

AHA/ASA SCIENTIFIC STATEMENT
MANAGEMENT OF CENTRAL RETINAL ARTERY OCCLUSION
A STATEMENT FOR HEALTHCARE PROFESSIONALS FROM THE
AMERICAN HEART ASSOCIATION/AMERICAN STROKE
ASSOCIATION

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ABSTRACT

PURPOSE

- Central retinal artery occlusion (CRAO) is a form of acute ischemic stroke which causes severe visual loss and is a harbinger of further cerebrovascular and cardiovascular events. there is a paucity of scientific information on the appropriate management of CRAO with most strategies being based on observational literature and expert opinion.
- In this scientific statement, we critically appraise the literature on CRAO and provide a framework within which to consider acute treatment and secondary prevention.

METHODS

- The writing group performed a literature review of randomized, controlled clinical trials, prospective and retrospective cohort studies, case-control studies, case reports, clinical guidelines, review papers, basic science papers and editorials concerning the management of CRAO.
- A writing group panel was assembled comprising experts in the fields of vascular neurology, neuro-ophthalmology, vitreo-retinal surgery, immunology, endovascular neurosurgery and cardiology and document sections were divided among the writing group members.
- Each member received an assignment to perform a literature review, synthesize the data and offer considerations for practice.
- Multiple drafts were circulated among the group until consensus was achieved.

RESULTS

- Acute CRAO is a medical emergency. Systems of care should evolve to prioritize early recognition and triage of CRAO to emergency medical attention.
- There is considerable variability in management patterns among practitioners, institutions and subspecialty groups.
- The current literature suggests that treatment with intravenous tissue plasminogen activator (TPA) may be effective.
- Patients should undergo urgent screening and treatment of vascular risk factors.
- There is a need for high-quality, randomized clinical trials in this field.

INTRODUCTION

INTRODUCTION

- Central retinal artery occlusion (CRAO) is a form of acute ischemic stroke¹.
- Despite over 150 years of research, there are no effective evidence-based forms of therapy for this condition.
- Less than 20% of affected patients regain functional visual acuity in the affected eye^{2, 3}.
- Analogous to cerebral ischemic stroke, CRAO is associated with a risk of recurrent vascular events⁴⁻⁸.
- The efficacy of widely-employed treatment strategies for this condition have not been tested in randomized, placebo-controlled, clinical trials.
- In this scientific statement, we discuss the management of CRAO with particular reference to acute therapy and cardiovascular secondary prevention strategies.

DEFINITIONS

DEFINITIONS

- Ischemic stroke is defined as an “episode of neurological dysfunction caused by focal cerebral, spinal or retinal infarction”¹.
- The cerebrum, spinal cord and retina comprise the central nervous system (CNS) and CNS infarction is “brain, spinal cord, or retinal cell death attributable to ischemia, based on
 - 1. pathological, imaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; or
 - 2. clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury based on symptoms persisting >24 hours or until death, and other etiologies excluded.”¹
- “Central retinal artery occlusion” refers to compromise of blood flow via the central retinal artery to the inner layers of the retina.
- This may result in infarction of the retina and – when it does – this conforms to the diagnosis of acute ischemic stroke.
- For the remainder of this document, the authors used “CRAO” to refer to “CRAO with retinal infarction” to maintain consistency with its use in the published literature.
- In addition, retinal infarction can result from occlusion of branch retinal arteries (BRAO) in which smaller segments of the retina may be implicated.

DEFINITIONS CONTINUED

- Ophthalmic artery occlusion (OAO) variably involves infarction of the inner and outer retina, optic nerve head, globe and ocular tissues (with the extent of tissue involvement dependent on the degree of collateral flow via the external carotid artery circulation).
- The diagnosis of CRAO is made by identifying classic clinical findings of sudden, painless vision loss, a relative afferent pupillary defect and fundusoscopic findings indicative of retinal hypoperfusion.
- A distinct variant of CRAO with a more favorable visual outcome occurs when a cilioretinal artery is present and is spared (see section 4).
- Most cases (95%) of CRAO are classified as “non-arteritic” whereas 5% of cases are “arteritic” and occur as part of an inflammatory disorder such as giant cell arteritis (GCA)⁹.
- Definitions are summarized in table 1.

TABLE 1. DEFINITIONS.

Entity	Definition	Supporting evidence
Acute ischemic stroke	An episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction.	History, physical examination, radiographic or pathologic findings
Retinal infarction	Retinal cell death attributable to ischemia, based on 1. pathological, imaging, or other objective evidence of retinal focal ischemic injury in a defined vascular distribution; or 2. clinical evidence of retinal focal ischemic injury based on symptoms persisting ≥ 24 hours or until death, and other etiologies excluded.	Funduscopy examination, optical coherence tomography, histopathology
Central retinal artery occlusion (CRAO)	Interruption of blood flow through the central retinal artery due to thromboembolism or vasospasm with or without retinal ischemia	Clinical history, optical coherence tomography, funduscopy examination, fluorescein angiography
Branch retinal artery occlusion (BRAO)	Interruption of blood flow through a branch retinal artery due to thromboembolism or vasospasm with or without retinal ischemia	
Ophthalmic artery occlusion	Interruption of blood flow through the ophthalmic artery due to thromboembolism or vasospasm with or without retinal or choroidal ischemia	
Arteritic CRAO	CRAO occurring in the context of a systemic inflammatory condition	Clinical history, funduscopy examination, general physical examination, fluorescein angiography, serum inflammatory markers
Non-arteritic CRAO	CRAO occurring as a result of local thrombus formation or thromboembolism	
Retinal transient ischemic attack (Amaurosis fugax)	Transient, painless, monocular visual loss with no residual visual impairment	Clinical history, funduscopy examination
CRAO without cilioretinal artery sparing	CRAO occurring in the absence of a patent cilioretinal artery	Funduscopy examination, fluorescein angiography
CRAO with cilioretinal artery sparing	CRAO occurring in the presence of a patent cilioretinal artery	

EPIDEMIOLOGY AND RISK FACTORS

EPIDEMIOLOGY AND RISK FACTORS

- The age- and sex-adjusted incidence of CRAO is 1.9/100,000 person-years in the United States¹⁰, 1.8/100,000 person-years in South Korea¹¹ and 2.53/100,000 person-years in Japan¹².
- The incidence rises to 10.1/100,000 person-years in those above the age of 80¹¹.
- Men have a slightly higher incidence than women^{11, 13}.
- The incidence of asymptomatic branch retinal arterial emboli is far higher with a cumulative 10-year incidence of 2.9% in those ≥ 49 years old¹⁴.
- By contrast, the incidence of symptomatic BRAO is approximately 30% that of CRAO¹⁵.
- A large study based on the national readmissions database in the United States found that patients admitted with CRAO or BRAO are slightly younger than those with cerebral ischemic stroke (66.8 years compared with 70.8 years)¹⁵.

EPIDEMIOLOGY AND RISK FACTORS CONTINUED

- CRAO is most strongly associated with an ipsilateral internal carotid artery stenosis¹⁶.
- A single center study of 103 cases of CRAO found that 37% of patients had ipsilateral critical carotid disease (defined in this study as $\geq 70\%$ stenosis, arterial dissection or intra-arterial thrombus)¹⁷.
- In the European assessment group for lysis in the eye (eagle)¹³ study, 77 out of 84 patients had a comprehensive workup for potential etiologies in whom 31 (40%) patients had $\geq 70\%$ carotid artery stenosis¹⁸.
- Emboli to the central retinal artery can also arise from the heart (including the aortic and mitral valves), aortic arch or great vessels¹⁹.

EPIDEMIOLOGY AND RISK FACTORS CONTINUED

- This is reflected in the risk factor profile of patients with CRAO. the eagle study¹³ demonstrated a high prevalence of cardiovascular risk factors: obesity (82%), hypertension (73%), tobacco use (49%), hypercholesterolemia (49%), and diabetes mellitus (14%) in the 77 patients evaluated¹⁸.
- Overall, 67% of patients had at least one cardiovascular risk factor. additionally, 20% of patients had a cardiac arrhythmia, 17% had cardiac valvular disease, and 5% had heart failure.
- Patients with CRAO are more likely to have atrial fibrillation (AF) than age- and sex-matched controls²⁰ and CRAO portends a high risk of recurrent stroke in patients known to have AF²¹.
- A longer duration of cardiac monitoring is associated with a higher risk of detecting AF in patients with CRAO²².

