ssCRAO [14]. It remains to be seen, whether young patients with lower frequency of ssCRAO benefit more from thrombolysis and whether or not the risk of other complications from IVT (i.e. bleeding complication, angioedema) outweigh the risk of rapid IVT without OCCS to rule out ssCRAO.

Carotid endarterectomy has a strong secondary prophylactic effect in symptomatic high-grade ICA stenosis. However, in the current study the number of high-grade ICA stenosis (> 50% according to NASCET) was very low. Analysis on the presence or absence of the spot-sign may further contribute to the phenomenon of the low secondary prophylactic effect of CEA with at least transient ocular symptoms [37, 44–46]. In an analysis of CEA specimens Howard et al. performed a semi-quantitative analysis of plaque material of high-grade ICA-stenosis of 1317 patients with cerebral stroke and 323 patients with ocular ischemia (of which 81% amaurosis fugax and 19% manifest retinal ischemia) [18]. They found patients with symptomatic high-grade stenosis and cerebral events to have significantly more features of vulnerable plaque than patients with ocular events. Unfortunately, no sub-analysis for amaurosis fugax and IR was made that would add to the analysis of our study. Detailed analysis of CRAO by ocular sonography may further help to identify the best treatment strategies and may be an ideal study population to revive comparison of modern best medical treatment versus carotid endarterectomy and carotid artery stenting.

Limitations
Our study suffers from limitations, mainly (a) the retrospective design with perhaps incomplete analysis of risk factors and (b) the low frequency of MRI that may underestimate the true number of concurrent stroke. For the majority of patients, no follow-up data is available. Further prospective registries should be initiated to corroborate these findings. Also, CRAO was diagnosed by the ophthalmologist on call and fundoscopic images were not always taken, making fundoscopic characterization of additional retinal emboli not possible. However, ssCRAO may even be completely asymptomatic as demonstrated by a recent patient with a completely asymptomatic 40% predominantly echogenic ICA stenosis with a spot sign and normal flow in the central retinal artery (see Fig. 6). Further controlled studies also in the normal yet elderly population is needed.

Conclusion
Our study indicates a larger role– if not even the main role - of atherosclerosis in IR, even in early stages of atherosclerosis. The two subgroups of IR exhibit distinct atherosclerotic risk profiles, and TOAST and ESUS criteria might not be ideal to be applied on IR as they might overestimate the role of AF and underestimate the role of AS (as only stenoses > 50% are considered as relevant) in the etiology of IR. Thus, further efforts should be made to standardize the acute diagnostic work-up including OCCS and the etiological-pathological classification of CRAO in stroke units and ophthalmologic departments, that still employ the TOAST classification and often lack standardization [47, 48]. heCRAO and ssCRAO can be distinguished by OCCS, which should be regularly performed in CRAO, especially in patients undergoing thrombolysis as it may predict the therapeutic efficacy. Provided that these findings can be replicated in other cohorts, this may lead to different primary and perhaps secondary prevention strategies in patients with different stages of atherosclerosis and might be a first step towards a better understanding of the precise pathomechanism of CRAO. In addition, the ongoing randomized studies on IVT in CRAO might further help to understand the effect of thrombolytic therapies on he and ssCRAO.
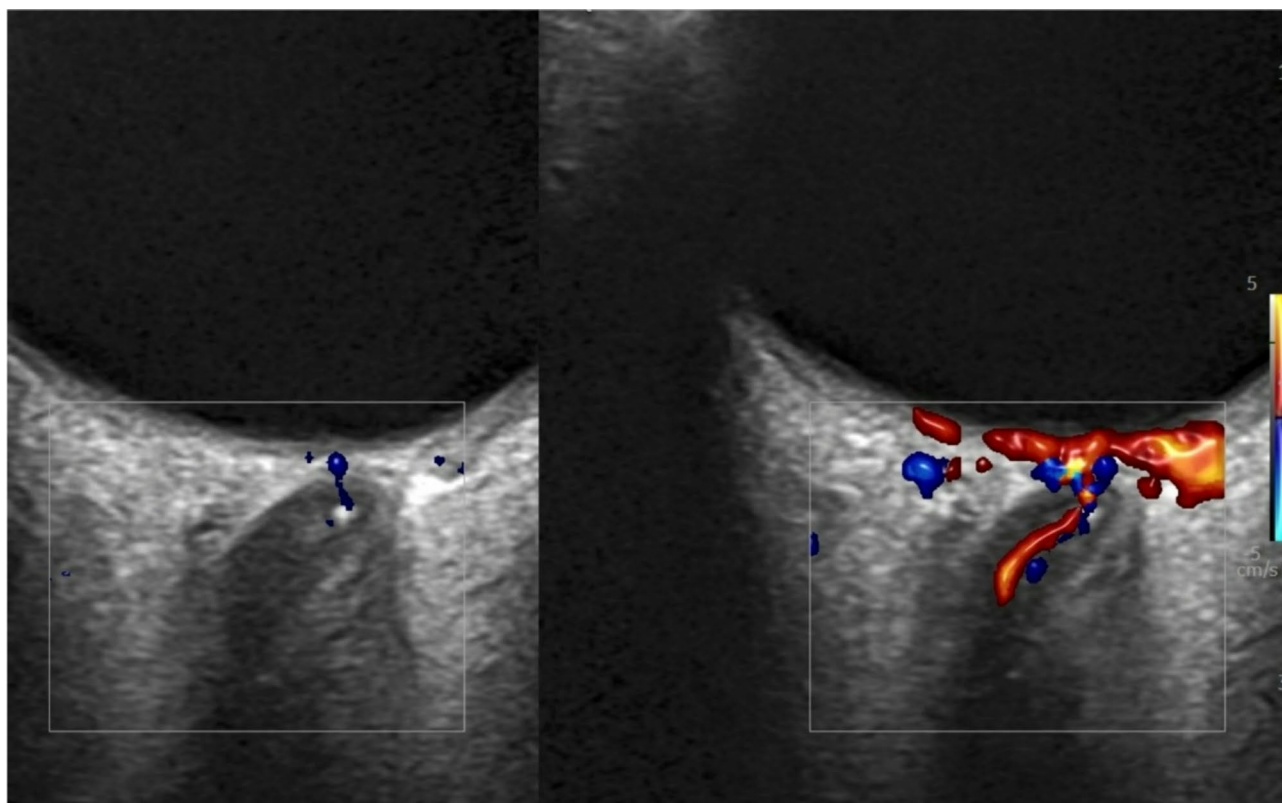
Fig. 6 asymptomatic "spot sign" in a patient with normal flow in the central retinal artery

