• Clinical Research •

Effectiveness and safety of superselective ophthalmic artery thrombolysis beyond 24h in central retinal artery occlusion

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Received: 2025-09-24 Accepted: 2025-12-30

Abstract

● **AIM:** To evaluate the effectiveness and safety of superselective ophthalmic artery thrombolysis (SOAT) for central retinal artery occlusion (CRAO) beyond 24h after onset.

● **METHODS:** This was a retrospective cohort study of CRAO patients treated from January 2019 to July 2025. Patients were divided into four groups by treatment (SOAT/conservative) and onset-to-treatment time (<24h/>24h). Main outcome measures were best-corrected visual acuity (BCVA, logMAR) and central macular thickness (CMT) assessed *via* spectral-domain optical coherence tomography (SD-OCT), recorded at baseline, 3d and 1mo after treatment. Ocular/systemic adverse events were documented.

● **RESULTS:** A total of 109 CRAO participants were enrolled, including 74 males (67.89%) and 35 females (32.11%), with a mean age of 52.30±11.76y. Underlying diseases were hypertension (78 cases, 71.56%), diabetes (40 cases, 36.70%), arterial atherosclerosis with plaque formation (81 cases, 74.31%), hyperlipidemia (14 cases, 12.84%), and hypercholesterolemia (16 cases, 14.68%). Four groups included 25, 28, 26, and 30 cases in Groups 1 (SOAT<24h), 2 (SOAT>24h), 3 (conservative <24h), and 4 (conservative >24h), respectively. In <24h cohort, BCVA improved significantly in both Group 1 (2.36±0.53 to 1.71±0.81 logMAR, $P<0.05$) and Group 3 (2.42±0.40 to 1.92±0.76 logMAR, $P<0.05$). In >24h cohort, thrombolysis improved BCVA (1.84±0.88 to 1.31±0.53 logMAR, $P<0.05$), while conservative treatment showed no significant change (2.04±0.74 to 1.92±0.73 logMAR, $P=0.808$). Clinically significant improvement (≥0.3 logMAR) was more frequent with SOAT in both time windows ($P<0.05$). SOAT significantly reduced CMT in both <24h (256±25.65 to 209±21.22 μm, $P<0.001$) and >24h groups (242±23.33 to 204±27.22 μm, $P<0.001$), while conservative treatment had no significant effect on CMT (all $P>0.05$). Adverse events included orbital swelling (11.3%), new cerebral infarction (7.55%), dizziness/headache (7.55%), and nausea/vomiting (5.66%). No intracranial hemorrhage occurred.

● **CONCLUSION:** SOAT provides meaningful visual and anatomical benefit even beyond 24h after symptom onset. However, potential ocular and systemic adverse events necessitate careful patient selection and individualized risk assessment.

● **KEYWORDS:** central retinal artery occlusion; superselective ophthalmic artery thrombolysis; time window

DOI:10.18240/ijo.2026.04.11

Citation: Zhang KK, Li M, Liao YH, Yu ZH, Tu C, Shi YC, Yang WH, Gong Y. Effectiveness and safety of superselective ophthalmic artery thrombolysis beyond 24h in central retinal artery occlusion. *Int J Ophthalmol* 2026;19(4):720-732

INTRODUCTION

Central retinal artery occlusion (CRAO) is recognized as an ophthalmic emergency. Clinically, patients present with sudden, painless, and profound visual loss in the affected eye[1]. Approximately 10% of affected eyes have cilioretinal artery sparing of the fovea, only about one in five patients regain functional vision in the affected eye[2-3].

The occurrence rate of CRAO in the general population is approximately 1.8-2.7 cases per 100 000 individuals annually. The incidence increases exponentially with age, with males demonstrating a 1.47-fold higher risk compared to females[4-6].

Based on pathophysiology, CRAO can be classified into arteritic CRAO (A-CRAO) and non-arteritic CRAO (NA-CRAO). The latter shares pathogenic mechanisms with ischemic stroke[7], potentially resulting from either retinal artery hypoperfusion or occlusion.

Currently, conventional treatments for NA-CRAO include ocular massage, intraocular pressure-lowing reduction, carbogen inhalation, vasodilators and hemodilution[8-10]. However, these treatment modalities are not recommended in the American Academy of Ophthalmology Preferred Practice Pattern for CRAO[11].

Emboli in CRAO primarily originate from atherosclerotic plaques, carotid artery stenosis, inflammatory vascular diseases, or cardiac pathology[12]. A recent study by Cho *et al*[13] reported that platelet-fibrin emboli were the most prevalent, accounting for 52% of cases, followed by cholesterol emboli (40%) and calcified emboli (8%).

Beyond conventional treatments, superselective ophthalmic artery thrombolysis (SOAT) represents an advanced therapeutic option. This technique involves the direct infusion of tissue-type plasminogen activator (tPA) into the ophthalmic artery *via* superselective microcatheterization for localized thrombolysis. Compared with systemic thrombolysis, SOAT offers the advantage of reduced total drug dosage and minimized systemic adverse events[14]. The tPA is a well-established pharmacologic agent for ischemic cerebrovascular events. Its administration must comply with stringent safety protocols outlined in multiple neurology and neurosurgery guidelines to maximize therapeutic effectiveness while mitigating risks[15]. Notably, CRAO meets the diagnostic criteria for acute ischemic stroke as defined by the American Heart Association/American Stroke Association[16]. Early thrombolysis not only facilitates visual recovery but also reduces the risk of ocular neovascularization and neovascular glaucoma through timely reperfusion[17].

Dumitrascu *et al*[17] reported that superior visual outcomes were achieved when patients were associated with any form of tPA therapy within the recommended time window (≤4.5h for intravenous tPA and ≤6h for intra-arterial tPA). However, CRAO patients typically experience delayed hospital presentation relative to symptom onset due to two primary factors: First, binocular vision may mask monocular visual impairment, as the unaffected contralateral eye compensates for the affected eye, thereby prolonging symptom recognition[18]. Second, patients often delay seeking medical attention under the assumption that sudden vision loss may spontaneously resolve[19]. CRAO is a vision-threatening emergency with no universally accepted treatment. Conventional management methods have shown limited efficacy. SOAT allows direct delivery of thrombolytic agents to the occlusion site, but its benefit beyond 24h remains uncertain. This study aims to evaluate the safety and effectiveness of SOAT versus conservative therapy in CRAO patients treated within and beyond 24h, thereby addressing the current gap in evidence on delayed intervention.