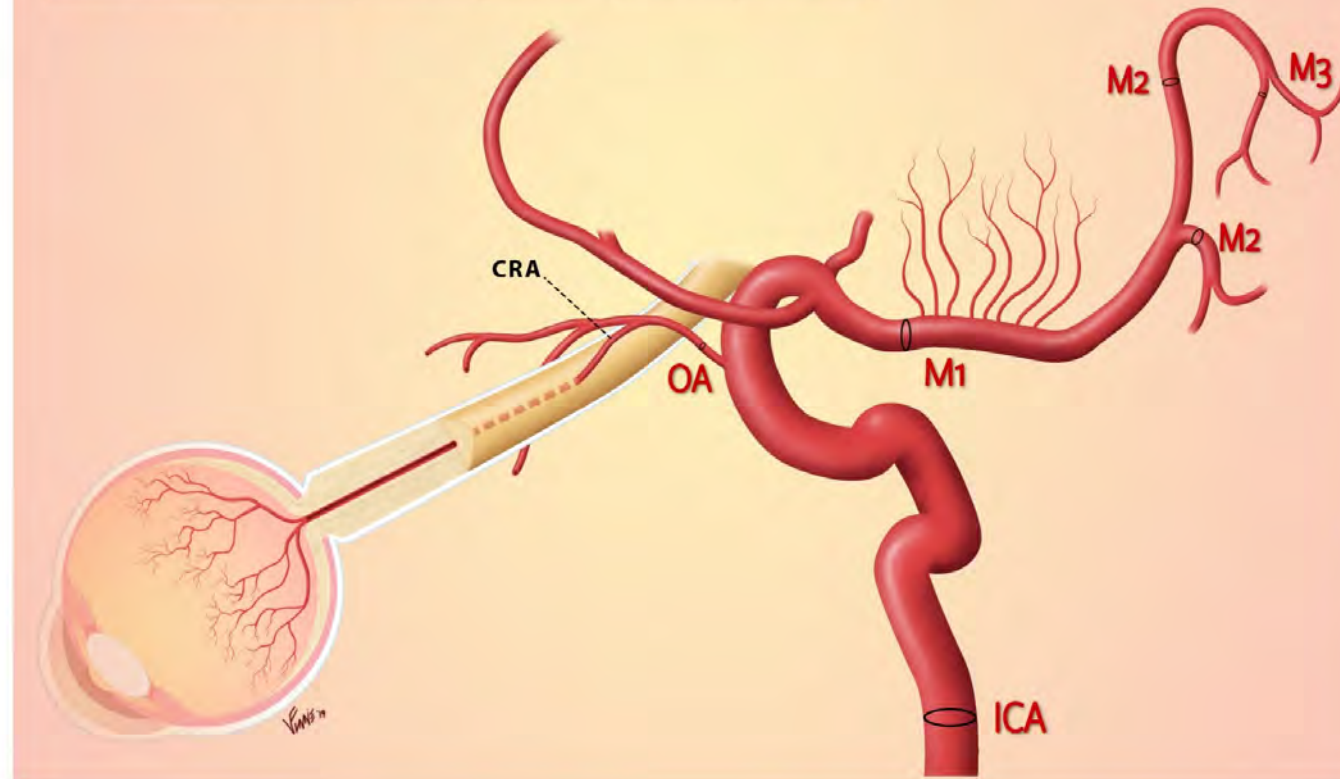
PATHOPHYSIOLOGY

PATHOPHYSIOLOGY

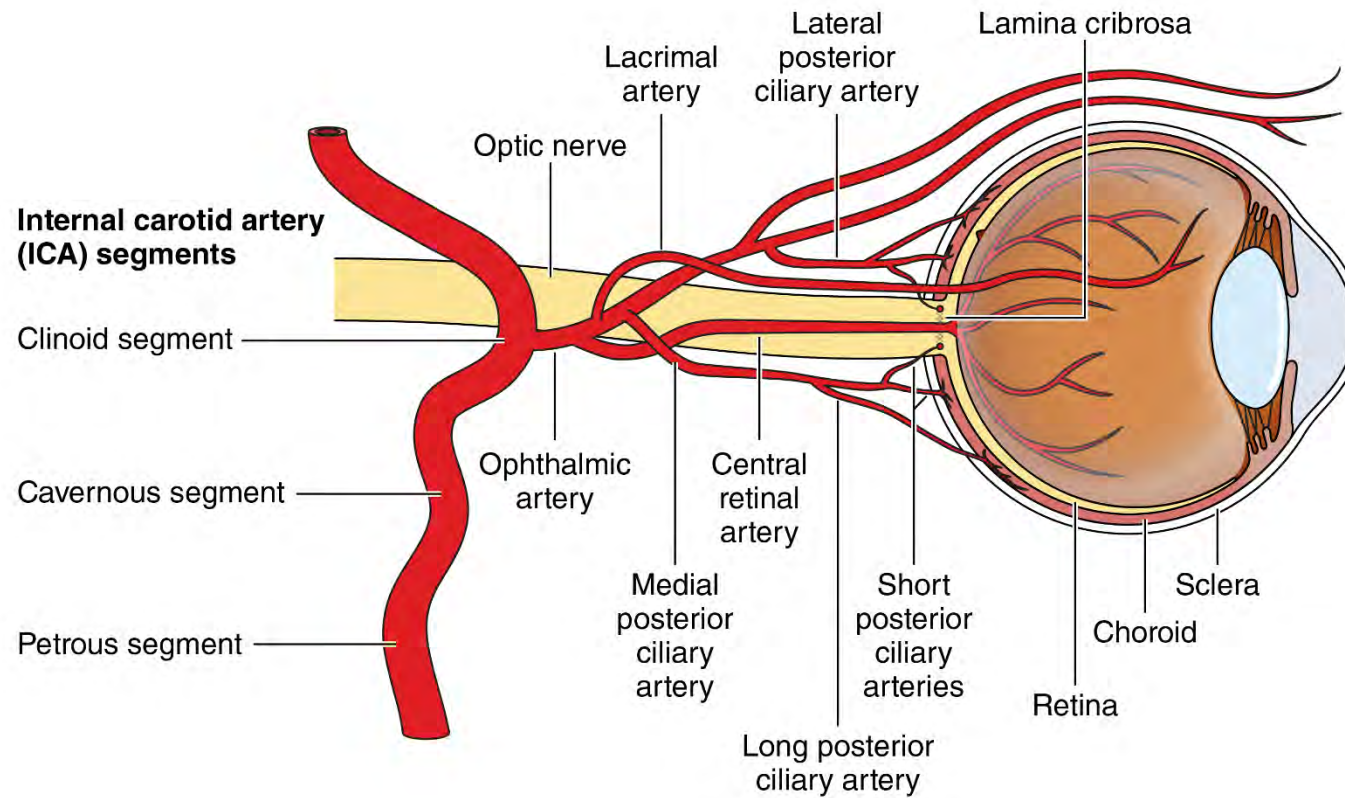
- The central retinal artery and its branches supply the inner retina.
- The inner retina is comprised of the retinal nerve fiber layer, the ganglion cell layer and the inner plexiform layer.
- The central retinal artery originates from the ophthalmic artery, which is the first branch of the internal carotid artery in most people (figure 1).
- In about a third of eyes, a cilioretinal artery is present and often supplies the fovea which is critical for central vision²³.
- The cilioretinal artery originates from the posterior ciliary circulation, not the central retinal arterial circulation.
- Therefore, when it is present, visual acuity may be near normal following a CRAO²³, while peripheral vision will be severely impaired.

DIAMETER OF ANTERIOR CIRCULATION VASCULATURE

	ICA	M1	M2	OA	M3
Vessel Diameter	3.6 mm	3.1 mm	2.4 mm	1.6 mm	1.5 mm
Rate of recanalization	6%	30%	44-55%	-	66%



ARTERIAL SUPPLY TO THE RETINA



PATHOPHYSIOLOGY CONTINUED

- The most important determinant of retinal damage and final visual outcome is the duration of occlusion of the central retinal artery.
- A crucial point in modelling the pathophysiology of CRAO is the partitioning of the inner retinal circulation (provided by the central retinal artery) and the outer retinal/choroidal circulation (provided by the posterior ciliary circulation).
- In CRAO, there is passive diffusion of oxygen from the outer retina to the thin inner retina^{24, 25} (which forms the theoretical basis for hyperbaric oxygen therapy, section 7).
- Additionally, robust collateralization exist between these two circulations at the optic nerve head and via pial anastomoses of the central retinal artery²⁶.

PATHOPHYSIOLOGY CONTINUED

- It has been posited that retinal ganglion cells may be susceptible to damage within 12-15 minutes of arterial occlusion²⁷, but clinical and experimental evidence indicates a longer window of viability^{2, 28}.
- In elderly, atherosclerotic and hypertensive rhesus monkeys, CRAO produced no detectable optic nerve or retinal damage if present for less than 97 minutes while after 240 minutes of occlusion, severe and irreversible damage occurred^{29, 30}.

PATHOPHYSIOLOGY CONTINUED

- Several mechanisms can lead to the acute disruption of the retinal blood supply in the absence of inflammation of the vessels.
- The most common is the embolic occlusion of the central retinal artery or branch retinal arteries via remote embolization from the ipsilateral internal carotid artery, aortic arch or the heart.
- This assertion is based on a study of 234 patients with non-arteritic CRAO; 85% had cervical vessel imaging performed and 71% of these had ipsilateral carotid plaque.
- Only 18% of patients in this study had >80% stenosis rendering hemodynamic impairment less likely as a mechanism of CRAO.
- The arteritic subtype – in which arteries are occluded by an inflammatory process – is less common than the thromboembolic subtype.
- The most common cause of arteritic CRAO is giant cell arteritis (GCA) which affects medium and large sized extracranial arteries including distal branches of the carotid artery^{3, 31} resulting in occlusive intimal hyperplasia³².

PATHOPHYSIOLOGY CONTINUED

- Eyes with GCA-induced CRAO may have co-existent arteritic anterior ischemic optic neuropathy (AION) and choroidal ischemia, resulting from the vasculitic occlusion of the posterior ciliary arteries³.
- Occasionally, in GCA, arteritic occlusion of the posterior ciliary arteries can lead to disruption of blood flow in the cilioretinal artery as well, and present as GCA-associated cilioretinal artery occlusion (CLRAO).
- In a large cohort of patients with biopsy-proven GCA, 8.2% developed permanent vision loss, attributable to AION in 6.9%, to CRAO in 1.6% and to CLRAO in 0.4%³³.
- Inflammatory disease of the proximal ophthalmic artery, such as in GCA, can induce concomitant ischemia of the inner and outer retina as well as of the optic nerve head.
- For instance, in the above cohort³³ 1 patient (0.4%) had CRAO and a contralateral AION and 1 (0.4%) had combined cilioretinal artery occlusion and AION in the same eye.