Abbreviations

ACA	Anterior cerebral artery
AF	Atrial fibrillation
AS	Atherosclerosis
CCA	Common carotid artery
cCT	Cerebral computed tomography
CEA	Carotid endarterectomy
cMRI	Cerebral magnetic resonance imaging
CRAO	Central retinal artery occlusion
ssCRAO	Spot sign positive CRAO
heCRAO	Spot sign negative (hypoechoic) CRAO
ESUS	Embolic stroke of undetermined source
ICA	Internal carotid artery
IR	Retinal ischemia
IS	Ischemic stroke
IVT	Intravenous thrombolysis
MCA	Middle cerebral artery
NASCET	North American Symptomatic Carotid Endarterectomy Trial
OCCS	Orbital color-coded sonography
TOAST	Trial of Org 10172 in Acute Stroke

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s42466-025-00413-z.

Supplementary Material 1

Acknowledgements

Author contributions

FS was responsible for the study concept. IF and SW were responsible for data acquisition. FS, IF and CW reevaluated any available neuroimaging by cerebral computed tomography (cCT) and cerebral magnetic resonance imaging (cMRI). FS (DEGUM certified) classified the echogenicity of atherosclerotic carotid plaque. SW performed the statistical analysis and visualization. FS and SW drafted and wrote the manuscript. IF, ME, MK, FA, DP, HH, CWKP, LK, MAG and RL critically revised the manuscript. MAG and HH confirmed the ophthalmological findings.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethical Review Board of the University of Regensburg (reference: 19-1542-104).

Consent for publication

Not applicable.

Competing interests

None.