PARTICIPANTS AND METHODS

Ethical Approval This study adheres to the Declaration of Helsinki and has been approved by the Ethical Review Committee of Ningbo Eye Hospital (Ningbo Eye Medical Ethics Review 2024 Research No.009). All patients and their families were informed and provided written informed consent. The clinical trial registration number: ChiCTR2400089406.

Study Design We conducted a retrospective cohort study involving 109 patients diagnosed with NA-CRAO at Ningbo Eye Hospital between January 2019 and July 2025. Clinical data including age, gender, risk factors, time from symptom onset to treatment initiation, treatment plans, and adverse events were systematically collected. All patients underwent carotid Doppler ultrasonography and comprehensive ophthalmic examinations, including best-corrected visual acuity (BCVA), slit-lamp microscopy, color fundus photography and optical coherence tomography (OCT). A subset of patients additionally underwent fundus fluorescein angiography (FFA), optical coherence tomography angiography (OCTA), and computerized perimetry.

Inclusion criteria: 1) diagnosis of NA-CRAO confirmed by fundus examination, OCT, FFA or OCTA showing absent or markedly delayed central retinal artery perfusion; 2) age >18y.

Exclusion criteria: 1) ocular factors: a) A-CRAO, cilioretinal artery occlusion, or NA-CRAO with preserved cilioretinal artery; retinal vein occlusion; b) concurrent ocular diseases contributing to visual impairment; c) elevated intraocular pressure (≥30 mm Hg); d) recent invasive ocular surgery leading to CRAO; 2) systemic factors: a) history of intracranial/intraspinal surgery, severe head trauma, or stroke within the past 3mo; b) central nervous system tumors, intracranial tumors, arteriovenous malformations, or aneurysms; c) uncontrolled hypertension (≥180/100 mm Hg) without medication; d) major surgery or severe trauma within the past

2wk; e) gastrointestinal or genitourinary bleeding within the past 3wk; f) concurrent neurological deficits; g) myocardial infarction within the past 6wk, or intracranial hemorrhage (including parenchymal hemorrhage, intraventricular hemorrhage, subarachnoid hemorrhage, subdural/extradural hematoma) or related surgery within the past 4wk; h) active bleeding or known bleeding tendency (*e.g.*, coagulation disorders, thrombocytopenia); i) severe cardiac, hepatic, or renal insufficiency, or uncontrolled diabetes mellitus; j) history of contrast agent allergy; k) inflammatory vascular diseases (*e.g.*, giant cell arteritis, granulomatosis with polyangiitis); l) iatrogenic CRAO secondary to cosmetic facial injections.

Treatment Procedure Patients in the conservative therapy group underwent the following interventions: ocular massage for 10–15min, low-flow oxygen inhalation at 2 L/min (administered for 10min per session, hourly during daytime from 08:00 to 20:00 and every 4h after 20:00), intraocular pressure reduction using brinzolamide and carteolol hydrochloride eye drops, acetazolamide, or mannitol. Sublingual nitroglycerin (0.5 mg) was administered for vasodilation. Compound anisodine hydrobromide (2 mL) was injected subcutaneously near the superficial temporal artery, while racemic anisodine hydrochloride (5-10 mg) was administered *via* retrobulbar injection to alleviate vasospasm. Microcirculation was improved using ginkgo dipyridamole, salvianolate ligustrazine, or pancreatic kininogenase. Additionally, Ginkgo biloba extract was administered to promote blood circulation and resolve stasis, and mecobalamin was provided for nerve nutrition. All the patients in this group receive all of these treatments. Patient condition changes and prognosis were meticulously documented. Notably, none of the patients in this group received anterior chamber paracentesis, a procedure commonly employed by clinicians for managing CRAO.

All patients in the thrombolysis group underwent therapy—SOAT—in the Department of Vascular Intervention at the Outer Bund Campus of the First Affiliated Hospital of Ningbo University. The procedural protocol was as follows: First, under local anesthesia, femoral artery puncture was performed, and a vascular sheath was inserted. To evaluate the intracranial vascular system and the patency of the ipsilateral internal carotid and ophthalmic arteries, carotid angiography of the common carotid artery was performed before advancing the catheter into the internal carotid artery. A guiding catheter (MidAccess, Precision) was placed in the internal carotid artery. Subsequently, a microcatheter (EV3, Medtronic) and a microguidewire (EV3, Medtronic) were then advanced under fluoroscopic guidance to superselectively into the ophthalmic artery or ostium. If the patient's ophthalmic artery originated from the middle meningeal artery, the microcatheter was superselected *via* the external carotid artery into the middle meningeal artery, thereby positioning the microcatheter at the orifice of the ophthalmic artery. Angiography was performed to assess blood flow in the central retinal artery and the severity of occlusion. A slow infusion of thrombolytic agents—urokinase (200 000-500 000 IU) or alteplase (10-50 mg)—along with dexamethasone (5-20 mg), nitroglycerin (100-200 μg), and heparinized saline or papaverine (10-30 mg) was administered through the microcatheter in the ophthalmic artery. After every 100 000 IU of urokinase or 10 mg of alteplase, ophthalmic artery angiography was repeated to evaluate the degree of recanalization. The thrombolytic dose was optimized to achieve effectiveness at the minimal effective dose until blood flow in the central retinal artery was restored and uniform perfusion of the retinal region was confirmed. Throughout the procedure, close monitoring of visual acuity changes, neurological symptoms, and signs was maintained. Angiographic reassessment was performed promptly if necessary. The procedure was immediately terminated in case of adverse reactions. Throughout the SOAT procedure, patients were continuously monitored for vital signs (heart rate, blood pressure, oxygen saturation) and neurological status. Potential adverse reactions included ocular pain, orbital swelling, nausea, vomiting, dizziness, or signs suggestive of cerebral vasospasm or contrast allergy. If any severe or progressive reaction occurred, the infusion was immediately stopped and supportive measures were initiated.

Postoperative management: Routine anticoagulation therapy was administered with low-molecular-weight heparin at 4100 anti-Xa IU subcutaneously every 12h for 3d. Vasodilation was achieved using papaverine hydrochloride, while microcirculation improvement and blood stasis resolution were facilitated by ginkgo-dipyridamole or puerarin. Anti-inflammatory and anti-edema measures included dexamethasone or methylprednisolone, and gastric protection was ensured with omeprazole. Intraocular pressure was reduced using mannitol, plaque stabilization was maintained with atorvastatin, and nerve nutrition was supported by mecobalamin. Oral antiplatelet therapy with enteric-coated aspirin (0.1 g once daily) was initiated 24h postoperatively. Upon discharge, patients continued oral antiplatelet and neurotrophic medications.

