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Early Thrombolysis and Outcomes in Central Retinal Artery Occlusion: An Individual Participant Data Meta-Analysis

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BACKGROUND: This individual participant data meta-analysis aimed to determine whether time to treatment influences the effect of intraarterial thrombolysis (IAT), intravenous thrombolysis, and conservative standard therapy on visual outcomes in nonarteritic central retinal artery occlusion.

METHODS: We searched MEDLINE, CENTRAL, and Embase up to June 2023 for studies reporting treatment modality and peri-treatment best-corrected visual acuity (BCVA) for ≥5 participants, excluding patients with nonsevere vision loss (BCVA <1.0 logarithm of the minimum angle of resolution [logMAR]) or treated after 24 hours of symptom onset. The primary outcome was recovery from severe vision loss (final BCVA <1.0 logMAR). We used mixed-effect models and local polynomial regression to investigate nonlinear relationships between time to treatment and recovery from severe vision loss.

RESULTS: Of 4074 screened studies, individual participant data were sought from 52, with 35 contributing individual participant data for 1038 participants. In total, 783 patients met inclusion criteria (age, 64.8±13.3 years; 35.5% female; baseline BCVA, 2.3±0.5 logMAR). For every hour decrease in time to treatment, thrombolysis was associated with greater improvement in BCVA (intraarterial, 0.02 logMAR [95% CI, 0–0.04]; intravenous, 0.04 logMAR [95% CI, 0.00–0.07]) than conservative standard therapy (0.01 logMAR [95% CI, 0–0.02]). A nonlinear relationship was detected for intraarterial thrombolysis with a changepoint at 8 hours (95% CI, 6.7–9.4). Thrombolysis was associated with increased recovery from severe vision loss compared with conservative standard therapy (intraarterial within 6 hours: odds ratio, 2.72 [95% CI, 1.02–7.28], 27.2% versus 12.0%; intravenous within 4.5 hours: odds ratio, 3.32 [95% CI, 1.24–8.92], 28.8% versus 11.1%). Findings were consistent in subgroup analysis restricted to patients receiving recombinant tissue-type plasminogen activator. Monte-Carlo simulations showed that a randomized controlled trial would require 95 participants per group to achieve 80% power to detect an odds ratio of 3.0 for recovery from severe vision loss.

CONCLUSIONS: Early intervention in nonarteritic central retinal artery occlusion is associated with improvement in visual recovery, with intraarterial thrombolysis and intravenous thrombolysis outperforming nonthrombolytic treatments. These findings warrant confirmation in sufficiently powered randomized controlled trials.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: ischemia ■ odds ratio ■ perfusion ■ plasminogen ■ retina ■ retinal artery ■ retinal artery occlusion

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Nonstandard Abbreviations and Acronyms

AHA	American Heart Association
BCVA	best-corrected visual acuity
CRAO	central retinal artery occlusion
CST	conservative standard treatment
EAGLE	European Assessment Group for Lysis in the Eye
IAT	intraarterial thrombolysis
IPD	individual participant data
IVT	intravenous thrombolysis
logMAR	logarithm of the minimum angle of resolution
MA	meta-analysis
OR	odds ratio
RCT	randomized controlled trial
rDRV	recovery of driving vision
rFVL	recovery from functional vision loss
rSVL	recovery from severe vision loss
rtPA	tissue-type plasminogen activator

Management of nonarteritic central retinal artery occlusion (CRAO), an ophthalmic emergency that causes acute, painless, and severe vision loss,[1] aims to rapidly restore retinal perfusion and minimize visual morbidity.[1] At present, no conclusive evidence from randomized controlled trials (RCTs) supporting the efficacy of thrombolysis for CRAO exists. An RCT published in 2010 found no difference between intraarterial thrombolysis (IAT) and conservative standard treatment (CST),[2] and an RCT published in 2011 showed no difference between intravenous thrombolysis (IVT) and placebo.[3] However, both studies were limited by small sample sizes (n=84 for IAT trial and n=16 for IVT trial) and significant delays between symptom onset and treatment (average 11.6 hours). Subsequent study-level meta-analyses incorporating accumulating nonrandomized data have been equivocal regarding the efficacy of thrombolytic over nonthrombolytic therapy, but generally suggest improvement if thrombolysis is administered within 4.5 to 6 hours of symptom onset.[4–8] The American Heart Association (AHA) recently released an expert consensus statement calling for IVT within 4.5 hours and IAT within 6 hours if patients are not suitable for IVT,[1] spurring efforts to shorten time to diagnosis of CRAO.[9,10]

