Stroke

AHA SCIENTIFIC STATEMENT

# Management of Central Retinal Artery Occlusion

## A Scientific Statement From the American Heart Association

*The American Association of Neurological Surgeons/Congress of Neurological Surgeons Cerebrovascular Section affirms the educational benefit of this document.*

*Endorsed by the North American Neuro-Ophthalmology Society, the American Academy of Ophthalmology Quality of Care Secretariat, and the American Academy of Optometry.*

Brian Mac Grory, MB BCh BAO, MRCP, Chair; Matthew Schrag, MD, PhD, Vice-Chair; Valérie Biousse, MD; Karen L. Furie, MD, MPH, FAHA; Marie Gerhard-Herman, MD; Patrick J. Lavin, MB BCh BAO, MRCPI; Lucia Sobrin, MD, MPH; Stavropoula I. Tjoumakaris, MD; Cornelia M. Weyand, MD, PhD; Shadi Yaghi, MD, FAHA; on behalf of the American Heart Association Stroke Council; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Hypertension; and Council on Peripheral Vascular Disease

**PURPOSE:** Central retinal artery occlusion (CRAO) is a form of acute ischemic stroke that 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 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:** We performed a literature review of randomized controlled clinical trials, prospective and retrospective cohort studies, case-control studies, case reports, clinical guidelines, review articles, basic science articles, and editorials concerning the management of CRAO. We assembled a panel 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 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.

**Key Words:** AHA Scientific Statements ■ giant cell arteritis ■ hemodilution ■ ischemic stroke ■ paracentesis ■ retinal artery occlusion ■ thrombolytic therapy ■ tissue plasminogen activator



Central retinal artery occlusion (CRAO) is a form of acute ischemic stroke.[1] Despite >150 years of research, there are no effective evidence-based forms of therapy for this condition. Fewer 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 events.[4–8] The efficacy of widely used treatment strategies for this condition has 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

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 make up the central nervous system, and central nervous system infarction is defined as



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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 pathological findings |
| Retinal infarction | Retinal cell death attributable to ischemia on the basis of (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 h or until death and other causes excluded | Funduscopic examination, optical coherence tomography, histopathology |
| CRAO | Interruption of blood flow through the central retinal artery by thromboembolism or vasospasm with or without retinal ischemia | Clinical history, optical coherence tomography, funduscopic examination, fluorescein angiography |
| Branch retinal artery occlusion | Interruption of blood flow through a branch retinal artery by thromboembolism or vasospasm with or without retinal ischemia | |
| Ophthalmic artery occlusion | Interruption of blood flow through the ophthalmic artery by thromboembolism or vasospasm with or without retinal or choroidal ischemia | |
| Arteritic CRAO | CRAO occurring in the context of a systemic inflammatory condition | Clinical history, funduscopic examination, general physical examination, fluorescein angiography, serum inflammatory markers |
| Nonarteritic 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, funduscopic examination |
| CRAO without cilioretinal artery sparing | CRAO occurring in the absence of a patent cilioretinal artery | Funduscopic examination, fluorescein angiography |
| CRAO with cilioretinal artery sparing | CRAO occurring in the presence of a patent cilioretinal artery | |

CRAO indicates central retinal artery occlusion.



*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]

CRAO 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, we use 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 in which smaller segments of the retina may be implicated. Ophthalmic artery occlusion 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 funduscopic 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 the Pathophysiology section). Most cases (95%) of CRAO are classified as nonarteritic, 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.

## EPIDEMIOLOGY AND RISK FACTORS

The age- and sex-adjusted incidence of CRAO is 1.9 per 100 000 person-years in the United States,[10] 1.8 per 100 000 person-years in South Korea,[11] and 2.5 per 100 000 person-years in Japan.[12] The incidence rises to 10.1/100 000 person-years in those >80 years of age.[11] 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 of age.[14] In contrast, the incidence of symptomatic occlusion of branch retinal arteries is ≈30% that of CRAO.[15] A large study based on the National Readmissions Database in the United States found that patients admitted with CRAO or occlusion of branch retinal arteries are slightly younger than those with cerebral ischemic stroke (66.8 years versus 70.8 years).[15]