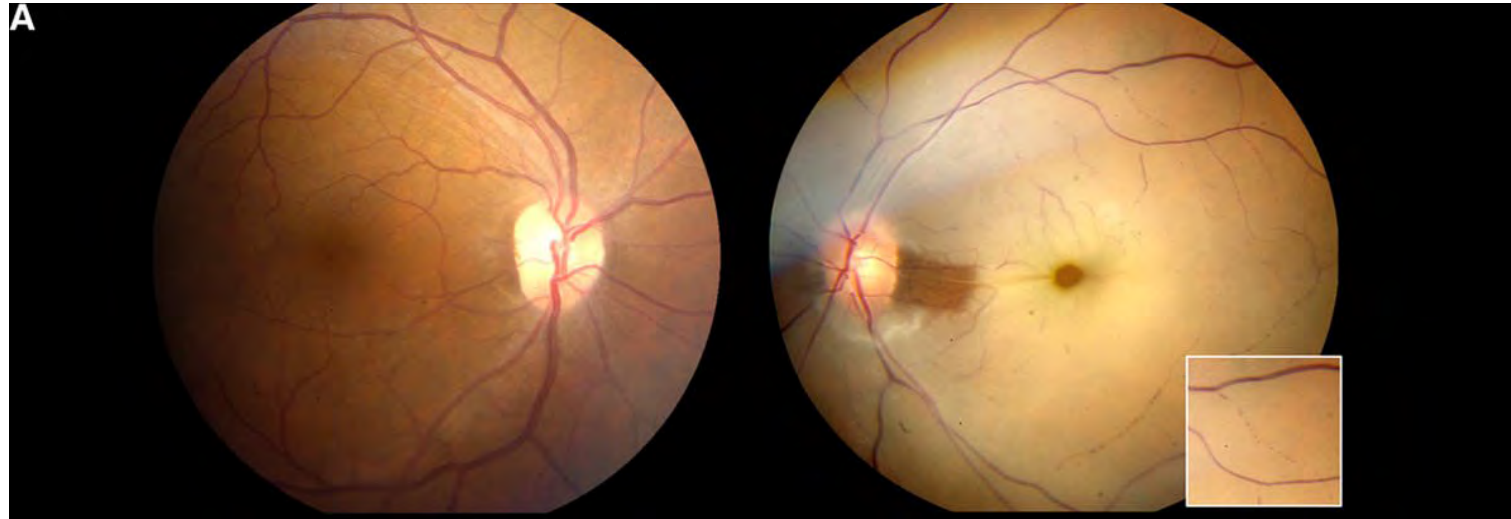
PATHOPHYSIOLOGY CONTINUED

- Also, CRAO has been reported as a manifestation of a wide range of infectious and inflammatory systemic diseases including other autoimmune vasculitides.
- Rarely, thrombosis of the central retinal artery can occur with a hypercoagulable state³⁴.
- Iatrogenic CRAO may occur as a complication of cosmetic facial injections if the synthetic material is inadvertently introduced into the facial arteries that collateralize with the ophthalmic artery³⁵.
- Generally, in such cases, the prognosis is poor and as the material is not fibrin-based the discussion of thrombolysis (in section 7) does not apply.

DIAGNOSIS

DIAGNOSIS

- Typically, CRAO presents as sudden, painless monocular loss of visual acuity and/or peripheral vision.
- The degree of visual loss is variable - in over 80% of patients, the initial visual acuity is “count fingers” or worse but it can be near normal in the presence of a cilioretinal artery.
- Impaired color vision is proportional to visual acuity.
- Most patients have an ipsilateral relative afferent pupillary defect (that may not be present if there is contralateral optic neuropathy).
- The typical funduscopic findings include retinal edema (evident as retinal whitening), a cherry red spot (as a result of preserved choroidal circulation underlying the fovea which is surrounded by pale, ischemic retina), slow segmental blood flow (known as “box-carring”) in the retinal arteries which are attenuated, and usually a normal appearing optic disc (figure 2).

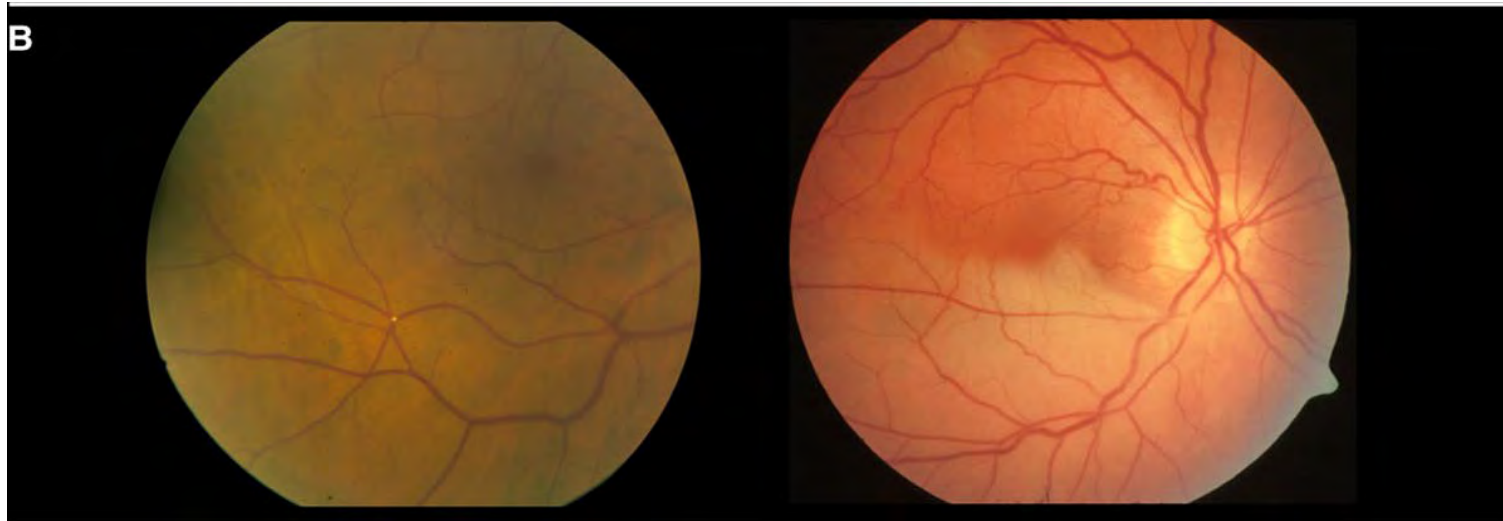


Normal Retina

**Infarcted Retina with
Cilioretinal Artery Sparing**

DIAGNOSIS CONTINUED

- In patients with CRAO, retinal emboli are visible in the branch retinal arteries less than 10% of the time and emboli within the central retinal artery itself are rarely visible as the majority of its course is retrobulbar.
- The association of optic disc edema with acute CRAO indicates the rare combination of AION and inner retinal ischemia, likely reflecting a vasculitis affecting the posterior ciliary arteries as well.
- Arteritic CRAO should be suspected in patients over the age of 50 with systemic symptoms including jaw claudication, polymyalgia rheumatica, diffuse posterior neck pain, scalp tenderness with or without nodules, new-onset headache, or elevated inflammatory markers³⁶⁻³⁸.



**Calcified embolus in
branch retinal artery**

Branch retinal artery occlusion

DIAGNOSIS CONTINUED

- An ophthalmological evaluation, including a dilated funduscopic examination or a non-mydriatic color fundus photograph, is necessary to confirm the diagnosis of CRAO and rule out other disorders that can cause acute painless loss of vision, including vitreous and chorioretinal hemorrhage, retinal detachment, and acute optic neuropathy.
- Less often, disorders of the anterior segment of the eye (cornea and lens) may cause acute visual loss³⁹.
- When feasible, the emergency provider should be guided by an eye care specialist to confirm the diagnosis of CRAO.
- If an eye care specialist is not available on site for an emergency evaluation, and the treating physician is not comfortable establishing the diagnosis, ocular fundus photography can be obtained and relayed to an eye care specialist by telemedicine/telestroke for confirmation of the diagnosis³⁹.

VITREO-RETINAL HEMORRHAGE ON FUNDOSCOPY AND ON CT



DIAGNOSIS CONTINUED

- Early in the occlusive event, the fundus may appear relatively normal and seemingly perfused.
- The history of sudden painless vision loss, presence of a relative afferent pupil defect, attached retina, and normal optic nerve strongly implicate central artery occlusion.
- Imaging modalities, such as optical coherence tomography (OCT), oct angiography or fluorescein angiography, can support the diagnosis of CRAO particularly when the expected findings are subtle or absent.
- Optical coherence tomography can detect retinal edema easily and rapidly in the acute setting (Figure 2, C & D).
- Fluorescein angiography can show delayed or absent retinal perfusion and retinal arterial branch occlusions but is time consuming and usually not necessary to establish a definite diagnosis⁴⁰.
- Further detail concerning the clinical diagnosis of CRAO and other retinal vascular conditions may be found in the American academy of ophthalmology's preferred practice pattern concerning retinal and ophthalmic artery occlusions⁴¹.

NATURAL HISTORY

NATURAL HISTORY

- Several studies suggest that the natural history of CRAO with respect to visual recovery is poor.
- One study including 177 patients with non-arteritic CRAO (of whom 121 had visual acuity recorded during follow-up) found that nearly 80% of patients had a visual acuity of “count fingers” or worse at follow-up⁹.
- A meta-analysis of 8 studies reporting visual outcomes of 396 untreated patients with CRAO found that only 17.7% (70/396) exhibited a functional visual recovery (defined as improvement of visual acuity from 20/200 or worse at presentation to 20/100 or better) with minimal heterogeneity between studies².

NATURAL HISTORY CONTINUED

- In general, a reduction in vision leads to long term disability. unilateral uncorrectable visual loss is associated with an increased likelihood of falls (or = 2.86, 95% ci 1.16 to 7.08) and functional dependence (or = 7.50, 95% ci 1.97 to 28.6)⁴².
- This may be disabling enough to warrant placement in a long-term care facility^{42, 43}.
- A mixed-methods study⁴⁴ investigated the impact of unilateral visual loss on health-related quality of life by means of a 36-item health survey (SF-36)⁴⁵, administered to 3,108 participants.