Given the current lack of convincing RCT or study-level data to underpin current recommendations, large-scale individual participant data sharing is the best available method for evaluating the totality of available evidence for thrombolysis in CRAO. Such approaches enable control over inclusion criteria at the individual participant level, harmonization of outcome measures between studies, and increased statistical power.[11] Three individual participant data meta-analyses (IPD-MAs) have been conducted for CRAO, 1 for IAT and IVT[12] and 2 for IVT.[13,14] Although these IPD-MAs demonstrate a time-dependent benefit of IVT given within 4.5 hours after symptom onset, only the cumulative efficacy of IAT at different time points was assessed. As such, the efficacy of IAT between different time points is unknown. Moreover, none of the IPD-MAs evaluated the efficacy of CST at different time points, compared thrombolysis to CST administered within the same time interval, nor compared IAT to IVT. Previous MAs have also not used IPD for changepoint analyses[15] to estimate optimal treatment windows for thrombolysis, nor estimated sample sizes required to confirm findings in RCTs.

The primary aim of this systematic review and meta-analysis was to determine whether time to treatment influences the effect of IAT, IVT, and CST on visual outcomes in nonarteritic CRAO using assembled patient-level data. Subgroup analysis restricted to alteplase was performed to remove the effects of historic thrombolytic agents, such as streptokinase and urokinase. Secondary aims included determining an optimal administration window for each intervention, comparing the efficacy of IAT, IVT, and CST at early versus late time points, and conducting power analyses to guide the design of future RCTs. An international consortium with multidisciplinary representation was formed during the 4-year course of this study.

METHODS

Data Availability

This systematic review and IPD meta-analysis was registered on INPLASY (International Platform of Registered Systematic Review and Meta-Analysis Protocols; INPLASY202350095) and conducted in accordance to the Preferred Reporting Items for Systematic Review and Meta-Analyses of Individual Participant Data (PRISMA-IPD) and Meta-analyses of Observational Studies in Epidemiology (MOOSE) guidelines.[16,17] De-identified collected IPD can be shared on reasonable request and with a signed data sharing agreement. The code used to analyze the data will be publicly available at https://github.com/kzaslavsky/CRAO_IPD.

Search Strategy and Eligibility Criteria

MEDLINE, CENTRAL (Cochrane Central Register of Controlled Trials), and Embase were queried from database inception up to June 19, 2023, using search terms associated with CRAO. The complete search strategy, which was designed in collaboration with a librarian, is outlined in Table S1. We included original studies with full-text English translations that reported on visual outcomes of at least 5 individuals with nonarteritic CRAO (hereafter referred to as CRAO) after treatment with IAT, IVT, or CST. We adopted the exclusion criteria of the EAGLE (European Assessment Group for Lysis in the Eye) RCT[2]; namely, studies were excluded if CRAO was associated with an additional retinal vascular occlusion or a macula-supplying cilioretinal artery and if CRAO was secondary to giant cell arteritis, other autoimmune vasculitis, trauma, or an iatrogenic source. There was

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no restriction placed on any specific thrombolytic agent. CST included any therapeutic modality other than thrombolysis, but studies of prostaglandin E1 were excluded because this intervention is neither widely available nor accepted as standard of care, and the reported visual outcomes are highly heterogeneous. Reference lists of relevant studies and secondary research articles were reviewed to identify additional publications. For studies that only reported aggregate data, the corresponding author was invited to contribute IPD in a de-identified manner. Studies that did not contribute IPD after 2 follow-up invitations were excluded. From the IPD pool, only participants presenting with severe vision loss (best-corrected visual acuity [BCVA] 20/200 or worse [logarithm of the minimum angle of resolution (logMAR) ≥1.0]) and treated within 24 hours of symptom onset were included. Participants who lacked a recorded pretreatment or posttreatment BCVA or were treated >24 hours after symptom or within an unknown timeframe were excluded.

Outcomes

All BCVA measurements were converted to the logMAR scale for quantitative analysis.[18] The primary outcome was recovery from severe loss (rSVL, final BCVA <1.0 logMAR, equivalent to >20/200 on the Snellen scale). Secondary outcomes included recovery from functional vision loss (rFVL, final BCVA ≤0.7 logMAR, equivalent to ≥20/100), recovery of driving vision (rDRV, final BCVA ≤0.4 logMAR, equivalent to ≥20/50), change in BCVA, and iatrogenic complications. The threshold of rSVL was chosen based on common monocular definitions of legal blindness.[19] The threshold for rFVL was used in prior IPD-MAs.[12–14] The threshold for rDRV was chosen as the best approximation for common thresholds for monocular driving eligibility with restrictions (eg, may drive but not after 6 PM) across jurisdictions.[20] Major iatrogenic complications included symptomatic intracranial hemorrhage, ischemic or hemorrhagic stroke, extracranial bleeding involving a large blood vessel, anaphylactic shock, and death. Minor iatrogenic complications included extracranial bleeding from a small blood vessel, transient ischemic attack, and orolingual edema.