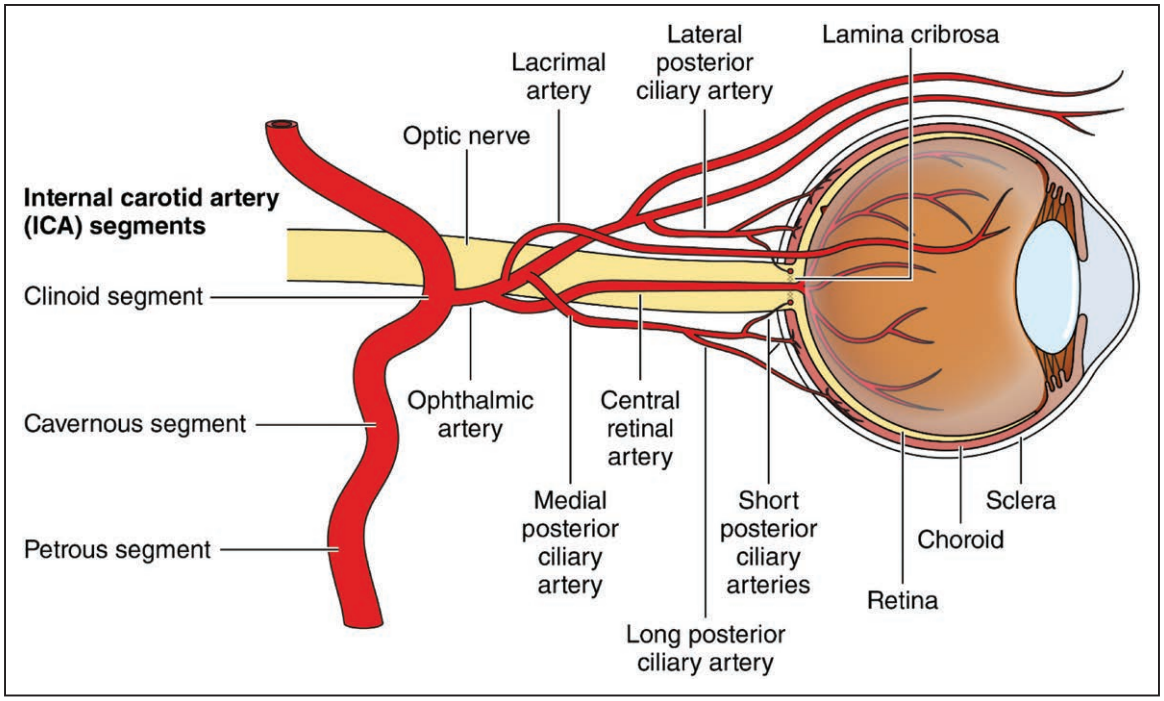


**Figure 1. Arterial supply to the retina.**

CRAO is most strongly associated with an ipsilateral internal carotid artery stenosis.[16] A single-center study of 103 cases of CRAO found that 37% of patients had ipsilateral critical carotid disease (defined in this study as ≥70% stenosis, arterial dissection, or intra-arterial thrombus).[17] In the EAGLE study (European Assessment Group for Lysis in the Eye),[13] 77 of 84 patients had a comprehensive workup for potential pathogeneses, in whom 31 (40%) had ≥70% carotid artery stenosis.[18] Emboli to the central retinal artery can also arise from the heart (including the aortic and mitral valves), aortic arch, or great vessels.[19] This is reflected in the risk factor profile of patients with CRAO. The EAGLE study[13] demonstrated a high prevalence of cardiovascular risk factors: obesity (82%), hypertension (73%), tobacco use (49%), hypercholesterolemia (49%), and diabetes (14%) in the 77 patients evaluated.[18] Overall, 67% of patients had at least 1 cardiovascular risk factor. In addition, 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 controls,[20] and CRAO portends a high risk of recurrent stroke in patients known to have AF.[21] A longer duration of cardiac monitoring is associated with a higher risk of detecting AF in patients with CRAO.[22]

## PATHOPHYSIOLOGY

The central retinal artery and its branches supply the inner retina. The inner retina is made up 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 one-third of eyes, a cilioretinal artery is present and often supplies the fovea, which is critical for central vision.[23] The cilioretinal artery originates from the posterior ciliary circulation, not the central retinal arterial circulation. Therefore, when it is present, visual acuity may be nearly normal after a CRAO,[23] whereas peripheral vision will be severely impaired.