Primary Outcome Measures The primary outcome measures included: 1) Analysis of baseline characteristics and associated risk factors in patients with CRAO; 2) BCVA was assessed using the Standard Logarithmic Visual Acuity Chart (Snellen chart) at baseline, 3d post-treatment, and 1mo post-treatment. Visual acuity was quantified as the logarithm of the minimum angle of resolution (logMAR). For patients unable to visualize the chart, vision was recorded based on their ability to

Table 1 Analysis of basic characteristics of central retinal artery occlusion patients

Basic characteristics	Thrombolysis group (n_1=25, n_2=28)	Conservative group (n_1=26, n_2=30)	$Z/t/\chi^2$	P
Age (mean±SD, y)				
<24h	50.67±13.54	52.17±11.78	-0.423	0.674
>24h	54.34±9.33	51.87±11.22	0.909	0.367
t	-1.152	0.097		
P	0.255	0.923		
Gender (male), n (%)				
<24h	18 (72.00%)	17 (65.38%)	0.259	0.611
>24h	19 (67.86%)	20 (66.67%)	0.009	0.923
χ^2	0.108	0.01		
P	0.743	0.92		
Time from onset to treatment, median (IQR)				
<24h	8 (5.50-11.5)	9 (6.75-13.0)	1.876	0.465
>24h	73 (28-145)	73 (36-133)	0.132	0.898
Z	37.643	34.985		
P	<0.001	<0.001		
Smoking history, n (%)				
<24h	11 (44.00%)	10 (38.46%)	0.161	0.688
>24h	10 (35.71%)	9 (30.00%)	0.215	0.643
χ^2	0.55	0.445		
P	0.458	0.505		

n_1: <24h group; n_2: >24h group; SD: Standard deviation; IQR: Interquartile range.

count fingers (CF), perceive hand motion (HM), detect light perception (LP) or no light perception (NLP). All low-vision categories were converted to logMAR values according to the criteria established by Mac Grory *et al*[20] and Lange *et al*[21], as follows: CF: 2.0 logMAR, HM: 2.3 logMAR, LP: 2.6 logMAR, NLP: 2.9 logMAR. The magnitude of visual improvement at 3d and 1mo post-treatment (or the last visit) was calculated as the change in BCVA from baseline. Clinically significant visual improvement was defined as a ≥0.3 logMAR gain, whereas a change of <0.3 logMAR indicated no functional visual recovery; 3) OCT was performed at baseline, 3d post-treatment, and 1mo post-treatment to measure central macular thickness (CMT); 4) The incidence of adverse events associated with the two treatment modalities was evaluated to assess safety. Patients with incomplete baseline or key outcome data were excluded. For patients with missing follow-up measurements, the last available data were carried forward (LOCF method) to maintain analytical consistency.

Statistical Analysis Statistical analysis was performed using SPSS 22.0 software. Normality tests were first conducted for all datasets. For normally distributed quantitative data, intergroup differences were analyzed by independent *t*-test, while repeated-measures outcome comparisons were evaluated using one-way ANOVA with Dunnett's T3 test for post hoc pairwise comparisons. Non-normally distributed data were analyzed using nonparametric tests for both intergroup comparisons and outcome assessments. Categorical variables across different groups were compared using Chi-square tests. A P<0.05 was considered statistically significant.

RESULTS

Table 1 presented the demographic characteristics of patients in the CRAO study. In the <24-hour treatment group: Thrombolysis group (n=25): 72.00% males (18/25) with a mean age of 50.67±13.54y; the time from onset to treatment median was 8h; conservative treatment group (n=26): 65.38% males (17/26) with a mean age of 52.17±11.78y; the time from onset to treatment median was 9h. In the >24-hour treatment group: Thrombolysis group (n=28): Comprised 19 males with a mean age of 54.34±9.33y; the time from onset to treatment median was 73h; conservative treatment group (n=30): Comprised 20 males with a mean age of 51.87±11.22y; the time from onset to treatment median was 73h.

Table 2 summarizes the risk factors associated with CRAO patients. In the <24-hour treatment group: Thrombolysis group (n=25): Hypertension was present in 72.00% (n=18) of cases, and atherosclerosis with plaque formation was observed in 84.00% (n=21). Conservative treatment group (n=26): Hypertension was present in 76.92% (n=20), and atherosclerosis with plaque formation was observed in 73.08% (n=19). In the >24-hour treatment group: Thrombolysis group (n=28): Hypertension was present in 67.86% (n=19), and atherosclerosis with plaque formation was observed in 67.86%

Table 2 Analysis of related risk factor of central retinal artery occlusion patients *n* (%)

Risk factors	Thrombolysis group (n_1=25, n_2=28)	Conservative group (n_1=26, n_2=30)	χ^2	*P*
Hypertension				
<24h	18 (72.00%)	20 (76.92%)	0.163	0.687
>24h	19 (67.86%)	21 (70.00%)	0.031	0.86
χ^2	0.108	0.340		
P	0.743	0.560		
Arterial atherosclerosis with plaque formation				
<24h	21 (84.00%)	19 (73.08%)	0.899	0.343
>24h	19 (67.86%)	22 (73.33%)	0.21	0.647
χ^2	1.859	0.001		
P	0.173	0.983		
Hyperlipidemia				
<24h	6 (24.00%)	2 (7.69%)	2.563	0.109
>24h	5 (17.86%)	1 (3.33%)	3.294	0.07
χ^2	0.303	0.522		
P	0.582	0.470		
Hyperhomocysteinemia				
<24h	1 (4.00%)	0	1.061	0.303
>24h	1 (3.57%)	0	1.09	0.296
χ^2	0.007	0		
P	0.935	1		
Hypercholesterolemia				
<24h	5 (20.00%)	3 (11.54%)	0.69	0.406
>24h	4 (14.29%)	4 (13.33%)	0.011	0.916
χ^2	0.306	0.041		
P	0.580	0.839		
Diabetes				
<24h	11 (44.00%)	9 (34.62%)	0.471	0.493
>24h	12 (42.86%)	8 (26.67%)	1.68	0.195
χ^2	0.007	0.416		
P	0.933	0.519		
Kidney disease				
<24h	2 (8.00%)	1 (3.85%)	0.397	0.529
>24h	2 (7.14%)	3 (10.00%)	0.15	0.698
χ^2	0.014	0.795		
P	0.906	0.373		
History of stroke				
<24h	0	1 (3.85%)	0.981	0.322
>24h	0	1 (3.33%)	1.09	0.296
χ^2	0	0.011		
P	1	0.918		
Epilepsy				
<24h	2 (8.00%)	0	2.165	0.141
>24h	1 (3.57%)	0	1.09	0.296
χ^2	0.485	0		
P	0.486	1		
Hyperuricemia				
<24h	5 (20.00%)	2 (7.69%)	1.63	0.202
>24h	4 (14.29%)	3 (10.00%)	0.251	0.617
χ^2	0.237	0.091		
P	0.626	0.763		

n_1: <24h group; n_2: >24h group.