Data Extraction and Quality Assessment

Article screening, data abstraction, and quality assessment were performed by 2 independent reviewers (A.L. and H.K.). Conflicts were resolved through discussion with arbitration by a senior author (J.S.X. or K.Z.) when consensus could not be reached. Treatment characteristics, time from symptom onset to treatment, pretreatment and posttreatment BCVA, and follow-up time were extracted for each participant. Treatment-related complications were extracted at the study level when IPD were not available. Demographic characteristics and medical comorbidities were also extracted but are not presented due to inconsistent reporting and a high proportion of missing data. Risk of bias was assessed using the ROBINS-I (Risk of Bias in Non-Randomized Studies of Interventions) tool[21] for observational studies and the RoB 2 tool[22] for RCTs. The included nonrandomized studies of interventions were evaluated using the ROBINS-I criteria by 2 independent reviewers (Y.M. and A.L.), which were assessed them as having moderate to serious risk of bias, regardless of the intervention evaluated (Figure S1).

Data Synthesis and Analysis

All analyses were conducted using R (version 4.2.1).[23] Time from symptom onset to treatment was analyzed both as a continuous variable and as a categorical variable with the following intervals: for the IAT group, ≤6 hours, >6.0 to 12.0 hours, and >12.0 to 24.0 hours; for the IVT group, ≤4.5 hours, >4.5 to 6.0 hours, >6.0 to 12.0 hours, and >12.0 to 24.0 hours; and for the CST group, all of the aforementioned intervals. These time intervals were chosen based on previous IPD meta-analyses and the current AHA guidelines on the management of acute CRAO.[1] Thrombolysis was administered in combination with CST in 2 IAT studies and 4 IVT studies (Table S2); individuals from those studies were assigned to thrombolysis groups. A 2-step MA was conducted to assess heterogeneity and publication bias at the study level.[24] Publication bias was assessed by visual inspection of funnel plots and the Egger test for funnel plot asymmetry.

A 1-step MA was conducted to determine the effect of time to treatment on change in BCVA in each intervention group using linear mixed-effects regression analysis with Bound Optimization by Quadratic Approximation optimization.[24,25] For each statistically significant association of time to treatment and change in BCVA, changepoint analysis was performed to test whether there was a specific time point at which a given modality became more effective. To compare outcomes between thrombolysis and CST groups, linear and logistic mixed effects regression models were developed using Bound Optimization by Quadratic Approximation optimization. Treatment modality was the fixed effect, and source studies served as random effects. Subgroup analysis was performed restricted to patients who received recombinant tissue-type plasminogen activator (rtPA) or CST only, excluding historic thrombolytic agents, such as streptokinase and urokinase. Another subgroup analysis was performed, restricted to comparative studies evaluating IAT or IVT as the interventional arm and CST as the control arm. Results are presented as odds ratios (ORs) with 95% CIs. Monte Carlo simulations (ie, sampling with replacement)[26] were performed to calculate sample sizes required for RCTs to operate at a power of 80%. An α-level of 0.05 was used to determine statistical significance. R packages used included lme4 for regression analysis[27] and ggplot2 for graph production.[28] Complete details on statistical analysis are presented in Supplemental Material S1.

Although single-arm, retrospective, interventional studies are typically not meta-analyzed together with RCTs, we reasoned that pooled analyses are appropriate given recent GRADE recommendations for meta-analyses of nonrandomized data.[29] In the current CRAO literature, (1) there are only 2 English-language RCTs that have compared thrombolytic therapy to CST and both provide low-very low certainty of evidence,[30] (2) nonarteritic CRAO is an emergent health condition with a natural history of severe, debilitating vision loss in over 85% of patients,[31] and (3) there is no evidence that any demographic or clinical factors influence visual prognosis in complete, nonarteritic CRAO without cilioretinal artery sparing.[3,32] Therefore, we expected confounding to be minimal and visual outcomes to depend almost entirely on the type and timing of intervention.

Sensitivity Analyses

If heterogeneity (I^2) exceeded 30, leave-one-out sensitivity analyses were performed. In addition, sensitivity analyses were completed by imputation of missing data. First, the type of missingness was evaluated by applying Little's missing completely

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at random test and logistic regression to determine if missingness was associated with other observed data to test for missing at random. If the missing completely at random and missing at random tests failed, the data were assumed as missing not at random. In that case, sensitivity analyses were performed by imputation of missing values by random sampling of observed values with replacement 1000× and recomputing our analyses. Mean estimates of effect sizes along with associated *P* values and their 95% CIs are reported.