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 modeling 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 [HBO] therapy; see the Acute Treatment section). In addition, robust collateralization exists between these 2 circulations at the optic nerve head and via pial anastomoses of the central retinal artery.[26] It has been posited that retinal ganglion cells may be susceptible to damage within 12 to 15 minutes of arterial occlusion,[27] 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 <97 minutes, whereas after 240 minutes of occlusion, severe and irreversible damage occurred.[29,30]

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 heart. This assertion is based on a study of 234 patients with nonarteritic 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 GCA that affects medium and large extracranial arteries, including distal branches of the carotid artery,[3,31] resulting in occlusive intimal hyperplasia.[32] Eyes with GCA-induced CRAO may have coexistent arteritic anterior ischemic optic neuropathy (AION) and choroidal ischemia resulting from the vasculitic occlusion of the posterior ciliary arteries.[3] 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. 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 cilioretinal artery occlusion 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 and of the optic nerve head. For instance, in the above cohort,[33] 1 patient (0.4%) had CRAO and a contralateral AION, and 1 patient (0.4%) had combined cilioretinal artery occlusion and AION in the same eye.

In addition, 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 state.[34] 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 artery.[35] Generally, in such cases, the prognosis is poor, and because the material is not fibrin based, the discussion of thrombolysis (in the Acute Treatment section) does not apply.

## DIAGNOSIS

Typically, CRAO presents as sudden, painless monocular loss of visual acuity and peripheral vision. The degree of visual loss is variable: In >80% of patients, the initial visual acuity is "count fingers" or worse, but it can be nearly 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 that is surrounded by pale, ischemic retina), slow segmental blood flow (known as boxcarring) in the retinal arteries that are attenuated, and usually a normal-appearing optic disc (Figure 2). In patients with CRAO, retinal emboli are visible in the branch retinal arteries <10% of the time, and emboli within the central retinal artery itself are rarely visible because 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 >50 years of age with systemic symptoms including jaw claudication, polymyalgia rheumatica, diffuse posterior neck pain, scalp tenderness with or without nodules, new-onset headache, or elevated inflammatory markers.[36–38]

An ophthalmological evaluation including a dilated funduscopic examination or a nonmydriatic 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 loss.[39] 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 diagnosis.[39]

Early in the occlusive event, the fundus may appear relatively normal and seemingly perfused. A history of sudden painless vision loss and the presence of a relative afferent pupil defect, an attached retina, and normal optic nerve strongly implicate central artery occlusion. Imaging modalities such as optical coherence tomography, optical coherence tomography 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 2C and 2D). 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 diagnosis.[40] Further details concerning the clinical diagnosis of CRAO and other retinal vascular conditions can be found in the American Academy of Ophthalmology's Preferred Practice Pattern concerning Retinal and Ophthalmic Artery Occlusions.[41]

## NATURAL HISTORY

Several studies suggest that the natural history of CRAO with respect to visual recovery is poor. One study including