Table 3 Changes in BCVA with different treatment methods in CRAO subgroup patients mean±SD or *n* (%)

BCVA	<24h		*P*	>24h		*P*
	Thrombolysis group (*n*=25)	Conservative group (*n*=26)		Thrombolysis group (*n*=28)	Conservative group (*n*=30)	
Pre-treatment logMAR	2.36±0.53	2.42±0.40	0.649	1.84±0.88	2.04±0.74	0.352
Post-treatment logMAR at 3d	1.96±0.72	2.02±0.75	0.772	1.54±0.82	1.99±0.67	<0.001
Post-treatment logMAR at 1mo	1.71±0.81[a]	1.92±0.76[a]	0.344	1.31±0.53	1.92±0.73	<0.001
F	5.54	4.233		3.434	0.214	
P	0.006	0.019		0.037	0.808	
Difference in logMAR between 1mo post-treatment and pre-treatment						
No visual improvement (<0.3 logMAR)	7 (28.00)	16 (61.54)	0.016	12 (42.86)	23 (76.67)	0.009
Clinically significant improvement (≥0.3 logMAR)	18 (72.00)	10 (38.46)		16 (57.14)	7 (23.33)	

[a]*P*<0.05 comparison within the group with pre-treatment logMAR. BCVA is expressed in logMAR, based on the logMAR visual acuity values of Grory, Lange, and others, counting fingers is recorded as 2.0, hand movement as 2.3, light perception as 2.6, and no light perception as 2.9. BCVA: Best corrected visual acuity; CRAO: Central retinal artery occlusion; SD: Standard deviation; logMAR: Logarithm of the minimum angle of resolution.

(*n*=19). Conservative treatment group (*n*=30): Hypertension was present in 70.00% (*n*=21), and atherosclerosis with plaque formation was observed in 73.33% (*n*=22).

Table 3 shows BCVA changes in the CRAO subgroup with different treatments. For onset under 24h, logMAR differences between thrombolysis and conservative groups at 3d and 1mo were not significant (both *P*>0.05). However, within-group comparisons showed significant improvement in the thrombolysis group (2.36±0.53 to 1.71±0.81 logMAR, *P*<0.05) and conservative group (2.42±0.40 to 1.92±0.76 logMAR, *P*<0.05). Clinically significant visual improvement (≥0.3 logMAR) was seen in 72% of the thrombolysis group, significantly higher than the conservative group (*P*<0.05). In the over-24-hour onset group, logMAR differences between thrombolysis and conservative groups at 3d and 1mo were significant (*P*<0.001). The thrombolysis group improved significantly from 1.84±0.88 to 1.31±0.53 logMAR (*P*=0.037), while the conservative group did not (*P*=0.808). Clinically significant visual improvement was seen in 57.14% of the thrombolysis group, significantly higher than the conservative group (*P*=0.009; Figure 1).

Table 4 presents the within-group comparison of BCVA across different time windows in CRAO subgroup patients, showing that the therapeutic effect of thrombolysis is closely related to the time window.

Table 5 shows CMT changes in the CRAO subgroup with different treatments. For onset under 24h, after 3d, the thrombolysis group's CMT decreased from 256±25.65 to 219±29.77 μm, and the conservative group's CMT decreased from 262±23.22 to 257±31.22 μm (*P*<0.001). After 1mo, the thrombolysis group's CMT decreased to 209±21.22 μm, and the conservative group's CMT decreased to 245±23.87 μm (*P*<0.001). Within-group comparisons showed significance in the thrombolysis group (*F*=23.05, *P*<0.001) but not in the conservative group (*F*=2.858, *P*=0.064). In the over-24-hour onset group, after 3d, thrombolysis group's CMT decreased from 242±23.33 to 220±29.33 μm, and conservative group's CMT decreased from 250±31.22 to 248±32.98 μm (*P*=0.001). After 1mo, thrombolysis group's CMT decreased to 204±27.22 μm, while conservative group's CMT remained almost the same (250±36.22 μm; *P*<0.001). Within-group comparison showed significance in thrombolysis group (*F*=14.354, *P*<0.001) but not in conservative group (*F*=0.926, *P*=0.465; Figure 2).

Table 6 presents the within-group comparison of CMT across different time windows in CRAO subgroup patients, indicating that time is associated with the effect of thrombolytic therapy.

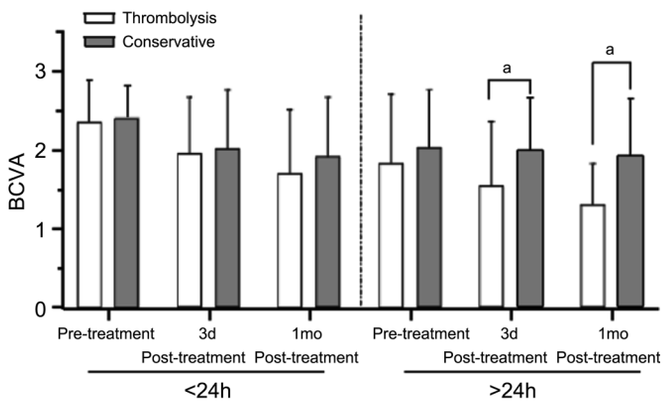

Figure 1 Changes in BCVA with different treatment methods in CRAO subgroup patients BCVA is expressed in logMAR among patients treated within 24h of symptom onset, BCVA showed mild improvement at 3d and at 1mo in both the thrombolysis and conservative groups, with no significant differences between the two treatment modalities at any time point. In contrast, in patients treated after 24h, BCVA improvements differed substantially between the two groups. The thrombolysis group demonstrated significantly better BCVA than the conservative group at both 3d and 1mo post-treatment (*P*<0.05 for both comparisons). No significant difference was observed at baseline. [a]*P*<0.001. BCVA: Best corrected visual acuity; CRAO: Central retinal artery occlusion; logMAR: Logarithm of the minimum angle of resolution.