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References

1. Hayreh, S. S. (2011). Acute retinal arterial occlusive disorders. *Progress in Retinal and Eye Research*, *30*(5), 359–394. https://doi.org/10.1016/j.preteyeres.2011.05.001
2. Hayreh, S. S. (2014). Ocular vascular occlusive disorders: Natural history of visual outcome. *Progress in Retinal and Eye Research*, *41*, 1–25. https://doi.org/10.1016/j.preteyeres.2014.04.001
3. Dattilo, M., Newman, N. J., & Biousse, V. (2018). Acute retinal arterial ischemia. *Ann Eye Sci*, *3*. https://doi.org/10.21037/aes.2018.05.04
4. Wang, X., Liu, Y., Suo, Y., et al. (2021). Intravenous Recombinant Tissue-Type plasminogen activator thrombolysis for acute central retinal artery occlusion. *The Journal of Craniofacial Surgery*, *32*(1), 313–316. https://doi.org/10.1097/SCS.0000000000007134
5. Akai, R., Ishida, M., Ueda-Consolvo, T., & Hayashi, A. (2024). Comparative efficacy of conservative, hyperbaric oxygen, and endovascular retinal surgery approaches in central retinal artery occlusion. *International Ophthalmology*, *44*(1), 419. https://doi.org/10.1007/s10792-024-03335-y
6. Ferreira, D., Soares, C., Tavares-Ferreira, J., Fernandes, T., Araújo, R., & Castro, P. (2020). Acute phase treatment in central retinal artery occlusion: Thrombolysis, hyperbaric oxygen therapy or both? *Journal of Thrombosis and Thrombolysis*, *50*(4), 984–988. https://doi.org/10.1007/s11239-020-02072-0
7. Sharma, R. A., Newman, N. J., & Biousse, V. (2021). Conservative treatments for acute nonarteritic central retinal artery occlusion: Do they work? *Taiwan J Ophthalmol*, *11*(1), 16–24. https://doi.org/10.4103/tjo.tjo_61_20
8. Dumitrascu, O. M., Shen, J. F., Kurli, M., et al. (2017). Is intravenous thrombolysis safe and effective in central retinal artery occlusion?? A critically appraised topic. *The Neurologist*, *22*(4), 153–156. https://doi.org/10.1097/NRL.0000000000000129
9. Dumitrascu, O. M., Newman, N. J., & Biousse, V. (2020). Thrombolysis for central retinal artery occlusion in 2020: Time is vision! J Neuro-Ophthalmol off. *J North Am Neuro-Ophthalmol Soc*, *40*(3), 333–345. https://doi.org/10.1097/WNO.0000000000001027
10. Flowers, A. M., Chan, W., Meyer, B. I., Bruce, B. B., Newman, N. J., & Biousse, V. (2021). Referral patterns of central retinal artery occlusion to an academic center affiliated with a stroke center. *J Neuro-Ophthalmol Off J North Am Neuro-Ophthalmol Soc*, *41*(4), 480–487. https://doi.org/10.1097/WNO.0000000000001409
11. Hattenbach, L. O., Kuhli-Hattenbach, C., Scharrer, I., & Baatz, H. (2008). Intravenous thrombolysis with low-dose Recombinant tissue plasminogen activator in central retinal artery occlusion. *American Journal of Ophthalmology*, *146*(5), 700–706. https://doi.org/10.1016/j.ajo.2008.06.016
12. Mac Grory, B., Schrag, M., Biousse, V. Management of central retinal artery occlusion: A scientific statement from the American heart association. *Stroke Published Online March* 2021:STR0000000000000366. https://doi.org/10.1161/STR.0000000000000366
13. Poli, S., Grohmann, C., Wenzel, D. A., et al. (2024). Early reperfusion therapy with intravenous Alteplase for recovery of VISION in acute central retinal artery occlusion (REVISION): Study protocol of a phase III trial. *International Journal of Stroke: official Journal of the International Stroke Society*, *19*(7), 823–829. https://doi.org/10.1177/17474930241248516
14. Schultheiss, M., Spitzer, M. S., Hattenbach, L. O., & Poli, S. [Update on intravenous Lysis treatment: The REVISION trial]. ophthalmol Z Dtsch ophthalmol ges. Published online August 2021. https://doi.org/10.1007/s00347-021-01467-5
15. Schumacher, M., Schmidt, D., Jurklies, B., et al. (2010). Central retinal artery occlusion: Local intra-arterial fibrinolysis versus Conservative treatment, a multicenter randomized trial. *Ophthalmology*, *117*(7), 1367–75e1. https://doi.org/10.1016/j.ophtha.2010.03.061
16. Kaufman, E. J., Mahabadi, N., & Patel, B. C. (2021). Hollenhorst plaque. *StatPearls [Internet]*. StatPearls Publishing.