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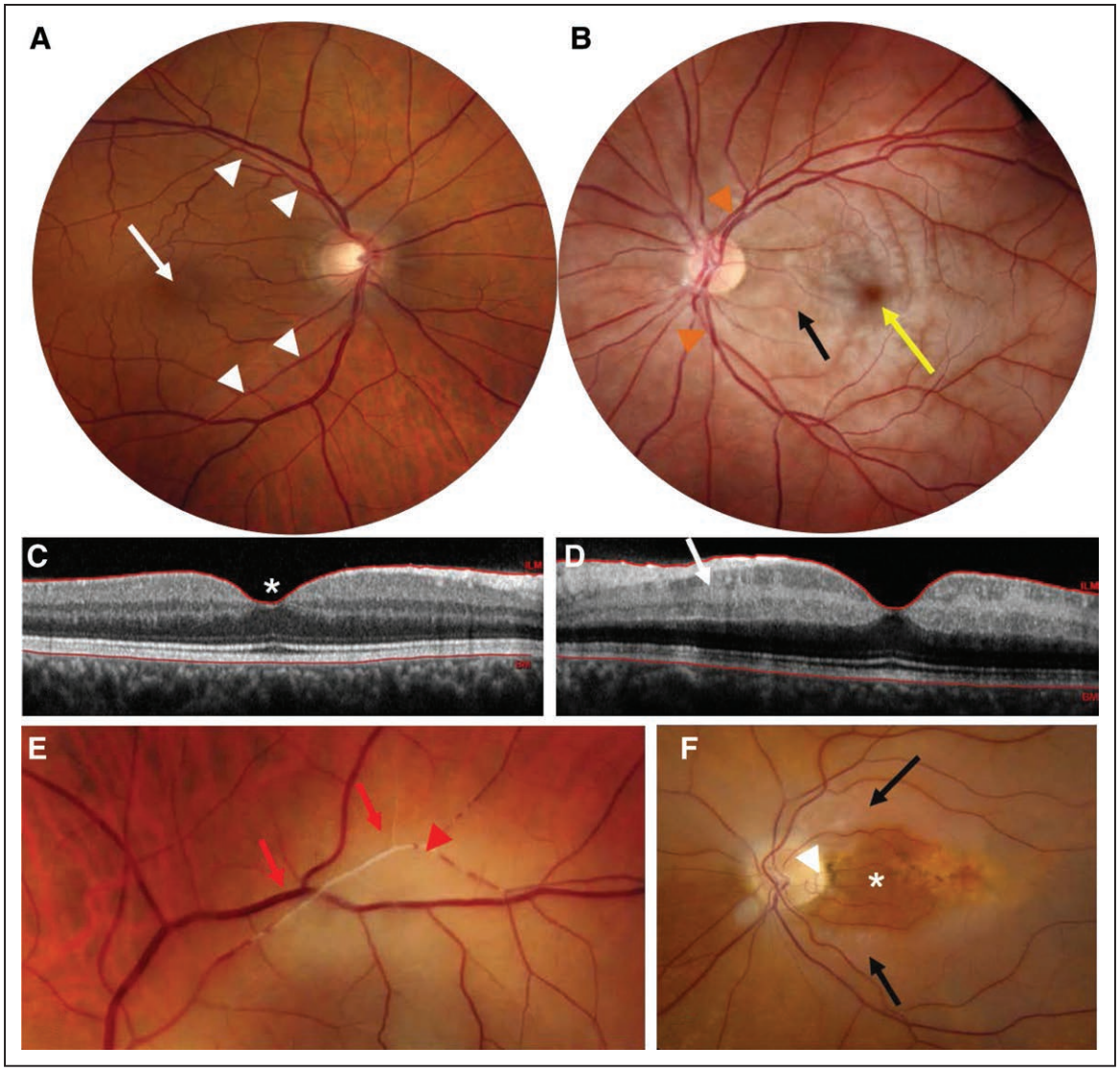


**Figure 2. Examination findings in acute central retinal artery occlusion (CRAO; left eye).**
**A** through **D**, Acute CRAO in the left eye seen 5 hours after onset of visual loss. **A**, Fundus photograph of the normal right eye. Note the normal fovea (white arrow) and the normal retinal arteries (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. **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. **E**, Fibrin-platelet emboli in the superior branch of the retinal artery (red arrows) with slow segmental blood flow ("boxcarring") 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).

177 patients with nonarteritic 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-up.[9] A meta-analysis of 8 studies reporting visual outcomes of 396 untreated patients with CRAO found that only 17.7% (70 of 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 studies.[2]

In general, a reduction in vision leads to long-term disability. Unilateral uncorrectable visual loss is associated with an increased likelihood of falls (odds ratio 2.86 [95% CI, 1.16–7.08]) and functional dependence (odds ratio, 7.50 [95% CI, 1.97–28.6]).[42] This may be disabling enough to warrant placement in a long-term care facility.[42,43] A mixed-methods study[44] investigated the impact of unilateral visual loss on health-related quality of life by means of a 36-item health survey (Short-Form Health Survey)[45] administered to 3108 participants. Those respondents with moderate to severe vision loss had limitations in physical and social functioning and self-reported functional limitations attributable to emotional

problems. A survey of adults with normal vision evaluating patients' preference for the treatment of CRAO[46] showed that 39% of surveyed adults would accept some risk of stroke and 37% would even accept some risk of death to triple the chances of recovering 20/100 visual acuity in 1 eye when the unaffected eye is sighted. More than 80% of individuals would accept these risks if the unaffected eye is not sighted.[46]

## 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 trials.[47] 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. The efficacy of thrombolysis has not been evaluated in the setting of arteritic CRAO, but early screening and immediate steroid therapy are indicated to preserve vision in the contralateral eye.[48] A more detailed discussion of the management of arteritic CRAO is beyond the scope of this review.