Table 4 Within-group comparison of BCVA across different time windows in CRAO subgroup patients mean±SD or *n* (%)

BCVA	Thrombolysis group (n_1=25, n_2=28)	Conservative group (n_1=26, n_2=30)	χ^2	*P*
Pre-treatment logMAR				
<24h	2.36±0.53	2.42±0.40	-0.458	0.649
>24h	1.84±0.88	2.04±0.74	-0.938	0.352
t	2.588	2.369		
P	0.013	0.021		
Post-treatment logMAR at 3d				
<24h	1.96±0.72	2.02±0.75	-0.291	0.772
>24h	1.54±0.82	1.99±0.67	-13.961	<0.001
t	1.975	0.158		
P	0.054	0.875		
Post-treatment logMAR at 1mo				
<24h	1.71±0.81	1.92±0.76	-0.955	0.344
>24h	1.31±0.53	1.92±0.73	-15.84	<0.001
t	2.134	0		
P	0.038	1		
No visual improvement (<0.3 logMAR) between 1mo post-treatment and pre-treatment				
<24h	7 (28.00)	16 (61.54)		
>24h	12 (42.86)	23 (76.67)		
χ^2	1.268	1.508		
P	0.260	0.219		
Clinically significant improvement (≥0.3 logMAR)				
<24h	18 (72.00)	10 (38.46)		
>24h	16 (57.14)	7 (23.33)		
χ^2	1.268	1.508		
P	0.260	0.219		

n_1: <24h group; n_2: >24h group; BCVA: Best-corrected visual acuity; CRAO: Central retinal artery occlusion; SD: Standard deviation; logMAR: Logarithm of the minimum angle of resolution.

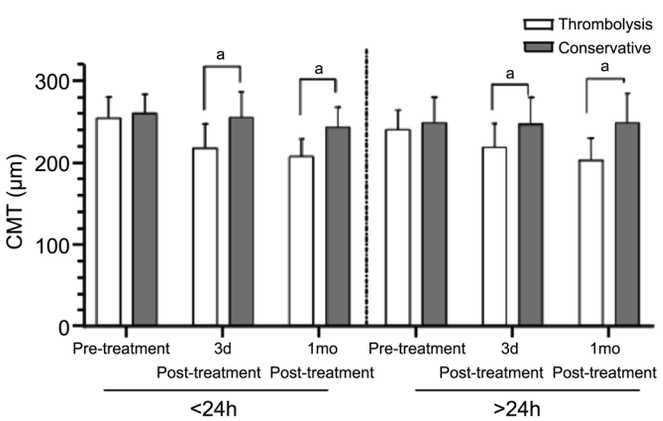

Figure 2 Changes in CMT with different treatment methods in CRAO subgroup patients [a]*P*<0.001. CMT: Central macular thickness; CRAO: Central retinal artery occlusion.

Table 7 shows adverse events in the CRAO thrombolysis group (*n*=53): Ocular events included orbital swelling (11.32%, *n*=6). Systemic events included new cerebral infarction (7.55%, *n*=4), decreased muscle strength (7.55%, *n*=4), upper limb numbness/weakness (5.66%, *n*=3), nausea/vomiting (5.66%, *n*=3), and dizziness/headache (7.55%, *n*=4).

DISCUSSION

The application of intra-arterial thrombolysis (IAT) in CRAO treatment remains a subject of ongoing debate. Since Schmidt *et al*[22] first introduced localized IAT as a therapeutic intervention for CRAO in the early 1990s, evidence has been mixed. While the EAGLE trial demonstrated comparable outcomes between IAT and conservative therapy, the high incidence of adverse events led to recommendations against IAT[23]. However, this conclusion has been challenged by multiple case studies and Meta-analyses revealing inferior outcomes with conservative approaches, suggesting that IAT may provide superior visual acuity improvement in acute CRAO[19,24-27]. This conflicting evidence indicates that IAT should not be dismissed outright but rather considered as a viable treatment option requiring careful patient selection.

The theoretical foundation for IAT effectiveness stems from understanding retinal ischemic tolerance. Hayreh *et al*'s[28-31] seminal studies in rhesus monkeys demonstrated that transient CRAO causes no significant retinal damage when circulation is restored within 97min. However, prolonged ischemia results in progressively extensive permanent damage, with

Table 5 Changes in CMT with different treatment methods in CRAO subgroup patients mean±SD, μm

CMT	<24h		*P*	>24h		*P*
	Thrombolysis group (*n*=25)	Conservative group (*n*=26)		Thrombolysis group (*n*=28)	Conservative group (*n*=30)	
Pre-treatment	256±25.65	262±23.22	0.385	242±23.33	250±31.22	0.276
3d post-treatment	219±29.77[a]	257±31.22	<0.001	220±29.33[a]	248±32.98	0.001
1mo post-treatment	209±21.22[a]	245±23.87	<0.001	204±27.22[a]	250±36.22	<0.001
F	23.05	2.858		14.354	0.926	
P	<0.001	0.064		<0.001	0.465	

[a]*P*<0.05 comparison within the group compared to pre-treatment. CMT: Central macular thickness; CRVO: Central retinal artery occlusion; SD: Standard deviation.

Table 6 Within-group comparison of CMT across different time windows in CRAO subgroup patients mean±SD, μm

Time windows	Thrombolysis group (n_1=25, n_2=28)	Conservative group (n_1=26, n_2=30)	*t*	*P*
Pre-treatment				
<24h	256±25.65	262±23.22	-0.877	0.385
>24h	242±23.33	250±31.22	-1.101	0.276
t	2.078	1.622		
P	0.043	0.111		
3d post-treatment				
<24h	219±29.77	257±31.22	-4.445	<0.001
>24h	220±29.33	248±32.98	-3.410	0.001
t	-0.123	1.045		
P	0.903	0.301		
1mo post-treatment				
<24h	209±21.22	245±23.87	-5.683	<0.001
>24h	204±27.22	250±36.22	-5.447	<0.001
t	0.742	-0.606		
P	0.461	0.547		

n_1: <24h group; n_2: >24h group; CMT: Central macular thickness; CRAO: Central retinal artery occlusion; SD: Standard deviation.

Table 7 Adverse events occurrence in CRAO thrombolysis group patients

Adverse events	Number (*n*=53)	Proportion (%)
Ocular-related		
Orbital swelling	6	11.32
Ocular pain	2	3.77
Ptosis	1	1.89
Systemic-related		
Epilepsy	2	3.77
New cerebral infarction	4	7.55
Decreased muscle strength	4	7.55
Upper limb numbness and weakness	3	5.66
Nausea and vomiting	3	5.66
Dizziness and headache	4	7.55
Dysarthria	2	3.77
Facial palsy	1	1.89
Transient consciousness disturbance with aphasia	1	1.89
Epistaxis	1	1.89

CRAO: Central retinal artery occlusion.

approximately 240min of CRAO leading to substantial irreversible retinal injury.