RESULTS

Of the 4074 screened publications, IPD was sought from 52 studies of 2144 patients. Thirty-five studies contributed IPD for 1038 participants, representing a 48.4% capture rate. Of these, 864 participants from 32 studies[2,3,14,33–62] met patient-level inclusion criteria: 354 from 14 IAT studies, 191 from 11 IVT studies, and 322 from 13 CST studies (Figure 1A). Among the included studies, there were no missing participant-level data for pretreatment visual acuity, posttreatment visual acuity, and type of treatment. However, 84 individuals in the CST group lacked time to treatment data, leaving 783 for a complete-case analysis (n=238 for the CST group). The data was missing not at random, and sensitivity analyses were performed by imputation of missing values by random sampling of observed data. Thrombolytic agents included urokinase, streptokinase, and rtPA. rtPA was used for thrombolysis in 47.7% (n=169) of the IAT group and 91.1% (n=174) of the IVT group. CST included ocular massage, anterior chamber paracentesis, hyperbaric oxygen therapy, isovolemic hemodilution, heparin, topical intraocular pressure (IOP)-lowering agents, acetazolamide, corticosteroids, pentoxifylline, aspirin, anticoagulation, and intravenous saline (Table 1; Table S2). Patients treated with IAT were younger than those treated with IVT and CST. Sex distribution and follow-up time did not differ between groups. The number of participants treated with IAT, IVT, and CST within 4.5 hours of symptom onset was 30 (8.4%), 132 (69.1%), and 45 (18.9%), respectively; and within 6 hours was 125 (34.8%), 163 (85.3%), and 83 (34.9%), respectively. The CST group had better pretreatment BCVA but worse posttreatment BCVA than both thrombolysis groups (Table 1; Table S3). Patient characteristics and visual outcomes did not differ between patients we included and patients in studies who did not report IPD (Table S4).

To assess heterogeneity and publication bias at the study level by treatment modality, we first performed a 2-stage IPD MA. Given that measured outcomes differed among studies, we used the change in BCVA as the outcome after converting the reported BCVA values to the logMAR scale. For IAT, there was no evidence of heterogeneity (I^2=5.0) or publication bias (Egger test; *P*=0.08). For IVT, there was evidence of mild to moderate heterogeneity (I^2=34) and no publication bias (Egger test; *P*=0.72). For CST, there was substantial heterogeneity (I^2=70) and no publication bias (Egger test; *P*=0.57; Figure 1B). We hypothesized that, given no publication bias, heterogeneity stemmed from methodological differences between studies. Mean time to treatment was correlated with change in BCVA at the study level (Figure S2). Leave-one-out sensitivity analyses for IVT and CST groups demonstrated that effect size estimates for these modalities were robust, with 1 study (Weinberger et al.) significantly contributing to heterogeneity in the CST group (Figures S3 and S4).

To determine if time to treatment affects BCVA, we performed a 1-step MA using linear mixed effects models with time to treatment and thrombolytic agent as fixed effects and source publication as a random effect. For every hour decrease in time to treatment, IAT was associated with BCVA improvement by 0.02 logMAR (95% CI, 0–0.04; *P*=0.04), IVT with improvement by 0.04 (95% CI, 0–0.07; *P*=0.04), and CST with improvement by 0.01 logMAR (95% CI, 0–0.02; *P*=0.05; Figure 2A through 2C). Results were not affected by the thrombolytic agent used. Sensitivity analysis suggested the estimated effect sizes are reliable (Figures S3 and S4; Table S5). Post hoc analyses showed that age and sex did not affect outcomes for any modality (Tables S6 through S8). Although these linear models suggest that earlier intervention improves vision, nonlinear models may reveal a time point when treatment efficacy changes. After fitting local polynomial regression models, a changepoint was reliably detected at 8 hours for IAT (95% CI, 6.7–9.4), but not for IVT (95% CI, 2.1–22.1) or CST (none detected; Figure 2D through 2F).

Given that earlier treatment is associated with improved visual recovery in thrombolysis and nonthrombolysis groups, we estimated effect sizes of thrombolysis relative to CST at different time-to-treatment intervals to be tested in RCTs. Compared with CST, IAT given within 6 hours of symptom onset was associated with increased odds of rSVL (OR, 2.72 [95% CI, 1.02–7.28]; *P*=0.05), rFVL (OR, 3.12 [95% CI, 1.06–9.14]; *P*=0.04), and rDRV (OR, 5.94 [95% CI, 1.50–23.62]; *P*=0.01). Compared with CST, IVT within 4.5 hours increased odds of rSVL (OR, 3.32 [95% CI, 1.24–8.92]; *P*=0.02) and rFVL (OR, 3.56 [95% CI, 1.06–12.02]; *P*=0.04), but not rDRV (Figure 3; Table 2; Table S9). IVT did not show a benefit over CST beyond 4.5 hours, including the 4.5- to 6-hour interval. Leave-one-out and sensitivity analyses with missing data imputation demonstrated that the findings were robust in complete-case analysis (Tables S10 and S11). There were no differences in any visual outcome at any time interval between IAT and IVT. Subgroup analysis of participants treated with rtPA showed similar findings and effect sizes at the same time intervals (Tables S12 through S15).