17. Pfaffenbach, D. D., & Hollenhorst, R. W. (1973). Morbidity and survivorship of patients with embolic cholesterol crystals in the ocular fundus. *American Journal of Ophthalmology*, *75*(1), 66–72. https://doi.org/10.1016/0002-9394(73)90653-3
18. Howard, D. P. J., van Lammeren, G. W., Redgrave, J. N., et al. (2013). Histological features of carotid plaque in patients with ocular ischemia versus cerebral events. *Stroke*, *44*(3), 734–739. https://doi.org/10.1161/STROKEAHA.112.678672
19. Albers, G. W., Amarenco, P., Easton, J. D., Sacco, R. L., & Teal, P. Antithrombotic and thrombolytic therapy for ischemic stroke: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126(3 Suppl):483S-512S. https://doi.org/10.1378/chest.126.3_suppl.483S
20. Fazekas, F., Chawluk, J. B., Alavi, A., Hurtig, H. I., & Zimmerman, R. A. (1987). MR signal abnormalities at 1.5 T in alzheimer's dementia and normal aging. *Ajr. American Journal of Roentgenology*, *149*(2), 351–356. https://doi.org/10.2214/ajr.149.2.351
21. Arning, C., Widder, B., von Reutern, G. M., Stiegler, H., & Görtler, M. (2010). [Revision of DEGUM ultrasound criteria for grading internal carotid artery stenoses and transfer to NASCET measurement]. *Ultraschall Med Stuttg Ger 1980*, *31*(3), 251–257. https://doi.org/10.1055/s-0029-1245336
22. Touboul, P. J., Hennerici, M. G., Meairs, S. Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011). An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th, 15th and 20th European Stroke Conferences, Mannheim, Germany, 2004,. Cerebrovasc Dis Basel Switz. 2012;34(4):290–296. https://doi.org/10.1159/000343145
23. Ertl, M., Barinka, F., Torka, E., et al. (2014). Ocular color-coded sonography - a promising tool for neurologists and intensive care physicians. *Ultraschall Med Stuttg Ger 1980*, *35*(5), 422–431. https://doi.org/10.1055/s-0034-1366113
24. Callizo, J., Feltgen, N., Pantenburg, S., et al. (2015). Cardiovascular risk factors in central retinal artery occlusion: Results of a prospective and standardized medical examination. *Ophthalmology*, *122*(9), 1881–1888. https://doi.org/10.1016/j.ophtha.2015.05.044
25. Cheng, S. F., Zarkali, A., Richards, T., Simister, R., & Chandratheva, A. (2019). Carotid artery stenosis, an underestimated cause of stroke recurrence in patients with ischaemic monocular visual loss. *Annals of the Royal College of Surgeons of England*, *101*(8), 579–583. https://doi.org/10.1308/rcsann.2019.0071
26. Mead, G. E., Lewis, S. C., Wardlaw, J. M., & Dennis, M. S. (2002). Comparison of risk factors in patients with transient and prolonged eye and brain ischemic syndromes. *Stroke*, *33*(10), 2383–2390. https://doi.org/10.1161/01.str.0000029827.93497.97
27. Lusk, J. B., Wilson, L., Nalwade, V., et al. (2023). Atrial fibrillation as a novel risk factor for retinal stroke: A protocol for a population-based retrospective cohort study. *PloS One*, *18*(12), e0296251. https://doi.org/10.1371/journal.pone.0296251
28. Man, J. J., Beckman, J. A., & Jaffe, I. Z. (2020). Sex as a biological variable in atherosclerosis. *Circ Res*, *126*(9), 1297–1319. https://doi.org/10.1161/CIRCRESAHA.120.315930
29. Altmann, M., Ertl, M., Helbig, H., et al. (2015). Low endogenous recanalization in embolic central retinal artery occlusion–the retrobulbar spot sign. *J Neuroimaging Off J Am Soc Neuroimaging*, *25*(2), 251–256. https://doi.org/10.1111/jon.12112
30. Nedelmann, M., Graef, M., Weinand, F., et al. (2015). Retrobulbar spot sign predicts thrombolytic treatment effects and etiology in central retinal artery occlusion. *Stroke*, *46*(8), 2322–2324. https://doi.org/10.1161/STROKEAHA.115.009839
31. Adams, H. P., Bendixen, B. H., Kappelle, L. J., et al. (1993). Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of org 10172 in acute stroke treatment. *Stroke*, *24*(1), 35–41. https://doi.org/10.1161/01.STR.24.1.35
32. Cole, J. W. (2017). Large artery atherosclerotic occlusive disease. *Contin Lifelong Learn Neurol*, *23*(1), 133–157. https://doi.org/10.1212/CON.0000000000000436
33. Kim, J. T., Yoo, S. H., Kwon, J. H., Kwon, S. U., & Kim, J. S. (2006). Subtyping of ischemic stroke based on vascular imaging: Analysis of 1,167 acute, consecutive patients. *J Clin Neurol*, *2*(4), 225. https://doi.org/10.3988/jcn.2006.2.4.225