NATURAL HISTORY CONTINUED

- Those respondents with moderate to severe vision loss had limitations in physical and social functioning as well as self-reported functional limitations due to emotional problems.
- A survey of adults with normal vision evaluating patients' preference for the treatment of CRAO⁴⁶ showed that 39% of surveyed adults would accept some risk of stroke and 37% would accept some risk even of death to triple the chances of recovering 20/100 visual acuity in one eye when the unaffected eye is sighted.
- More than 80% of persons would accept these risks if the unaffected eye is not sighted⁴⁶.

ACUTE TREATMENT

TRIAGE AND RAPID EVALUATION OF PATIENTS WITH SUSPECTED CRAO

- Reliable systems to rapidly identify and treat patients with CRAO are being developed and are critical both to making treatment widely available and to ensuring adequate enrollment in clinical trials⁴⁷.
- The use of existing stroke code systems ensures rapid and reproducible evaluation of risk factors for hemorrhage.
- Two additions to the stroke code process are necessary in the setting of CRAO
 - 1) a funduscopic examination to confirm the diagnosis and exclude alternative causes such as vitreal or retinal hemorrhage and
 - 2) screening for arteritis.

TRIAGE AND RAPID EVALUATION OF PATIENTS WITH SUSPECTED CRAO CONTINUED

- The efficacy of thrombolysis has not been evaluated in the setting of arteritic CRAO, but early screening and immediate steroid therapy is indicated to preserve vision in the contralateral eye⁴⁸.
- Please note, a more detailed discussion of the management of arteritic CRAO is beyond the scope of this review.
- There is a narrow time window for effective treatment of CRAO and high rate of serious comorbid illness. thus, when diagnosed in an ophthalmology, optometry, neurology or primary clinic immediate triage to an emergency department is necessary and should not be delayed to obtain further outpatient evaluation or institute other treatments⁴¹.

TRIAGE AND RAPID EVALUATION OF PATIENTS WITH SUSPECTED CRAO CONTINUED

- The sequence of thrombolytic treatment for CRAO in the emergency department should begin with an immediate ophthalmological examination in parallel with a structural neurological assessment (via a calculation of the NIHSS), serum testing (platelet count, erythrocyte sedimentation rate, C-reactive protein and coagulation testing) and a CT/CT angiogram of the brain and neck.
- After this process is complete, and a patients' candidacy for acute therapy determined, an expedited inpatient workup should be pursued.
- A suggested treatment protocol for acute CRAO is presented in figure 3.

INTRAVENOUS TPA

- Intravenous tissue plasminogen activator (TPA) is an evidence-based therapy for acute ischemic stroke⁴⁹.
- In patients presenting within 4.5 hours of time last known well, with no evidence of intracranial or systemic hemorrhage, it improves long-term functional outcomes⁵⁰.
- The most commonly used agent is alteplase, delivered via an intravenous infusion (0.9mg/kg with 10% given over one minute and the remainder over 59 minutes).

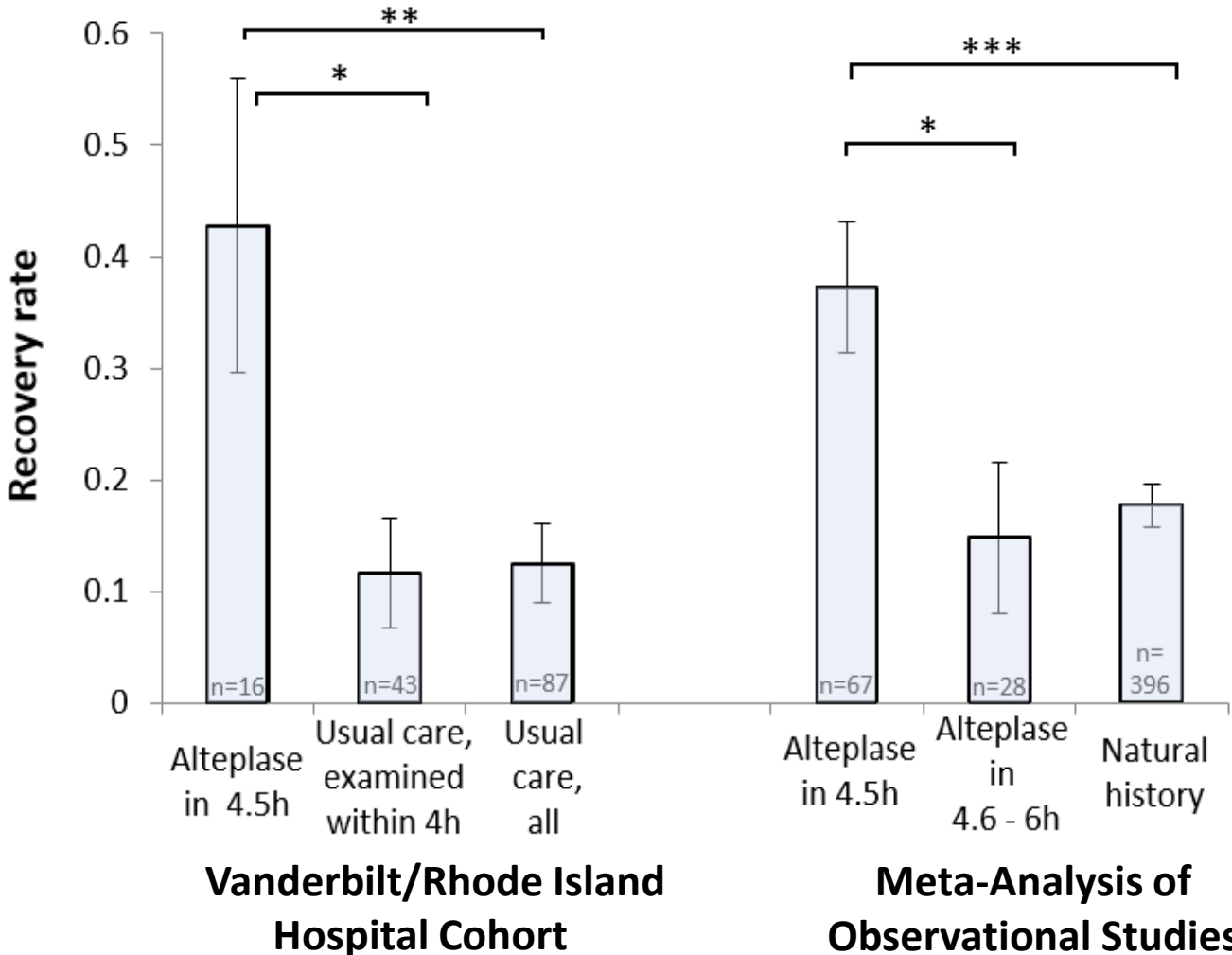
INTRAVENOUS TPA CONTINUED

- Since the 1960s, intravenous thrombolytic agents have been used empirically to treat CRAO and TPA is currently administered in 5.8% of patients admitted with CRAO in the united states¹⁵.
- In a patient-level meta-analysis of observational studies, Schrag et al.² found that patients with acute CRAO treated with any lytic drug exhibited a 50% rate of clinical recovery when treated within 4.5 hours of onset².
- An important accomplishment of this study was the standardization of outcome measures for CRAO, termed “visual recovery”.
- This was defined as a final visual acuity of 20/100 or better in the affected eye when the initial best-corrected visual acuity was 20/200 or worse.
- This definition captures a minimum of three lines of improvement in visual acuity and functional clinical improvement.
- Moreover, this measure is reproducible between studies and performs better than older definitions which were inconsistent and often ambiguous.
- Based on the strength of the observational data - and in the absence of other effective treatments - more than half of academic neurologists treat selected patients with acute CRAO with intravenous TPA.

INTRAVENOUS TPA CONTINUED

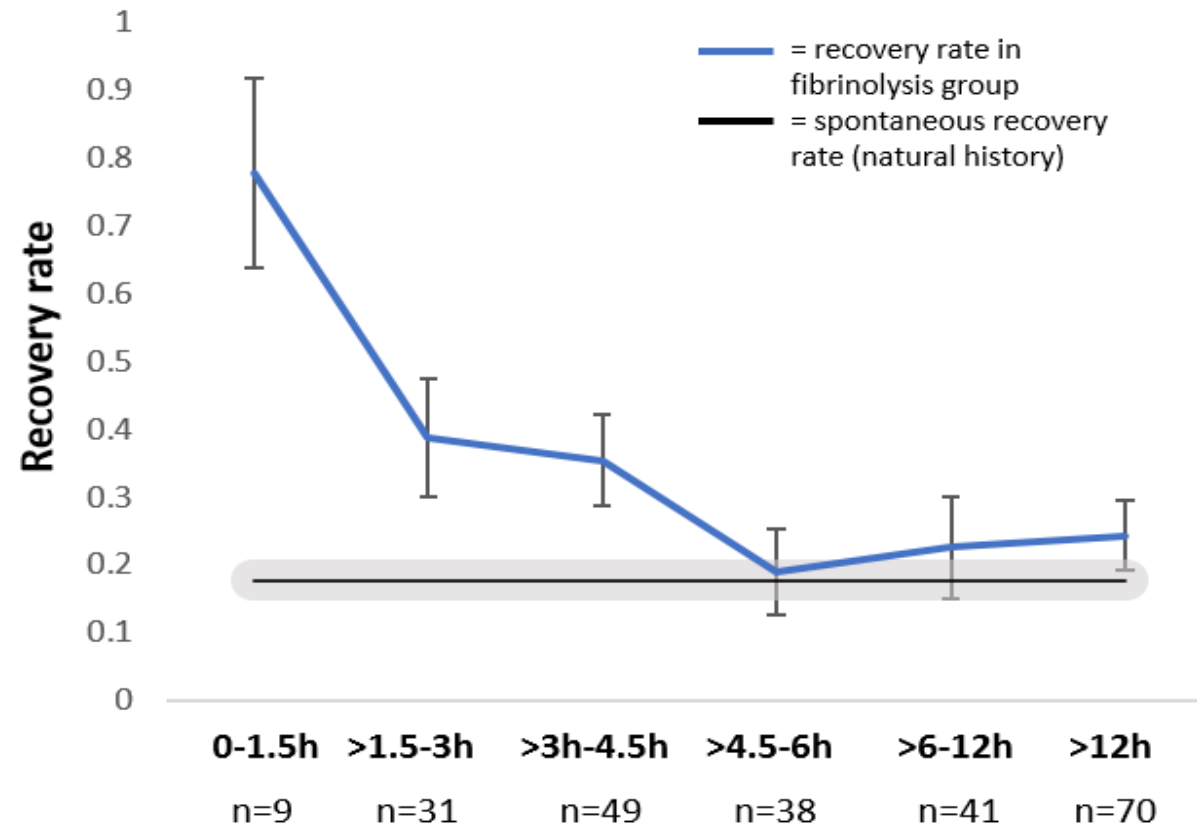
- To-date there have been no adequate randomized clinical trials of intravenous TPA as previous attempts were limited due to difficulty with patient enrollment. since the publication of the meta-analysis of observational studies², intravenous TPA was re-evaluated in four modern cohorts with acute CRAO within 4.5 hours of onset^{28, 51-53}.
- An updated meta-analysis including these modern cohorts again demonstrated a strong effect with treatment within 4.5 hours²⁸.
- This analysis robustly reproduced the earlier findings and formed the basis for several ongoing clinical trials.
- Three randomized trials are being conducted in Europe and will evaluate treatment with IV thrombolysis compared with placebo for the treatment of adults with CRAO presenting within 4.5 hours of symptoms onset
 - 1) THEIA (NCT03197194; comparing TPA with placebo)
 - 2) revision (pending NCT registration; comparing TPA with placebo)
 - 3) TENCRAOS (NCT 04526951; comparing tenecteplase with placebo)
- Until a fully powered efficacy trial has been resulted, we feel that there is equipoise regarding the utility of iv tpa for CRAO and the decision to use this therapy rests on a thorough discussion between the treating specialist and the affected patient which includes an acknowledgement of the limitations inherent in the literature to-date.