Subgroup analysis restricted to comparative studies (Table S16) included 3 studies comparing IAT (n=130) to CST (n=83)[2,41,43,44] and 3 studies comparing IVT

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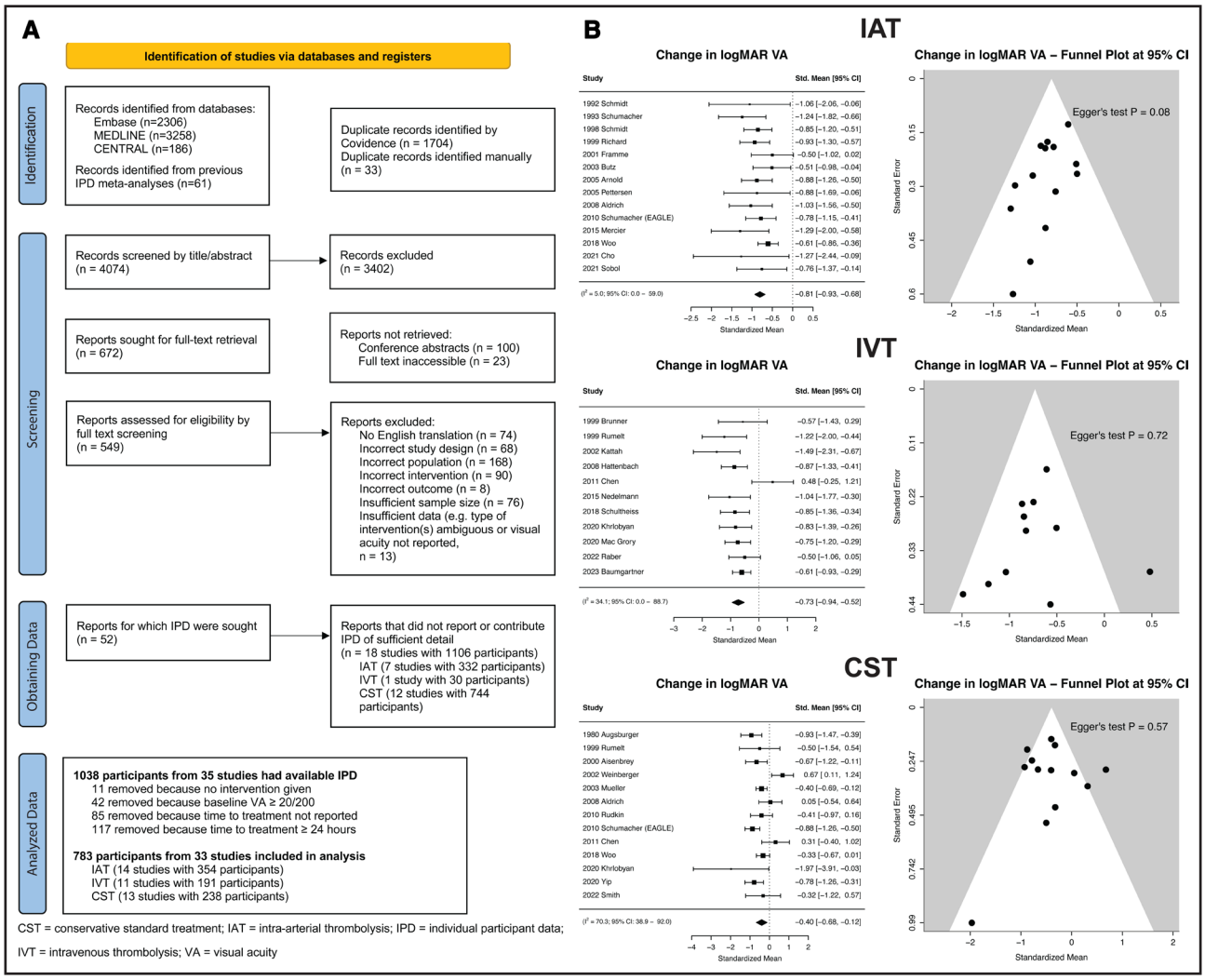

Figure 1. Individual participant data extraction and study-level summary by intervention type.
A, PRISMA individual participant data (IPD) flow diagram detailing the search strategy and results of IPD extraction. **B**, Study level summaries for the single group standardized mean change in logarithm of the minimum angle of resolution (logMAR) visual acuity (VA) with forest plots and funnel plots by treatment modality show minimal evidence of publication bias. The shaded area represents values outside of the 95% CI. CENTRAL indicates Cochrane Central Register of Controlled Trials; CST, conservative standard treatment; IAT, intraarterial thrombolysis; and IVT, intravenous thrombolysis.