A narrow time window for effective treatment of CRAO and a high rate of serious comorbid illness exist. Thus, when CRAO is 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 treatments.[41] Stroke centers should develop relationships with community ophthalmologists and optometrists to promote efficient pathways for transfer of patients with CRAO; this may allow more patients to reach the emergency department within the window for tissue plasminogen activator (tPA). Public outreach campaigns should emphasize sudden, painless, monocular visual loss as a symptom of potential stroke akin to sudden, unilateral weakness, facial droop, and speech difficulty.

The sequence of thrombolytic treatment for CRAO in the emergency department should begin with an immediate ophthalmological examination in parallel with a structured neurological assessment (via a calculation of the National Institutes of Health Stroke Scale) and a computed tomography scan of the brain without contrast. When there is a high suspicion for a coagulopathy, a platelet count and coagulation studies (prothrombin time/international normalized ratio and activated partial thromboplastin time) should be performed, and in patients with a high clinical suspicion for GCA, testing of the erythrocyte sedimentation rate and CRP (C-reactive protein) is reasonable before a final decision is made on the administration of tPA. After this process is complete and a patient's candidacy for acute therapy is determined, an expedited inpatient workup should be pursued. A suggested treatment protocol for acute CRAO is presented in Figure 3.

### Intravenous tPA

Intravenous tPA is an evidence-based therapy for acute ischemic stroke.[49] 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 outcomes.[50] The most commonly used agent is alteplase delivered via an intravenous infusion (0.9 mg/kg with 10% given over 1 minute and the remainder over 59 minutes).

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 States.[15] 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 onset.[2] An important accomplishment of this study was the standardization of outcome measures for CRAO, called 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 3 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. On the basis of 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.

To date, there have been no adequate randomized clinical trials of intravenous tPA because previous attempts were limited as a result of difficulty with patient enrollment. Since the publication of the meta-analysis of observational studies,[2] intravenous tPA was re-evaluated in 4 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 hours.[28] This analysis robustly reproduced the earlier findings and formed the basis for several ongoing clinical trials. Three randomized trials being conducted in Europe will evaluate treatment with intravenous thrombolysis compared with placebo in adults with CRAO presenting within 4.5 hours of symptoms onset: THEIA (A Phase III Randomized, Blind, Double Dummy, Multicenter Study Assessing the Efficacy and Safety of IV Thrombolysis [Alteplase] in Patients With Acute