Importantly, our study challenges the rigid application of these time constraints in clinical practice. We observed that SOAT maintained advantages in achieving retinal reperfusion even in patients presenting beyond 24h after symptom onset.

The mechanism underlying this extended therapeutic window likely relates to the concept of retinal "ischemic penumbra". In cases of CRAO, residual retinal perfusion may be maintained through collateral circulation or cilioretinal arteries, creating a state of relative rather than complete retinal ischemia[32]. Within this penumbra, retinal neurons are not completely necrotic and may retain viability for extended periods. Significant interindividual variability in pathological characteristics leads to marked differences in retinal ischemic tolerance among patients, with some retinal ganglion cells demonstrating better damage tolerance and potential for functional recovery following blood flow restoration.

Understanding the vascular anatomy underlying CRAO provides insight into both its pathogenesis and treatment rationale. The central retinal artery and its branches supply the inner retinal layers (retinal nerve fiber layer, ganglion cell layer, and inner plexiform layer), originating from the ophthalmic artery—typically the first branch of the internal

carotid artery[33]. This anatomical relationship explains why stenosis or occlusion of the internal carotid artery significantly increases CRAO likelihood.

Consistent with previous studies, our investigation revealed that CRAO patients typically present with multiple cardiovascular risk factors, including hypertension, diabetes, carotid artery stenosis, carotid atherosclerotic disease, cardiac abnormalities, smoking, alcohol consumption, and even acute cerebral infarction[34-38]. Our findings similarly demonstrated higher CRAO probability in individuals with hypertension, diabetes, carotid atherosclerosis with plaque formation, and smoking history. This risk profile underscores CRAO's nature as a manifestation of systemic vascular disease rather than an isolated ocular condition.

Our clinical experience demonstrates the potential effectiveness of thrombolytic therapy across different presentation timeframes. The case presentations (Figures 3 to 9) illustrate several key principles:

Beyond 24-hour window (Figures 3, 4, and 5): Even in patients presenting after the traditional therapeutic window, thrombolytic therapy demonstrated measurable benefits. Pre-treatment imaging typically revealed complete CRA trunk occlusion, diffuse retinal pallor and edema, and complete visual field loss. Post-thrombolysis evaluation showed increased arterial blood flow, reduced retinal edema, restoration of cherry-red spots, and partial visual field recovery.

Within 24-hour window (Figures 6, 7, 8, and 9): Patients treated within the conventional timeframe showed more dramatic improvements. Pre-treatment findings included attenuated retinal vessels and localized retinal edema. Post-treatment outcomes demonstrated well-perfused retinal vessels, significantly reduced edema, and substantial visual field improvement.

Notably, patients demonstrating meningeal artery collateral circulation appeared to derive particular benefit from treatment, regardless of presentation timing. This observation supports the ischemic penumbra concept and suggests that collateral circulation may serve as a biomarker for treatment responsiveness.

Safety analysis revealed a favorable profile for thrombolytic therapy in our series. The conservative treatment group experienced only one case of periorbital edema, while the thrombolytic therapy group experienced several minor adverse events that resolved after treatment. Critically, no cases of intracranial hemorrhage or mortality occurred.

However, this favorable safety profile must be interpreted cautiously given our study's limitations and the inherent selection bias in our patient cohort. Currently, no reliable biomarkers or imaging modalities adequately distinguish viable retinal tissue from irreversible retinal infarction[33], making patient selection challenging. The potential benefits of treatment must therefore be carefully weighed against the frequency and severity of adverse events on an individual basis.

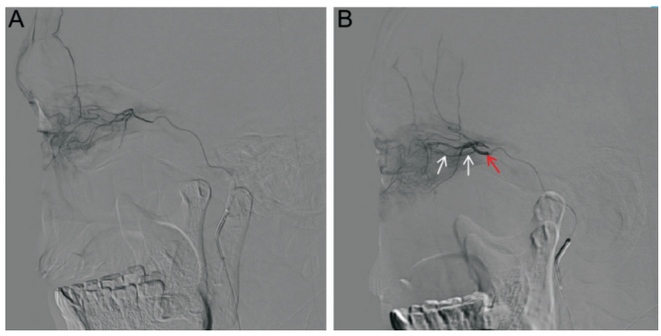

Figure 3 Ophthalmic artery angiography before thrombolysis (A) and after thrombolysis (B) The ophthalmic artery angiography showed the central retinal artery (white arrow in B) and the ophthalmic artery (red arrow in B).

The primary obstacles to effective CRAO management include narrow therapeutic windows, high comorbidity incidence, and inadequate public awareness. To address these challenges, we propose several systematic improvements:

Streamlined diagnostic pathways: When CRAO is diagnosed *via* OCT and color fundus photography in ophthalmology departments, we recommend omitting FFA and proceeding directly to digital subtraction angiography in interventional radiology units. This approach saves critical time for vision salvage and establishes efficient transfer pathways for acute CRAO patients to stroke centers.

Public health education: Significant deficiencies exist in public awareness regarding CRAO. Many patients delay hospitalization due to misconceptions that sudden visual acuity decline may spontaneously improve. Educational initiatives should emphasize: 1) recognition of ocular emergencies and "eye stroke" symptoms; 2) understanding that sudden, painless, monocular vision loss represents a potential medical emergency; 3) the critical importance of immediate presentation to emergency departments or ophthalmology clinics.

Several limitations constrain our conclusions. The relatively small sample size and retrospective design may have resulted in missing data. Symptom onset timing relied on patient recall and potentially incomplete medical records, introducing possible discrepancies between reported and actual onset times. Additionally, we performed no embolic type classification—while thrombolysis may effectively treat platelet-fibrin thrombi, its effectiveness may be limited for other embolic types, potentially influencing both therapeutic outcomes and complication rates. Noting that post-thrombolysis adjunctive therapies may introduce confounding effects and that future prospective, controlled studies are needed to isolate the pure effect of thrombolysis.