(n=35) to CST (n=15).[3,48,53] There was no difference in any visual outcome at any time interval between thrombolysis and CST, likely due to small sample sizes and insufficient statistical power (Table S17).

Given the challenges with conducting RCTs for CRAO, we used our IPD data set to estimate the sample sizes required for a hypothetical RCT to detect clinically meaningful effects with a power of 80%. Given that estimated ORs for the primary outcome of rSVL ranged from 2.72 to 3.56, we determined sample sizes necessary to detect ORs ranging from 2.5 to 3.5 (Table S18). Using Monte Carlo simulations with the CST group as the control population, we show that to detect an OR of 3.0 between CST and a hypothetical treatment with a power of 80%, an RCT will require 95 participants in each group to detect a change in rSVL, 110 for rFVL, and 165 for rDRV (Figure 4).

From a safety perspective, there were 5 (1.4%) major complications in the IAT group (3 symptomatic intracranial hemorrhages, 1 ischemic stroke, 1 femoral artery hemorrhage), 6 (3.1%) in the IVT group (2 symptomatic intracranial hemorrhages, 3 asymptomatic intracranial hemorrhages, 1 abdominal aortic aneurysm rupture), and 4 (1.7%) in the CST group (1 death, 3 undifferentiated strokes; Table S19). There were 13 (3.7%) minor complications for IAT, 1 for IVT (0.5%), and 8 (3.4%) for CST.

DISCUSSION

The role of thrombolysis in treating CRAO is controversial due to diverging findings between RCTs and synthesized nonrandomized data. Given the diagnostic delay and rarity of CRAO, large IPD-sharing initiatives

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Table 1. Demographics and Treatment Characteristics of Patients Included in Study

Variable	IAT group (n=354)	IVT group (n=191)	CST group (n=238)	All groups (N=783)	*P* value*
Age, y†	62.5 (13.9)	67.7 (11.9)	65.6 (13.0)	64.8 (13.3)	<0.01
No. of females‡	107 (35.7%)	62 (36.9%)	77 (34.2%)	246 (35.5%)	0.86
Treatment window					<0.01
≤4.5 h	30 (8.5%)	132 (69.1%)	45 (18.9%)	207 (26.4%)	
4.5–6 h	95 (26.8%)	31 (16.2%)	38 (16.0%)	164 (20.9%)	
6–12 h	159 (44.9%)	18 (9.4%)	76 (31.9%)	253 (32.3%)	
12–24 h	70 (19.8%)	10 (5.2%)	79 (33.2%)	159 (20.3%)	
No. treated with recombinant tPA	169 (47.7%)	174 (91.1%)	…	343 (62.9%)§	…
Follow-up time, d‖	97.0 (219.8)	140.7 (177.4)	99.7 (227.0)	107.0 (215.0)	0.19
	Range: 1 h–1939.2 d	Range: 1 d–912.5 d	Range: 1 h–1939.2 d	Range: 1 h–1939.2 d	
Pretreatment VA in logMAR	2.3 (0.5)	2.4 (0.4)	2.2 (0.5)	2.3 (0.5)	<0.01

Reported as mean (SD) for continuous variables and n (%) for categorical variables. CST indicates conservative standard treatment; IAT, intraarterial thrombolysis; IVT, intravenous thrombolysis; logMAR, logarithm of the minimum angle of resolution; tPA, tissue-type plasminogen activator; and VA, visual acuity.

*One-way ANOVA for continuous variables and χ^2 test for categorical variables.

†n=300 for IAT, 180 for IVT, and 238 for CST.

‡n=300 for IAT, 168 for IVT, and 225 for CST.

§Denominator excludes patients treated with CST.

‖n=220 for IAT, 108 for IVT, and 200 for CST.

remain the best mechanism for developing evidence to guide clinical decision-making. Our study represents a multiyear, international collaborative effort to address this knowledge gap. Using the largest IPD data set assembled to date, we investigated the efficacy of IAT (n=354), IVT (n=191), and CST (n=238) for nonarteritic CRAO in patients presenting with severe vision loss treated within 24 hours of symptom onset (Figure 1). We found comparable results when thrombolysis was limited to rtPA or was considered in combination with historic agents (ie, streptokinase and urokinase): earlier treatment was associated with improved BCVA in IAT, IVT, and CST groups. We also found a critical time point of 8 hours for IAT, before which its efficacy increased significantly (Figure 2). Both IAT and IVT were associated with increased rSVL and rFVL relative to CST if given within 6 hours (IAT) or 4.5 hours (IVT; Figure 3). Subgroup analysis restricted to comparative studies lacked the power required to detect these associations. Lastly, we computed the sample sizes required to detect these effect sizes in an RCT (Figure 4). There was no publication bias for IAT, IVT, or CST. Overall, these data support the AHA statement on the management of CRAO, which calls for IVT within 4.5 hours of symptom onset, and IAT within 6 hours if the patient is not a candidate for IVT.[1]