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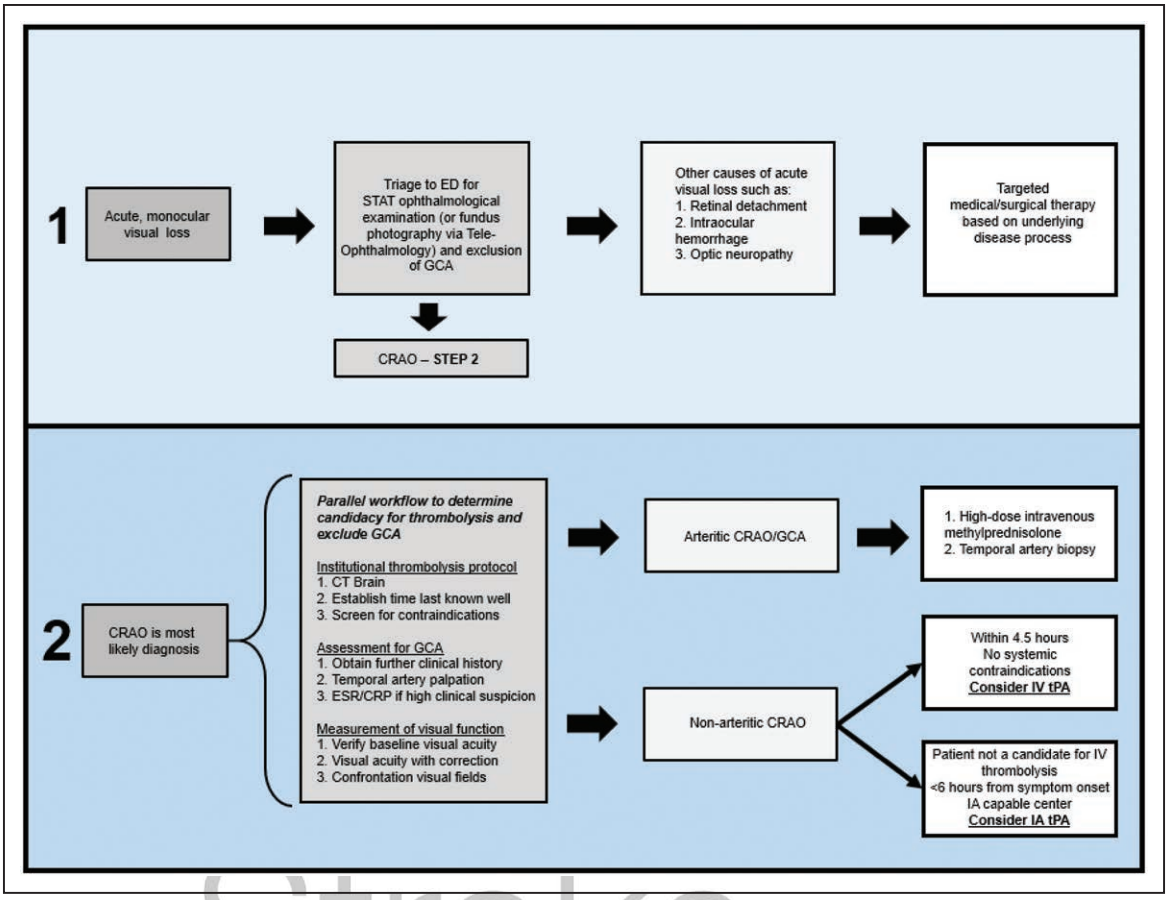


**Figure 3. Treatment protocol for central retinal artery occlusion (CRAO).**
CRP indicates C-reactive protein; CT, computed tomography; ED, emergency department; ESR, erythrocyte sedimentation rate; GCA, giant cell arteritis; IA, intra-arterial; IV, intravenous; STAT, immediately; and tPA, tissue plasminogen activator.



Central Retinal Artery Occlusion; URL: ClinicalTrials.gov. Unique identifier: NCT03197194; comparing tPA with placebo), REVISION (Early Reperfusion Therapy with Intravenous Alteplase for Recovery of Vision in Acute Central Retinal Artery Occlusion) (pending ClinicalTrials.gov registration; comparing tPA with placebo), and Ten-CRAOS (Tenecteplase in Central Retinal Artery Occlusion Study; URL: ClinicalTrials.gov. Unique identifier: NCT04526951; comparing tenecteplase with placebo). Until a fully powered efficacy trial has been completed, we feel that there is equipoise in the utility of intravenous 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 acknowledgment of the limitations inherent in the literature to date.

The risk of symptomatic intracranial hemorrhage appears to be low when tPA is administered to treat CRAO. There are no recorded cases of symptomatic intracranial hemorrhage when tPA is administered within 4.5 hours of symptom onset and without the concomitant administration of anticoagulation.[28] Larger data sets are needed to clarify the risk of symptomatic intracranial hemorrhage 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- to 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 that immediate optical coherence tomography 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 onset.[57]

## 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 hemorrhage.[58] Thus, the dose of tPA reaching the systemic circulation is much lower, so 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. Given the size of the vessels in question (the ophthalmic artery is 1.3 mm in diameter and the central retinal artery is 160 μm 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 outcomes.[59] The only prospective randomized controlled study was 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. Two patients had 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, a number of logistical and procedural challenges 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.

The recommended technique for superselective ophthalmic artery microcatheterization is placement of a small microcatheter (0.60 mm) in the ostium of the artery. Although distal microcatheterization of the ophthalmic artery is possible, overall, it is not recommended because 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 retinoblastoma[60]; however, the technical challenges are increased in the presence of atherosclerosis, which is likely in the majority of patients with nonarteritic CRAO. 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 15 mg accompanied by serial bedside ophthalmological examinations until visual acuity is restored, a choroidal blush is visualized, or a dose of 50 mg has been reached.[13] The literature favors continued study of intra-arterial tPA at early time points.