VISUAL RECOVERY AFTER IV TPA

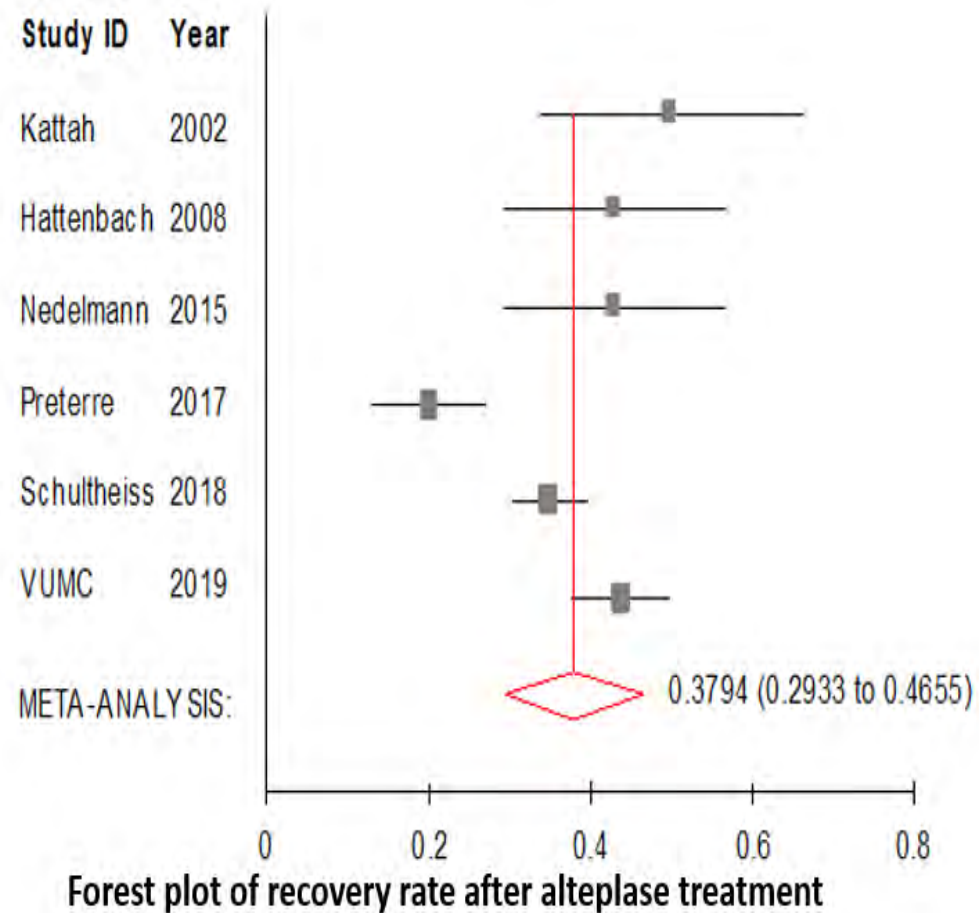


VISUAL RECOVERY AFTER IV TPA – META-ANALYSIS

B. Earlier treatment associated with improved recovery rate (any intravenous fibrinolytic treatment, n=228)



VISUAL RECOVERY AFTER IV TPA – META-ANALYSIS



INTRAVENOUS TPA CONTINUED

- The risk of symptomatic intracranial hemorrhage (SICH) appears to be low when TPA is administered for treatment of CRAO.
- There are no recorded cases of SICH when TPA is administered within 4.5 hours of symptom onset and without the concomitant administration of anticoagulation²⁸.
- Larger datasets will be needed to clarify the risk of SICH associated with Alteplase administration for CRAO.
- Because of a 30% incidence of concurrent cerebral ischemic stroke^{17, 56} and a reduced efficacy signal in the 4.5-6-hour time epoch^{2, 28}, treatment beyond 4.5 hours requires further study potentially including the exploration of novel biomarkers of retinal viability.
- Emerging evidence suggests acute OCT may be useful for identifying patients who are within the 4.5-hour window for treatment if they are unable to report the time of symptom onset⁵⁷.

INTRA-ARTERIAL TPA

- Introducing TPA directly into the ophthalmic circulation via superselective microcatheterization of the ostium of the ophthalmic artery (intra-arterial thrombolysis – IAT) has the theoretical advantage of directly administering thrombolytic therapy to the thrombus, while reducing the risk of intracranial and systemic hemorrhage⁵⁸.
- Thus, the dose of TPA reaching the systemic circulation is much lower and thus it may be considered in patients with systemic contraindications to intravenous thrombolysis such as recent surgery, gastrointestinal hemorrhage or coagulopathy.
- This reduction in systemic complications is accompanied by risks of arterial dissection, catheter-induced spasm and dislodgement of atheromatous plaque in the ophthalmic circulation with the possibility of distal embolization.

INTRA-ARTERIAL TPA CONTINUED

- Given the size of the vessels in question (the ophthalmic artery is 1.3mm in diameter and the central retinal artery is 160 μ m in diameter at its terminus), mechanical clot retrieval is not possible with existing technology. over the past 20 years, several retrospective studies have investigated this treatment with variable results.
- Some case series suggest that IAT may improve visual outcomes⁵⁹.
- The only prospective, randomized, controlled study was the European assessment group for lysis in the eye (eagle)¹³.
- Eagle enrolled patients up to 24 hours from symptom onset. it was stopped prematurely because of a failure of the treatment group to outperform the “conservative treatment” group.

INTRA-ARTERIAL TPA CONTINUED

- Two patients suffered an intracerebral hemorrhage. the mean time between symptom onset and treatment was 13 hours in this study, no patients were treated within 4.5 hours and only 4 of 41 were treated within 6 hours.
- Therefore, treatment with IAT at early time points remains untested.
- Although conceptually appealing, there are a number of logistical and procedural challenges that render the study of IAT at early time points difficult.
- For instance, IAT requires the mobilization of an on-call endovascular interventional team and preparation of a catheterization laboratory.
- It also has inherent difficulties because, in contrast to endovascular thrombectomy for cerebral stroke, it necessitates cannulation of the much smaller ophthalmic artery.