Three previous IPD MAs showed that earlier treatment improves IVT efficacy in acute CRAO.[12–14] We extend previous work by (1) demonstrating an association between earlier treatment and BCVA improvement for IAT, IVT, and CST, which was consistent in subgroup analysis restricted to rtPA; (2) estimating an optimal time window for IAT; (3) confirming the superiority of IVT over CST in early treatment windows; (4) demonstrating a benefit of IAT over CST within 0- to 6-hour treatment window; (5) assessing outcomes meaningful to clinicians and patients (ie, monocular BCVA thresholds for legal blindness and driving); and (6) leveraging IPD for power calculations to guide RCT design to test these findings.

A major challenge in recruiting patients for RCTs investigating thrombolysis in CRAO is identifying and treating patients sufficiently early.[63] We detected evidence for a changepoint in IAT efficacy at 8 hours from symptom onset, suggesting that even after 6 hours of symptom onset, IAT may trigger biologically significant reperfusion of the retina before the onset of irreversible cell loss (Figure 2D). It may, therefore, be reasonable to consider extending the IAT treatment window beyond the 6 hours recommended by AHA. Given the paucity of IVT patients treated beyond 6 hours, we were unable to reliably detect a changepoint for IVT. We did not detect a changepoint for CST (Figure 2F), suggesting that the small time-dependent improvement in BCVA reflects spontaneous reperfusion events or a lack of statistical power to detect a changepoint. Recently, Lema et al[9] implemented a remote consult model with point-of-care OCT at tertiary stroke centers, resulting in a time to thrombolysis of 2.4 hours from emergency department presentation and 9.1 hours from the time of last known well. Similarly, Gilbert et al[10] showed that a multidisciplinary telemedicine approach using fundus photography identified 85 patients with CRAO within 4.5 hours of symptom onset over a 2-year time span in a health system serving 4.5 million people, with patients receiving IVTs more likely to experience 3-line improvement in BCVA. Implementation of such methods can further streamline CRAO diagnosis, expand treatment access, and maximize participant enrollment.

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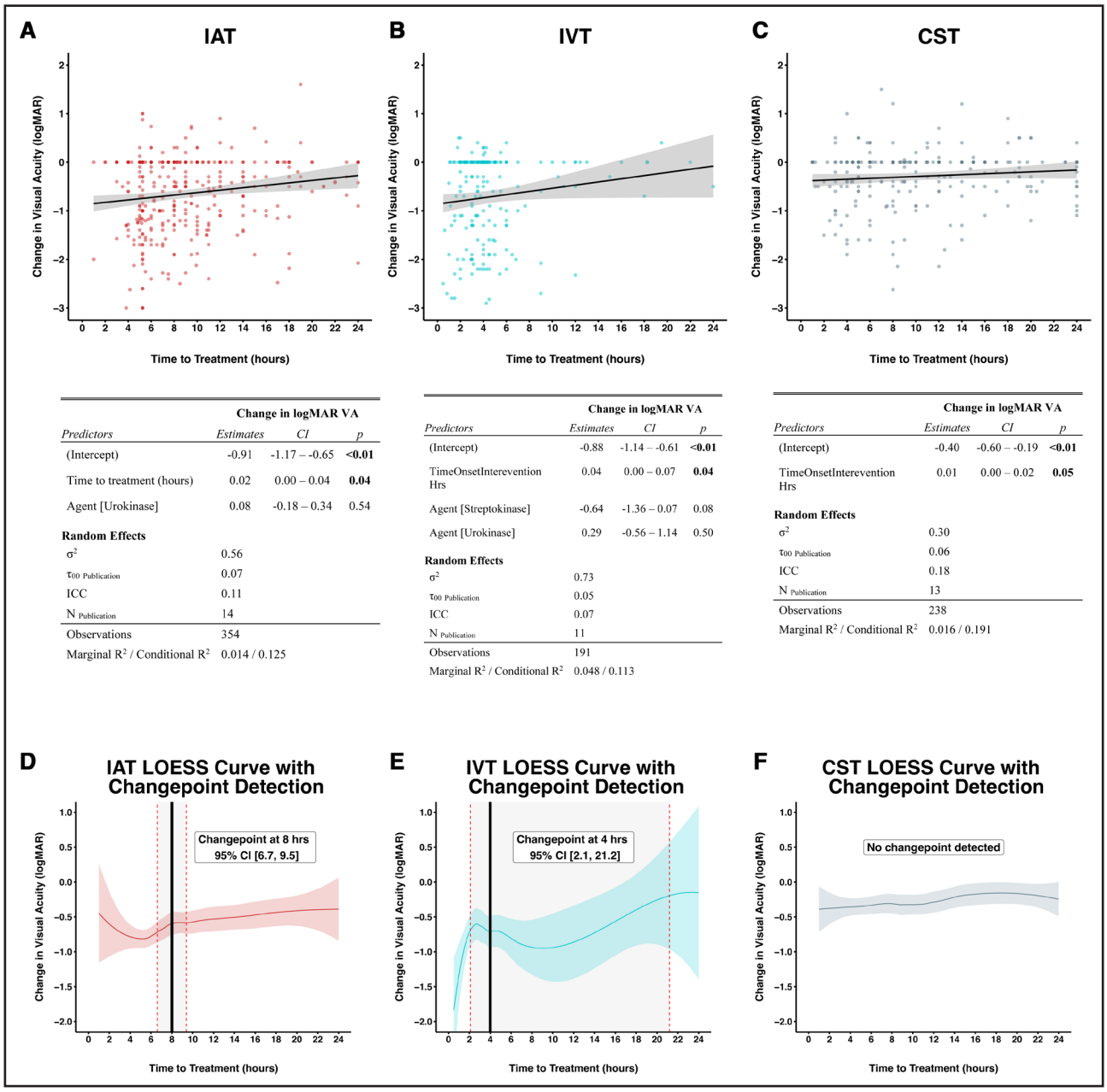