### Conservative Treatments

Several so-called conservative approaches have been used in an effort to restore vision. These include anterior chamber paracentesis, ocular massage, topical intraocular pressure-lowering agents, sublingual isosorbide dinitrate, systemic β-blockade, carbogen therapy (inhaling a 95% $O_2$/5% $CO_2$ mixture), and breathing into a paper bag. The putative rationale behind most conservative therapies is that modulation of intraocular pressure or vasodilation of the retinal vasculature may dislodge the obstruction and allow the embolus to migrate peripherally. Typically, ≥2 of these modalities are combined (eg, in the active control arm of the EAGLE trial, patients were treated with hemodilution, timolol, intravenous acetazolamide, and ocular massage[13]), making it difficult to disentangle the effect of one from the effect of another. None is known to be more effective than placebo.[61] Indeed, a meta-analysis suggested that patients treated with differing combinations of such strategies had a visual recovery rate of 7.4% compared with 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 carbogen[62] and the other with anterior chamber paracentesis alone,[63] 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 HBO therapy.[64] 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 for efficacy and suggestions of harm in the literature, these treatments are not currently endorsed in professional guidelines on the management of CRAO.[41]

HBO therapy is used as a method of salvaging retinal tissue in acute CRAO. In normal physiology, >50% of the retinal oxygen supply is derived from passive diffusion from the choroidal circulation,[25] whereas with hyperbaric oxygenation, it is as high as 97%.[65] Several case series[66–68] suggest that HBO improves visual outcome in CRAO. HBO may provide benefit as a temporizing measure while definitive reperfusion is pursued, although 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 increased.[69] We could find only 1 case report of concurrent use of HBO and tPA for CRAO.[70] HBO is labor intensive to deploy and available at only select centers in the United States.

## SECONDARY PREVENTION

The optimal approach to long-term secondary prevention in patients with CRAO should be guided by a







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**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.<br>It is defined on the basis of a compelling clinical history supported by the presence of a relative afferent pupillary defect and classic funduscopic findings. |
| Epidemiology and risk factors | The incidence of CRAO is ≈1.9/100 000 person years.<br>This risk increases with age and in the presence of vascular risk factors such as hypertension, hyperlipidemia, diabetes, tobacco exposure, and obesity. |
| Pathophysiology | In 95% of cases, CRAO occurs as a result of thromboembolic disease.<br>In 5% of cases, it occurs as arteritic CRAO, usually as a component of GCA. |
| Diagnosis | Sudden, painless, monocular visual loss most often results from CRAO, optic neuropathy (most often ischemic), retinal detachment, or intraocular hemorrhage. An ophthalmological examination, including a funduscopic examination, is necessary for the diagnosis of CRAO and to rule out intraocular hemorrhage. |
| Natural history | CRAO affects central vision (visual acuity), peripheral vision (visual fields), color vision, and stereovision.<br>The natural history of CRAO is poor, with only 17% of patients achieving a functional visual acuity in the affected eye. |
| Treatment | Triage: Patients with suspected CRAO should be triaged to the nearest emergency department. Public outreach campaigns should emphasize painless, monocular visual loss as a symptom of stroke.<br>Intravenous tPA: 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.<br>Intra-arterial tPA: 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 be considered only in light of the devastating visual outcome associated with CRAO.<br>Conservative treatments: There is no compelling evidence that conservative treatments for CRAO are effective, and trends in the observational literature suggest that ocular massage, anterior chamber paracentesis, and hemodilution may be harmful. |
| Secondary prevention | Secondary prevention (including monitoring for complications) should be a collaborative effort between neurology, ophthalmology, and primary care medicine.<br>Risk factor modification should include pharmacological and lifestyle interventions.<br>Antiplatelet therapy is a reasonable consideration for pharmacological secondary prevention when the cause is cryptogenic or attributed to atherosclerosis.<br>If AF or another cardioembolic source is detected during the diagnostic workup, anticoagulation may be appropriate for secondary prevention.<br>Severe stenosis of the carotid artery valves may require surgical intervention for secondary stroke prevention. |
| Future directions | 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.<br>Future research should explore biomarkers of retinal viability that may complement existing, time-based approaches to thrombolytic therapy.<br>The use of the novel thrombolytic agent tenecteplase and intra-arterial tPA at early time points should be explored in future studies. |