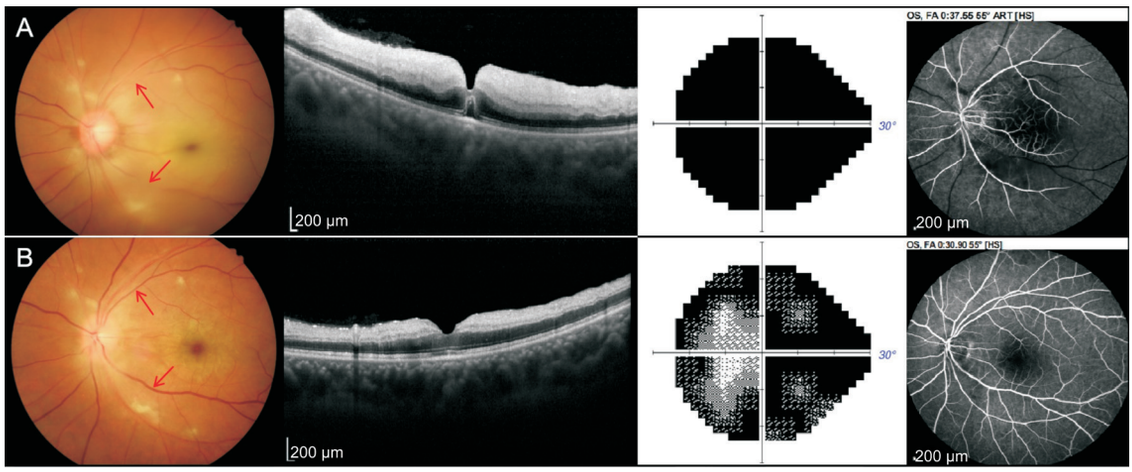

Figure 4 Before (A), and after thrombolysis (B) in color fundus photography, OCT, computerized visual field counting and FFA OCT: Optical coherence tomography; FFA: Fundus fluorescein angiography.

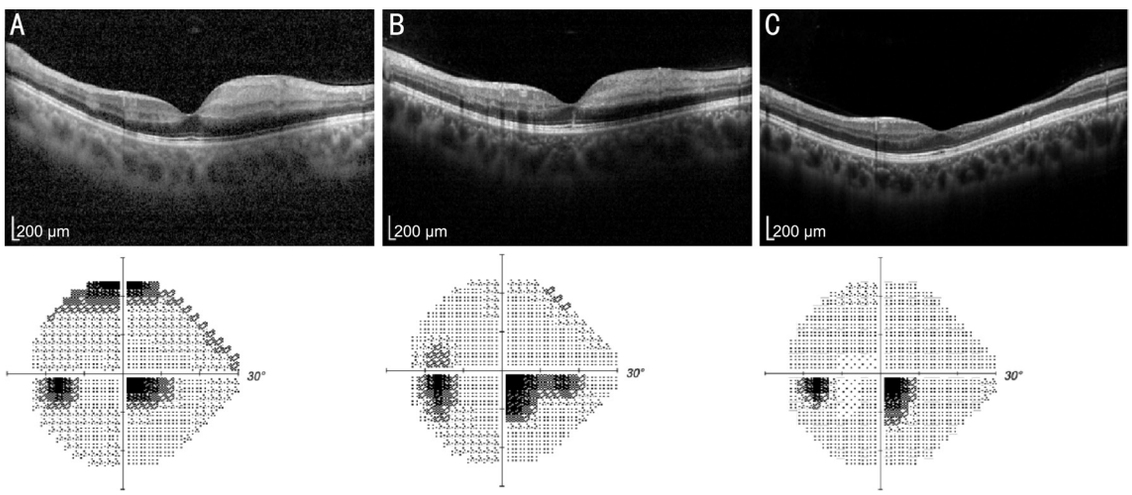

Figure 5 Before (A), after thrombolysis (B), and after thrombolysis 43mo (C) in OCT and computerized visual field count OCT: Optical coherence tomography.

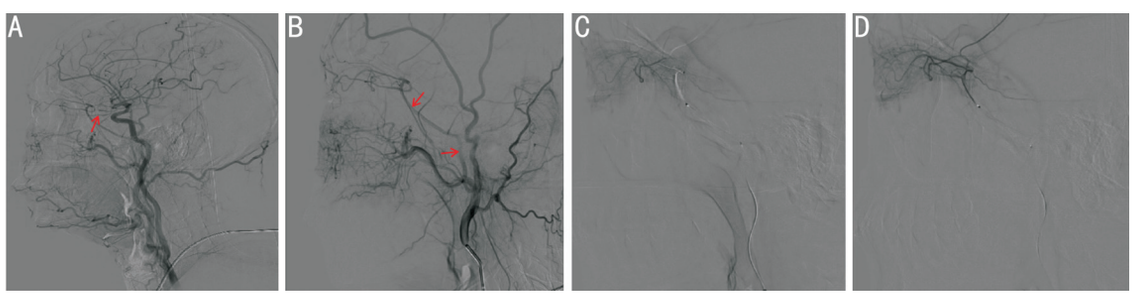

Figure 6 Lateral view of common carotid artery angiography (A), external carotid artery angiography (B), pre-thrombolysis angiography of the middle meningeal artery and ophthalmic artery (C) and post-thrombolysis angiography of the middle meningeal artery and ophthalmic artery (D) The angiography showed a thin ophthalmic artery (red arrow in A) and the presence of collateral circulation from the middle meningeal artery (red arrow in B). During the procedure, we found that the patient's right ophthalmic artery was slender, whereas the middle meningeal artery arising from the right external carotid artery was enlarged and supplied blood to the eye distally. Superselective catheterization of the right middle meningeal artery–ophthalmic artery using a microcatheter and microguidewire, followed by angiography, confirmed this finding. Consequently, under fluoroscopic guidance, slow infusion of thrombolytic agents was administered *via* the middle meningeal artery-ophthalmic artery pathway.

The critical challenge remains identifying which patients retain sufficient viable retinal tissue to benefit from intervention beyond conventional therapeutic windows. Future research should focus on developing reliable biomarkers or imaging techniques to assess residual retinal neuron survival probability, enabling more precise patient selection for late-presenting CRAO cases.