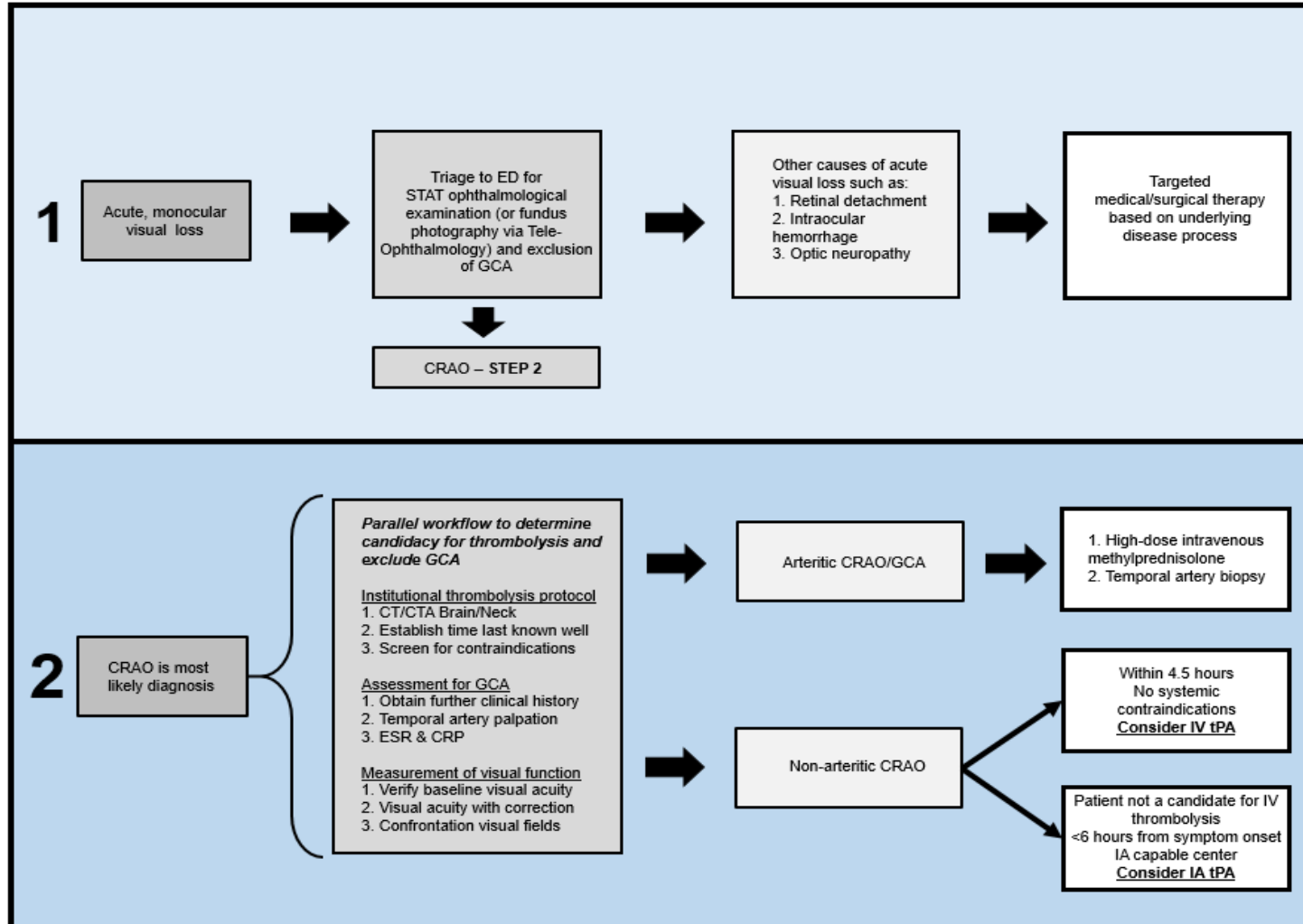
INTRA-ARTERIAL TPA CONTINUED

- The recommended technique for superselective ophthalmic artery microcatheterization is placement of a small microcatheter (0.60mm) into the ostium of the artery.
- Although distal microcatheterization of the ophthalmic artery is possible, overall, it is not recommended as it increases the risk of arterial dissection and thromboembolic events.
- This technique of proximal ophthalmic artery microcatheterization is used widely for the intra-arterial administration of chemotherapy for retinoblastoma⁶⁰; however the technical challenges are increased in the presence of atherosclerosis, which is likely present in the majority of patients with non-arteritic CRAO.

INTRA-ARTERIAL TPA CONTINUED

- In cases of occlusion or high-grade stenosis of the internal carotid artery, TPA can be injected into the external carotid artery and delivered to the ophthalmic artery via collateral flow from the distal middle meningeal artery.
- In CRAO, TPA is delivered in increments of 15mg accompanied by serial bedside ophthalmological examinations until visual acuity is restored, a “choroidal blush” is visualized, or a dose of 50mg has been reached¹³.
- The literature favors continued study of intra-arterial TPA at early time points.

FIGURE 3. TREATMENT PROTOCOL FOR CRAO.



CONSERVATIVE TREATMENTS

- Several so-called “conservative” approaches have been employed in an effort to restore vision.
- These include anterior chamber paracentesis, ocular massage, topical intraocular pressure-lowering agents, sublingual isosorbide dinitrate, systemic beta-blockade, carbogen therapy (inhaling a 95% o₂/5% co₂ mixture) and breathing into a paper bag.
- The putative rationale behind most conservative therapies is that modulation of intraocular pressure and/or vasodilation of the retinal vasculature may dislodge the obstruction and allow the embolus to migrate peripherally.
- Typically, two or more of these modalities are combined (for instance, in the active control arm of the eagle trial, patients were treated with hemodilution, timolol, intravenous acetazolamide and ocular massage¹³), making it difficult to disentangle the effect of one from another.
- None are known to be more effective than placebo⁶¹.

CONSERVATIVE TREATMENTS CONTINUED

- Indeed, one meta-analysis suggested that patients treated with differing combinations of such strategies had a visual recovery rate of 7.4% compared to the natural history of 17.7%².
- Most studies exploring such strategies are small, retrospective, uncontrolled and limited by selection and reporting bias.
- Two retrospective analyses, one of combined treatment with anterior chamber paracentesis and carbogen⁶² and the other with anterior chamber paracentesis alone⁶³, found no benefit of treatment independent of the timing of the intervention.
- An additional study found that anterior chamber paracentesis was independently associated with worse visual outcome when performed before hyperbaric oxygen therapy⁶⁴.

CONSERVATIVE TREATMENTS CONTINUED

- Ocular massage is intended to produce fluctuations in intraocular pressure and conceptually increase the chance of embolus migration and reperfusion.
- The use of ocular massage to treat CRAO dates to the 1880s, yet no study has demonstrated that it has any convincing effect.
- Other techniques used include pentoxifylline and isovolumic hemodilution (to reduce erythrocyte viscosity).
- Because of a lack of evidence concerning efficacy and suggestions of harm in the literature, these treatments are not currently endorsed in professional guidelines concerning the management of crao⁴¹.

CONSERVATIVE TREATMENTS CONTINUED

- Hyperbaric oxygen therapy (HBO) is employed as a method of salvaging retinal tissue in acute CRAO.
- In normal physiology, over 50% of the retinal oxygen supply is derived from passive diffusion from the choroidal circulation²⁵ whereas with hyperbaric oxygenation it is as high as 97%⁶⁵
- Several case series⁶⁶⁻⁶⁸ suggest HBO improves visual outcome in CRAO.
- HBO may provide benefit as a temporizing measure while definitive reperfusion is pursued, though is not felt to promote reperfusion itself.
- it is associated with a low risk of systemic complications and intracranial or systemic hemorrhage rates are not increased⁶⁹.
- Only one case report of concurrent use of HBO and TPA for CRAO⁷⁰.
- HBO is labor intensive to deploy and available at only select centers in the united states.



SECONDARY PREVENTION

SECONDARY PREVENTION

- The optimal approach to long-term secondary prevention in patients with CRAO should be guided by a multidisciplinary collaboration between a neurologist, ophthalmologist and primary care physician or internist.
- Patients with CRAO require ophthalmological follow-up for optimization of residual vision, serial visual assessment, monitoring for neovascularization-related complications⁷¹ and preservation of the health of the contralateral eye.
- The neurologist's role is to determine the cause, initiate an appropriate pharmacological secondary prevention strategy and work in concert with the patient's internist/primary care physician to control modifiable risk factors.

SECONDARY PREVENTION CONTINUED

- Treatment of hypertension, dyslipidemia, diabetes mellitus, obesity, obstructive sleep apnea as well as smoking cessation, implementation of a plant-based diet and regular physical activity are critical for secondary prevention after CRAO and should follow established professional guidelines for cerebral ischemic stroke⁷² (note that ischemic stroke guidelines do not explicitly mention CRAO at present although it is formalized in the AHA'S definition of ischemic stroke).
- For those without an indication for anticoagulation or surgery, an anti-thrombotic therapy regimen paralleling that seen in cryptogenic ischemic stroke is reasonable.

SECONDARY PREVENTION CONTINUED

- In patients with a presenting national institutes of health stroke scale score of ≤ 3 , an initial course of 21 days of dual anti-platelet therapy may be reasonable followed by long-term treatment with a single antiplatelet agent, typically aspirin 81mg daily or clopidogrel 75mg daily as recommended by current guidelines^{49, 72}.
- The THALES⁷³ and SOCRATES⁷⁴ trials suggest ticagrelor (either alone or in combination with aspirin) may reasonably form part of pharmacological secondary prevention in patients with TIA or minor stroke, and thus might be reasonable after CRAO.

SECONDARY PREVENTION CONTINUED

- The etiological workup should be done urgently as it will frequently unmask concurrent disease that requires prompt intervention^{17, 75}.
- High grade stenosis of the ipsilateral carotid artery should be identified rapidly with CT/MR angiography or cervical artery ultrasound and treated as symptomatic carotid stenosis.
- The choices in this scenario include surgical revascularization or medical management (anti-platelet therapy, a statin, risk factor modification, smoking cessation and other lifestyle measures) depending on the patient's surgical risk.
- Because of the high rate of structural heart disease among patients with CRAO¹⁷, it is reasonable to consider trans-thoracic echocardiography to examine for evidence of a cardioembolic source.

SECONDARY PREVENTION CONTINUED

- Transesophageal echocardiography should be reserved for those patients in whom there is a high suspicion for an occult structural cardiac lesion and an otherwise negative diagnostic workup.
- The ideal screening regimen for AF in patients with CRAO has not yet been defined, but some duration of ambulatory cardiac rhythm monitoring is appropriate in patients without a clear other cause for the CRAO.
- When AF is detected, oral anticoagulation should be initiated in accordance with established guidelines for stroke secondary prevention⁷².
- CRAO was not classed as an ischemic event in the derivation of the CHADS₂ and CHA₂DS₂-VASC score⁷⁶ in the authors opinion this should be classified as stroke for the purposes of determining an individual patient's score.
- Screening for less common causes of CRAO, including hypercoagulable states, paradoxical emboli and septic emboli should be considered in select high-risk patients.