34. Zhou, F., Tang, J., Li, P., Liao, B., & Qin, C. (2020). Distribution of cerebral artery stenosis and risk factors in ethnic Zhuang and Han patients with ischemic stroke in Guangxi Province. *Ann Palliat Med*, *9*(2), 256–263. https://doi.org/10.21037/apm.2020.02.32

35. Zhu, T., Ren, L., Zhang, L., et al. (2021). Comparison of plaque characteristics of small and large subcortical infarctions in the middle cerebral artery territory using high-resolution magnetic resonance vessel wall imaging. *Quant Imaging Med Surg*, *11*(1), 57–66. https://doi.org/10.21037/qims-20-310

36. Savastano, L., Brinjikji, W., Lutsep, H., Chen, H., & Chaturvedi, S. (2024). Symptomatic nonstenotic carotids: A topical review. *Stroke*, *55*(12), 2921–2931. https://doi.org/10.1161/STROKEAHA.123.035675

37. Benavente, O., Eliasziw, M., Streifler, J. Y., Fox, A. J., Barnett, H. J., & Meldrum, H. (2001). Prognosis after transient monocular blindness associated with carotid-artery stenosis. *New England Journal of Medicine*, *345*(15), 1084–1090. https://doi.org/10.1056/NEJMoa002994

38. Rothwell, P. M., Eliasziw, M., Gutnikov, S. A., Warlow, C. P., & Barnett, H. J. M. (2004). Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. *Lancet Lond Engl*, *363*(9413), 915–924. https://doi.org/10.1016/S0140-6736(04)15785-1

39. Streifler, J. Y., Eliasziw, M., Benavente, O. R., et al. (1995). The risk of stroke in patients with first-ever retinal vs hemispheric transient ischemic attacks and high-grade carotid stenosis. North American symptomatic carotid endarterectomy trial. *Archives of Neurology*, *52*(3), 246–249. https://doi.org/10.1001/archneur.1995.00540270034016

40. Lee, K. E., Tschoe, C., Coffman, S. A., et al. (2021). Management of acute central retinal artery occlusion, a retinal stroke: An institutional series and literature review. *J Stroke Cerebrovasc Dis Off J Natl Stroke Assoc*, *30*(2), 105531. https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.105531

41. Hoyer, C., Kahlert, C., Güney, R., Schlichtenbrede, F., Platten, M., & Szabo, K. (2021). Central retinal artery occlusion as a neuro-ophthalmological emergency: The need to Raise public awareness. *European Journal of Neurology*, *28*(6), 2111–2114. https://doi.org/10.1111/ene.14735

42. Fallico, M., Lotery, A. J., Longo, A., et al. (2020). Risk of acute stroke in patients with retinal artery occlusion: A systematic review and meta-analysis. *Eye Lond Engl*, *34*(4), 683–689. https://doi.org/10.1038/s41433-019-0576-y

43. Laczynski, D. J., Gallop, J., Lyden, S. P., et al. (2020). Retinal artery occlusion does not portend an increased risk of stroke. *Journal of Vascular Surgery*, *72*(1), 198–203. https://doi.org/10.1016/j.jvs.2019.08.279

44. Abbott, A. L. (2022). Extra-Cranial carotid artery stenosis: An objective analysis of the available evidence. *Frontiers in Neurology*, *13*, 739999. https://doi.org/10.3389/fneur.2022.739999

45. Abbott, A. L., Brunser, A. M., Giannoukas, A., et al. (2020). Misconceptions regarding the adequacy of best medical intervention alone for asymptomatic carotid stenosis. *Journal of Vascular Surgery*, *71*(1), 257–269. https://doi.org/10.1016/j.jvs.2019.04.490

46. Wolintz, R. J. (2005). Carotid endarterectomy for ophthalmic manifestations: Is it ever indicated? J Neuro-Ophthalmol off J North am Neuro-Ophthalmol Soc.;25(4):299–302. https://doi.org/10.1097/01.wno.0000189065.20552.88

47. Hoyer, C., Winzer, S., Matthe, E., et al. (2022). Current diagnosis and treatment practice of central retinal artery occlusion: Results from a survey among German stroke units. *Neurol Res Pract*, *4*, 30. https://doi.org/10.1186/s42466-022-00193-w

48. Diel, N. J., Gerner, S. T., Doeppner, T. R., et al. (2024). Comparison of vascular risk profile and clinical outcomes among patients with central (branch) retinal artery occlusion versus amaurosis Fugax. *Neurol Res Pract*, *6*, 27. https://doi.org/10.1186/s42466-024-00326-3

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