CRAO should be recognized not merely as an isolated ocular

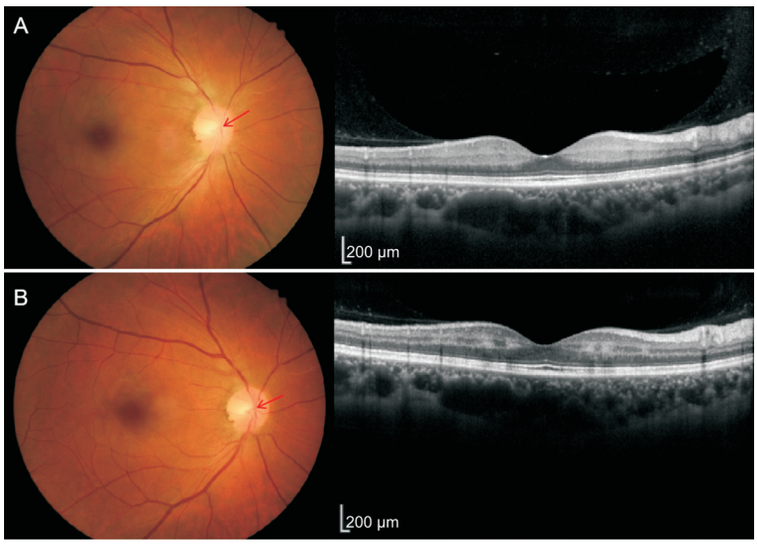

Figure 7 Before (A) and after thrombolysis (B) in color fundus photography and OCT OCT: Optical coherence tomography.

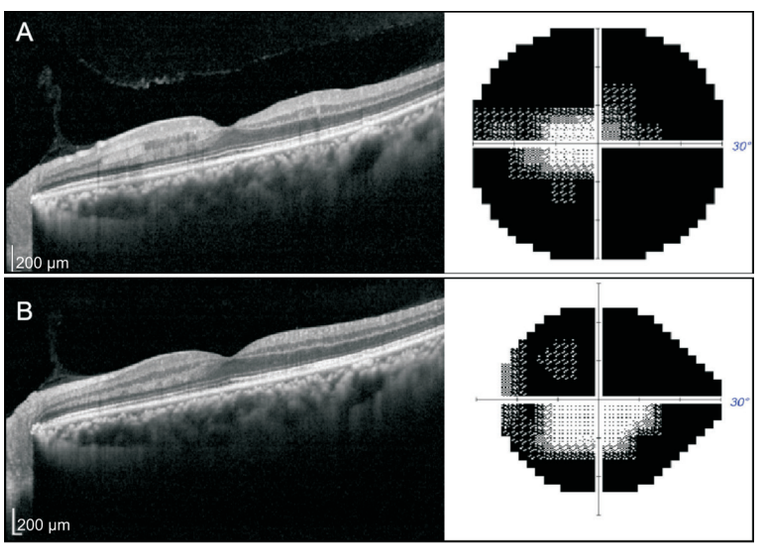

Figure 8 Before (A) and after thrombolysis (B) in OCT and computerized visual field count OCT: Optical coherence tomography.

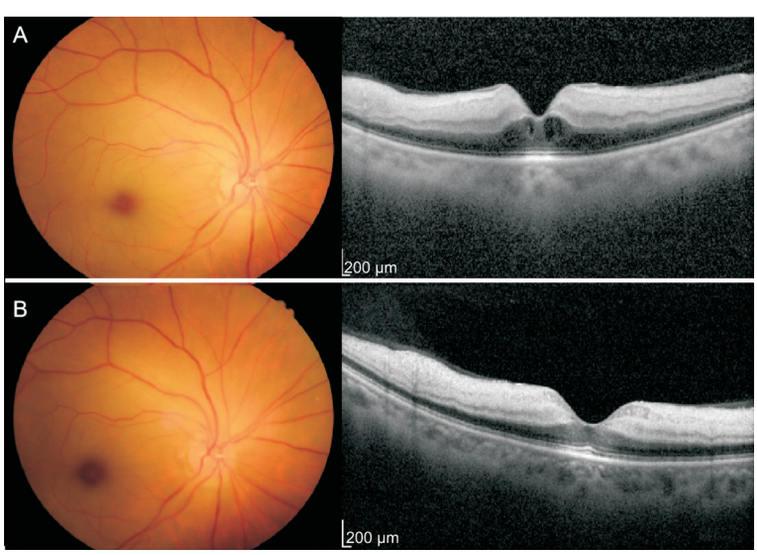

Figure 9 Before (A) and after thrombolysis (B) in color fundus photography and OCT OCT: Optical coherence tomography.

emergency but as a potential harbinger of systemic vascular disease. Studies demonstrate that CRAO patients exhibit increased risks of mortality, stroke, and myocardial infarction during both short- and long-term follow-up periods[39]. Current

guidelines from the American Academy of Ophthalmology recommend immediate stroke center referral for all retinal artery occlusion patients[40], while the American Heart Association advocates urgent medical evaluation for CRAO patients[33].

This evidence necessitates a fundamental shift in clinical perception of CRAO among physicians. Drawing parallels with ischemic stroke and myocardial infarction management protocols, a comprehensive CRAO care system should be established featuring interdisciplinary collaboration among ophthalmology, cardiology, neurology, vascular intervention, and emergency medicine specialists. Such a system should include standardized diagnostic pathways, rapid identification protocols, and optimized treatment strategies.

In conclusion, for patients with NA-CRAO presenting beyond 24h from symptom onset, SOAT demonstrates significant advantages in achieving retinal reperfusion, with notable visual acuity improvement observed in selected patients. However, the necessity for careful risk-benefit assessment, optimal treatment timing determination, embolic subtype evaluation, and systematic complication monitoring cannot be overstated.

Future efforts should focus on developing a standardized, time-targeted “eye stroke” care pathway analogous to existing stroke emergency protocols, enabling broader and more systematic application of IAT. Such comprehensive approaches would maximize therapeutic windows, minimize ischemia-related complications, prevent secondary vascular events, preserve contralateral eye health, and ultimately improve both visual and systemic patient outcomes.

ACKNOWLEDGEMENTS

Authors’ Contributions: Zhang KK wrote original draft, visualization, validation, methodology; Li M: Formal analysis, data curation, conceptualization; Yu ZH and Tu C: Editing, formal analysis, methodology; Liao YH and Shi YC: Resources, investigation, funding acquisition; Yang WH and Gong Y: Writing–review & editing, visualization, supervision, conceptualization, funding acquisition. All authors read and approved the final manuscript.

Data Availability Statement: The datasets during the current study are available from the corresponding author on reasonable request.

Foundations: Supported by the National Natural Science Foundation of China (No.524B2072); Zhejiang Medical and Health Technology Program (No.2023KY1141); Ningbo Municipal Bureau of Science and Technology (No.2023Z201; No.2024Z194); Ningbo Natural Science Foundation (No.2023J212); Ningbo Eye Hospital Foundation (No.2024YB003).

Conflicts of Interest: Zhang KK, None; **Li M,** None; **Liao YH,** None; **Yu ZH,** None; **Tu C,** None; **Shi YC,** None; **Yang WH,** None; **Gong Y,** None.

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