AF indicates atrial fibrillation; CRAO, central retinal artery occlusion; GCA, giant cell arteritis; IAT, intra-arterial thrombolysis; and tPA, tissue plasminogen activator.

multidisciplinary collaboration among a neurologist, an ophthalmologist, and a primary care physician or an internist. Patients with CRAO require ophthalmological follow-up for optimization of residual vision, serial visual assessment, monitoring for neovascularization-related complications,[71] 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.

Treatment of hypertension, dyslipidemia, diabetes, obesity, and obstructive sleep apnea; 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 stroke[72] (note that ischemic stroke guidelines do not explicitly mention CRAO at present, although it is formalized in the American Heart Association's definition of ischemic stroke). For those without an indication for anticoagulation or surgery, an antithrombotic therapy regimen paralleling that seen in

cryptogenic ischemic stroke is reasonable. In patients with a presenting National Institutes of Health Stroke Scale score of ≤3, an initial course of 21 days of dual antiplatelet therapy may be reasonable followed by long-term treatment with a single antiplatelet agent, typically aspirin 81 mg daily or clopidogrel 75 mg daily as recommended by current guidelines.[49,72] The THALES trial (Acute Stroke or Transient Ischaemic Attack Treated With Ticagrelor and ASA for Prevention of Stroke and Death)[73] and SOCRATES trial (Acute Stroke or Transient Ischemic Attack Treated With Aspirin or *Ticagrelor* and Patient Outcomes)[74] suggest that ticagrelor (either alone or in combination with aspirin) may reasonably form part of pharmacological secondary prevention in patients with transient ischemic attack or minor stroke and thus might be reasonable after CRAO.

The etiological workup should be done urgently because it frequently will unmask concurrent disease that requires prompt intervention.[17,75] High-grade stenosis of the ipsilateral carotid artery should be identified rapidly with computed tomography/magnetic resonance angiography or cervical artery ultrasound and treated as symptomatic carotid stenosis. The choices in this scenario include surgical revascularization or medical management (antiplatelet 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 CRAO,[17] it is reasonable to consider transthoracic echocardiography to examine for evidence of a cardioembolic source. 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 prevention.[72] CRAO was not classified as an ischemic event in the derivation of the $CHADS_2$ and $CHA_2DS_2$-VASc scores[76] but in our opinion 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

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 intravenous 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. Historical 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 require further study. We must develop systems of care for the urgent recognition, triage, and management of CRAO in a manner similar to cerebral ischemic stroke. Telemedicine will allow expert evaluation and initiation of treatment at peripheral centers that 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 among a neurologist, an ophthalmologist, and an internist. There is an unmet need for a pragmatic, multicenter, randomized, double-blind, placebo-controlled clinical trial comparing intravenous tPA with placebo at early time points in patients with CRAO. Prospective multicenter observational registries will aid in feasibility testing and sample size calculations for such a clinical trial. Future research should be directed toward 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 such as tenecteplase, HBO therapy, and novel neuroprotectants for use in tandem with recanalization therapy. Considerations for practice from this statement are summarized in Table 2.

## ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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### Writing Group Disclosures

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|---|---|---|---|---|---|---|---|---|
| Brian Mac Grory | Duke University School of Medicine | None | None | None | None | None | None | None |
| Matthew Schrag | Vanderbilt University School of Medicine | None | None | None | None | None | None | None |
| Valérie Biousse | Emory University | None | None | None | None | None | None | None |
| Karen L. Furie | Warren Alpert Medical School of Brown University | None | None | None | None | None | None | None |
| Marie Gerhard-Herman | Harvard Medical School | None | None | None | None | None | None | None |
| Patrick J. Lavin | Vanderbilt University School of Medicine | None | None | None | None | None | None | None |
| Lucia Sobrin | Harvard Medical School | None | None | None | None | None | None | None |
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|---|---|---|---|---|---|---|---|---|
| Anne H. Aamodt | Oslo University Hospital (Norway) | None | None | None | None | None | None | None |
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*Modest.

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