CONCLUSIONS AND FUTURE DIRECTIONS

CONCLUSIONS AND FUTURE DIRECTIONS

- CRAO and cerebral ischemic stroke share the same underlying mechanisms and therapeutic approaches.
- At present, there is no widely accepted therapy and practitioners vary in their management of this condition.
- To-date, the literature on IV TPA for CRAO is constrained by multiple variables including a very long treatment window and inconsistent or poorly-defined visual recovery outcomes.
- Intravenous TPA may be a reasonable treatment for patients with CRAO after a discussion of the benefits and risks with the patient or surrogate.
- Historic strategies (including anterior chamber paracentesis, ocular massage and hemodilution) are not beneficial with respect to visual outcome.
- Emerging treatments including HBO and intra-arterial TPA at early time points show promise but requires further study.
- We must develop systems of care for the urgent recognition, triage and management of CRAO in a similar manner to cerebral ischemic stroke.

CONCLUSIONS AND FUTURE DIRECTIONS CONTINUED

- Telemedicine will allow expert evaluation and initiation of treatment at peripheral centers which lack in-house specialists.
- Further studies are necessary to evaluate long-term quality of life after CRAO, and population-based studies are needed to more precisely clarify the modern epidemiology of CRAO.
- Vascular secondary prevention after CRAO should be a collaborative effort between a neurologist, ophthalmologist and internist.
- There is an unmet need for a pragmatic, multicenter, randomized, double-blind, placebo-controlled clinical trial comparing IV TPA with placebo at early time points in patients with CRAO.

CONCLUSIONS AND FUTURE DIRECTIONS CONTINUED

- Prospective, multi-center, observational registries will aid in feasibility testing and sample size calculations for such a clinical trial.
- Future research should be directed towards the development of novel biomarkers of retinal tissue viability that can be deployed in real time and complement existing time-based decision-making algorithms, potentially allowing the use of TPA at delayed time points in selected patients.
- Additional treatment modalities that require further study include evaluation of novel thrombolytic agents including tenecteplase, hyperbaric oxygen therapy and novel neuroprotectants for use in tandem with recanalization therapy.
- Considerations for practice from this statement are summarized in table 2.

SUMMARY OF SUGGESTIONS FOR CLINICAL PRACTICE ACCORDING TO SECTION

TABLE 2. SUMMARY OF SUGGESTIONS FOR CLINICAL PRACTICE ACCORDING TO SECTION

Section	Suggestions for Clinical Practice
Definitions	CRAO with retinal infarction conforms to the diagnosis of acute ischemic stroke. It is defined based on a compelling clinical history supported by the presence of a relative afferent pupillary defect and classic funduscopy findings.
Epidemiology and Risk Factors	The incidence of CRAO is approximately 1.9/100,000 person years. This risk increases with age and in the presence of vascular risk factors such as hypertension, hyperlipidemia, diabetes mellitus, tobacco exposure and obesity.
Pathophysiology	In 95% of cases, CRAO occurs as a result of thromboembolic disease. In 5% of cases, it occurs as “arteritic CRAO”, usually as a component of giant cell arteritis.
Diagnosis	Sudden, painless, monocular visual loss most often results from CRAO, optic neuropathy (most often ischemic), retinal detachment, or intra-ocular hemorrhage. An ophthalmologic examination, including a funduscopy examination is necessary for the diagnosis of CRAO and to rule out intra-ocular hemorrhage.
Natural History	CRAO impacts central vision (visual acuity), peripheral vision (visual fields), color vision and stereovision. The natural history of CRAO is poor with only 17% of patients achieving a functional visual acuity in the affected eye.

TABLE 2. SUMMARY OF SUGGESTIONS FOR CLINICAL PRACTICE ACCORDING TO SECTION CONTINUED

Section	Suggestions for Clinical Practice
Treatment	<p><u>Triage:</u> Patients with suspected CRAO should be triaged to the nearest emergency department.</p> <p><u>Intravenous tPA:</u> Intravenous tPA may be considered in patients who have disabling visual deficits and who otherwise meet criteria for systemic tPA after a thorough benefit/risk discussion with the affected patient.</p> <p><u>Intra-arterial tPA:</u> In centers capable of deploying endovascular therapy, intra-arterial tPA may be considered in patients with disabling visual deficits at early time points especially if they are not candidates for intravenous tPA. This consideration comes with the strong caveat that, at present, IAT is an unproven therapy and should only be considered in light of the devastating visual outcome associated with CRAO.</p> <p><u>Conservative treatments:</u> There is no compelling evidence that conservative treatments for CRAO are effective and trends in the observational literature suggest ocular massage, anterior chamber paracentesis and hemodilution may be harmful.</p>
Secondary Prevention	<p>Secondary prevention (including monitoring for complications) should be a collaborative effort between neurology, ophthalmology and primary care medicine.</p> <p>Risk factor modification should include pharmacological and lifestyle interventions.</p> <p>Anti-platelet therapy is a reasonable consideration for pharmacological secondary prevention when the etiology is cryptogenic or attributed to atherosclerosis</p> <p>If atrial fibrillation or another cardioembolic source is detected during the diagnostic workup, anticoagulation may be appropriate for secondary prevention.</p> <p>Severe stenosis of the carotid artery valves may require surgical intervention for secondary stroke prevention.</p>
Future Directions	<p>There is a need for a pragmatic, randomized, placebo-controlled, double-blind clinical trial comparing tPA with placebo as treatment for patients with CRAO presenting at early time points.</p> <p>Future research should explore biomarkers of retinal viability which may complement existing, time-based approaches to thrombolytic therapy.</p> <p>The use of the novel thrombolytic agent tenecteplase and intra-arterial tPA at early time points should be explored in future studies.</p>

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TABLE 1. DEFINITIONS.

Entity	Definition	Supporting evidence
Acute ischemic stroke	An episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction.	History, physical examination, radiographic or pathologic findings
Retinal infarction	Retinal cell death attributable to ischemia, based on 1. pathological, imaging, or other objective evidence of retinal focal ischemic injury in a defined vascular distribution; or 2. clinical evidence of retinal focal ischemic injury based on symptoms persisting ≥ 24 hours or until death, and other etiologies excluded.	Funduscopy examination, optical coherence tomography, histopathology
Central retinal artery occlusion (CRAO)	Interruption of blood flow through the central retinal artery due to thromboembolism or vasospasm with or without retinal ischemia	Clinical history, optical coherence tomography, funduscopy examination, fluorescein angiography
Branch retinal artery occlusion (BRAO)	Interruption of blood flow through a branch retinal artery due to thromboembolism or vasospasm with or without retinal ischemia	
Ophthalmic artery occlusion	Interruption of blood flow through the ophthalmic artery due to thromboembolism or vasospasm with or without retinal or choroidal ischemia	
Arteritic CRAO	CRAO occurring in the context of a systemic inflammatory condition	
Non-arteritic CRAO	CRAO occurring as a result of local thrombus formation or thromboembolism	
Retinal transient ischemic attack (Amaurosis fugax)	Transient, painless, monocular visual loss with no residual visual impairment	Clinical history, funduscopy examination
CRAO without cilioretinal artery sparing	CRAO occurring in the absence of a patent cilioretinal artery	Funduscopy examination, fluorescein angiography
CRAO with cilioretinal artery sparing	CRAO occurring in the presence of a patent cilioretinal artery	

TABLE 2. SUMMARY OF SUGGESTIONS FOR CLINICAL PRACTICE ACCORDING TO SECTION

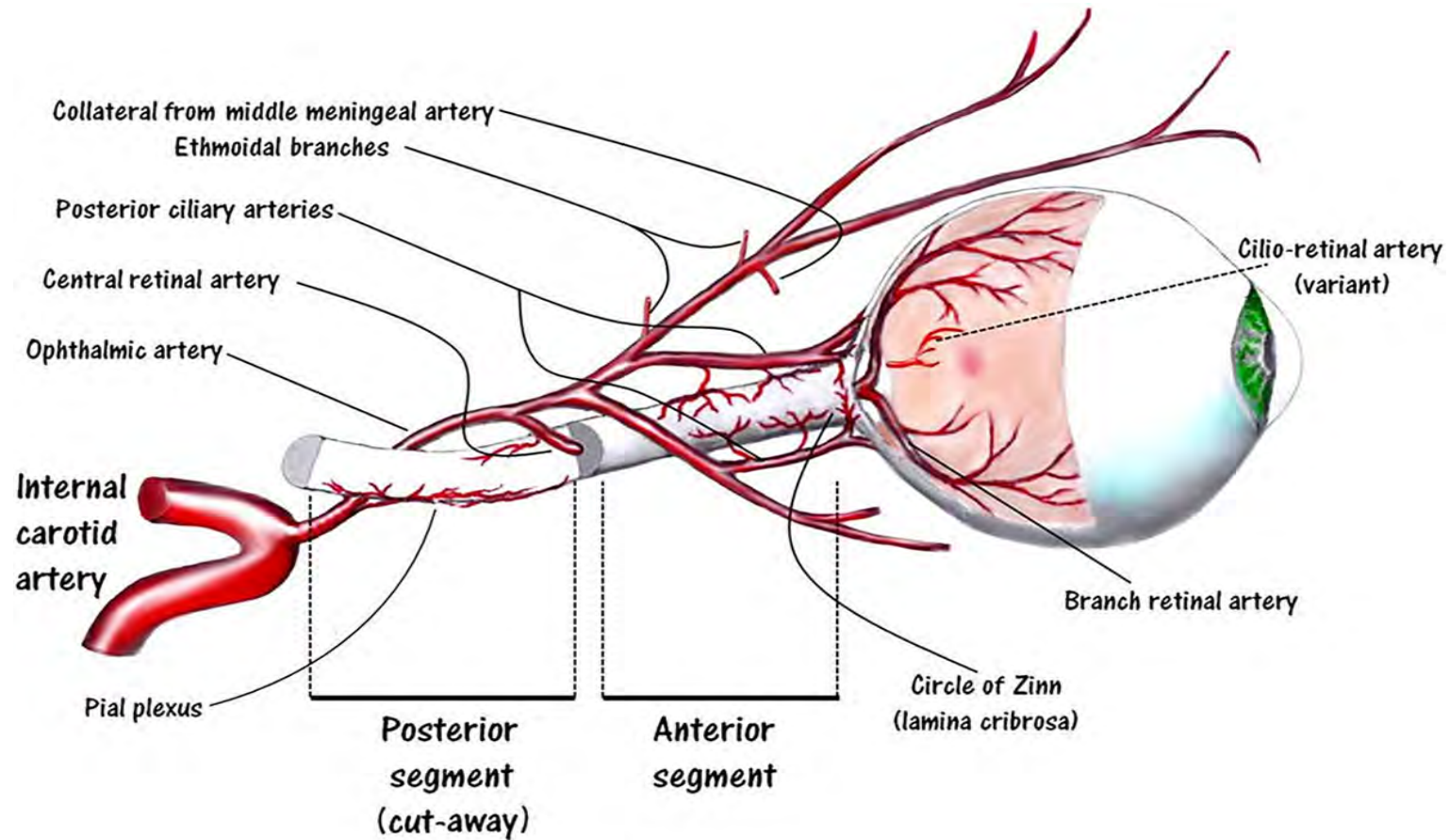
Section	Suggestions for Clinical Practice
Definitions	CRAO with retinal infarction conforms to the diagnosis of acute ischemic stroke. It is defined based on a compelling clinical history supported by the presence of a relative afferent pupillary defect and classic fundusoscopic findings.
Epidemiology and Risk Factors	The incidence of CRAO is approximately 1.9/100,000 person years This risk increases with age and in the presence of vascular risk factors such as hypertension, hyperlipidemia, diabetes mellitus, tobacco exposure and obesity.
Pathophysiology	In 95% of cases, CRAO occurs as a result of thromboembolic disease. In 5% of cases, it occurs as “arteritic CRAO”, usually as a component of giant cell arteritis.
Diagnosis	Sudden, painless, monocular visual loss most often results from CRAO, optic neuropathy (most often ischemic), retinal detachment, or intra-ocular hemorrhage. An ophthalmologic examination, including a fundusoscopic examination is necessary for the diagnosis of CRAO and to rule out intra-ocular hemorrhage.
Natural History	CRAO impacts central vision (visual acuity), peripheral vision (visual fields), color vision and stereovision. The natural history of CRAO is poor with only 17% of patients achieving a functional visual acuity in the affected eye.

TABLE 2. SUMMARY OF SUGGESTIONS FOR CLINICAL PRACTICE ACCORDING TO SECTION CONTINUED

Section	Suggestions for Clinical Practice
Treatment	<p><u>Triage:</u> Patients with suspected CRAO should be triaged to the nearest emergency department.</p> <p><u>Intravenous tPA:</u> Intravenous tPA may be considered in patients who have disabling visual deficits and who otherwise meet criteria for systemic tPA after a thorough benefit/risk discussion with the affected patient.</p> <p><u>Intra-arterial tPA:</u> In centers capable of deploying endovascular therapy, intra-arterial tPA may be considered in patients with disabling visual deficits at early time points especially if they are not candidates for intravenous tPA. This consideration comes with the strong caveat that, at present, IAT is an unproven therapy and should only be considered in light of the devastating visual outcome associated with CRAO.</p> <p><u>Conservative treatments:</u> There is no compelling evidence that conservative treatments for CRAO are effective and trends in the observational literature suggest ocular massage, anterior chamber paracentesis and hemodilution may be harmful.</p>
Secondary Prevention	<p>Secondary prevention (including monitoring for complications) should be a collaborative effort between neurology, ophthalmology and primary care medicine.</p> <p>Risk factor modification should include pharmacological and lifestyle interventions.</p> <p>Anti-platelet therapy is a reasonable consideration for pharmacological secondary prevention when the etiology is cryptogenic or attributed to atherosclerosis</p> <p>If atrial fibrillation or another cardioembolic source is detected during the diagnostic workup, anticoagulation may be appropriate for secondary prevention.</p> <p>Severe stenosis of the carotid artery valves may require surgical intervention for secondary stroke prevention.</p>
Future Directions	<p>There is a need for a pragmatic, randomized, placebo-controlled, double-blind clinical trial comparing tPA with placebo as treatment for patients with CRAO presenting at early time points.</p> <p>Future research should explore biomarkers of retinal viability which may complement existing, time-based approaches to thrombolytic therapy.</p> <p>The use of the novel thrombolytic agent tenecteplase and intra-arterial tPA at early time points should be explored in future studies.</p>

SUPPLEMENTARY FIGURES

SUPPLEMENTARY FIGURE 1: ARTERIAL SUPPLY TO RETINA AND OPTIC NERVE

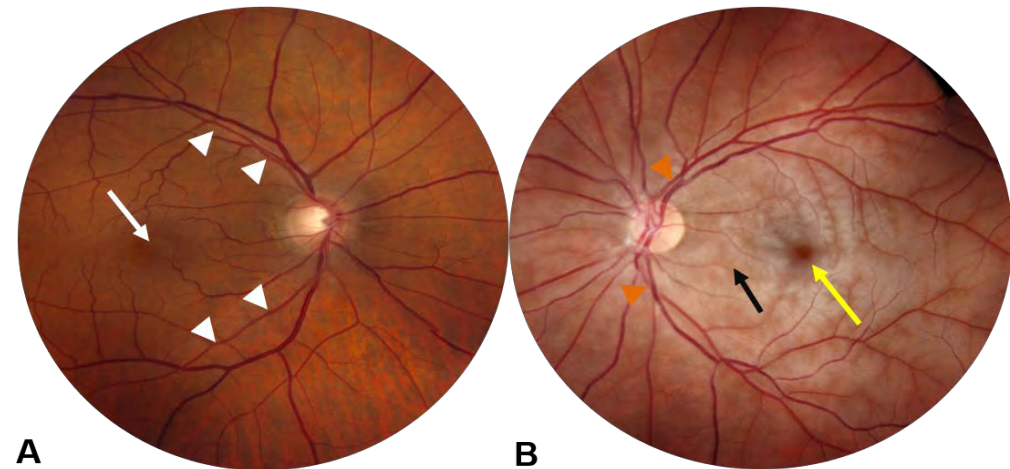


SUPPLEMENTARY FIGURE 2. EXAMINATION FINDINGS IN ACUTE CRAO (LEFT EYE)

ACUTE CRAO IN THE LEFT EYE SEEN 5 HOURS AFTER ONSET OF VISUAL LOSS.

A: FUNDUS PHOTOGRAPH OF THE NORMAL RIGHT EYE. NOTE THE NORMAL FOVEA (WHITE ARROW) AND THE NORMAL RETINAL ARTERIES (WHITE ARROWHEADS).

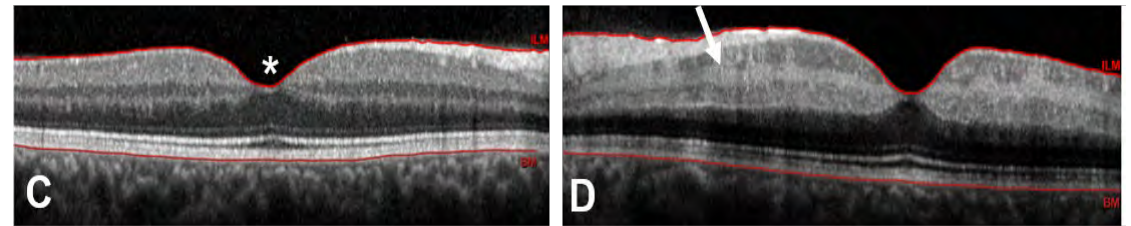
B: FUNDUS PHOTOGRAPH OF A LEFT CRAO, SHOWING DIFFUSE RETINAL WHITENING (BLACK ARROW) WITH A CHERRY RED SPOT (YELLOW ARROW), ATTENUATED ARTERIES (ORANGE ARROWHEADS). NOTE THE DIFFERENCE IN COLOR OF THE EDEMATOUS RETINA COMPARED WITH THE NORMAL RIGHT EYE.



SUPPLEMENTARY FIGURE 2. EXAMINATION FINDINGS IN ACUTE CRAO (LEFT EYE) CONTINUED

C: NORMAL MACULAR OPTICAL COHERENCE TOMOGRAPHY OF THE RIGHT EYE SHOWING NORMAL RETINAL LAYERS AND THE FOVEA WHERE THE INNER RETINAL LAYERS ARE OF NORMAL THICKNESS (*).

D: MACULAR OPTICAL COHERENCE TOMOGRAPHY OF THE LEFT EYE WITH ACUTE CRAO, DEMONSTRATING THICKENING AND IRREGULARITY OF THE INNER RETINAL LAYERS CORRESPONDING TO RETINAL EDEMA SECONDARY TO ACUTE RETINAL ISCHEMIA (WHITE ARROW). NOTE THE BRIGHTER APPEARANCE OF THE INNER RETINA WHICH IS "HYPERREFLECTIVE" COMPARED WITH THE NORMAL RIGHT EYE.



SUPPLEMENTARY FIGURE 2. EXAMINATION FINDINGS IN ACUTE CRAO (LEFT EYE) CONTINUED

E: FIBRIN-PLATELET EMBOLI IN THE SUPERIOR BRANCH OF THE RETINAL ARTERY (RED ARROWS) WITH SLOW SEGMENTAL BLOOD FLOW (“BOX-CARRING”) IN DISTAL RETINAL ARTERIES (RED ARROWHEAD).

F: CILIORETINAL ARTERY SPARING IN ACUTE CRAO (LEFT EYE). THERE IS DIFFUSE RETINAL WHITENING (BLACK ARROWS) CORRESPONDING TO THE INFARCTED EDEMATOUS RETINA IN CONTRAST TO THE NORMAL CENTRAL AREA (*) VASCULARIZED BY CILIORETINAL ARTERIES (WHITE ARROWHEAD).