Change in logMAR VA			
Predictors	*Estimates*	*CI*	*p*
(Intercept)	-0.91	-1.17 – -0.65	**<0.01**
Time to treatment (hours)	0.02	0.00 – 0.04	**0.04**
Agent [Urokinase]	0.08	-0.18 – 0.34	0.54
Random Effects			
σ^2	0.56		
$\tau_{00\ Publication}$	0.07		
ICC	0.11		
$N_{Publication}$	14		
Observations	354		
Marginal R^2 / Conditional R^2	0.014 / 0.125		

Change in logMAR VA			
Predictors	*Estimates*	*CI*	*p*
(Intercept)	-0.88	-1.14 – -0.61	**<0.01**
TimeOnsetInterevention Hrs	0.04	0.00 – 0.07	**0.04**
Agent [Streptokinase]	-0.64	-1.36 – 0.07	0.08
Agent [Urokinase]	0.29	-0.56 – 1.14	0.50
Random Effects			
σ^2	0.73		
$\tau_{00\ Publication}$	0.05		
ICC	0.07		
$N_{Publication}$	11		
Observations	191		
Marginal R^2 / Conditional R^2	0.048 / 0.113		

Change in logMAR VA			
Predictors	*Estimates*	*CI*	*p*
(Intercept)	-0.40	-0.60 – -0.19	**<0.01**
TimeOnsetInterevention Hrs	0.01	0.00 – 0.02	**0.05**
Random Effects			
σ^2	0.30		
$\tau_{00\ Publication}$	0.06		
ICC	0.18		
$N_{Publication}$	13		
Observations	238		
Marginal R^2 / Conditional R^2	0.016 / 0.191		

Figure 2. Effect of time from onset to treatment on change in logarithm of the minimum angle of resolution (logMAR) VA (visual acuity) by treatment modality and changepoint analysis.
A–**C**, Scatterplots of change in logMAR VA vs time to treatment for eyes treated with (**A**) intraarterial thrombolysis (IAT), (**B**) intravenous thrombolysis (IVT), and (**C**) conservative standard treatment (CST). Each point represents 1 eye. The line and shaded area represent the least-squares line of best fit with 95% CI. The corresponding mixed effects linear regression with time to treatment as a fixed variable and publication source as a random variable for IAT, IVT, and CST is demonstrated below the scatterplots. **D**–**F**, Changepoint analysis of local polynomial curves fit to the data using the LOESS method for IAT (**D**), IVT (**E**), and CST (**F**). ICC indicates intraclass correlation coefficient; and LOESS, locally estimated scatterplot smoothing.

We argue that CST, rather than natural history, should be the comparator to thrombolysis in future RCTs (Supplemental Material S2). We found that n=95 per group is the minimum required for a power of 80% to detect an OR of 3.0 for rSVL, which shows that both prior RCTs of thrombolysis in CRAO were severely underpowered.[2,3] Currently, there are 3 unreported clinical trials comparing IVT within 4.5 hours to CST or placebo (NCT04965038 or REVISION [Reperfusion Early Vision Improvement Study in Occurrence of Non-Arteritic Central Retinal Artery Occlusion],[64] NCT04526951 or THEIA [Thrombolysis in Acute Central Retinal Artery Occlusion], NCT03197194 or TenCRAOS), and 1 trial comparing IAT within 7 days to CST (NCT05562284). Two of the recently completed

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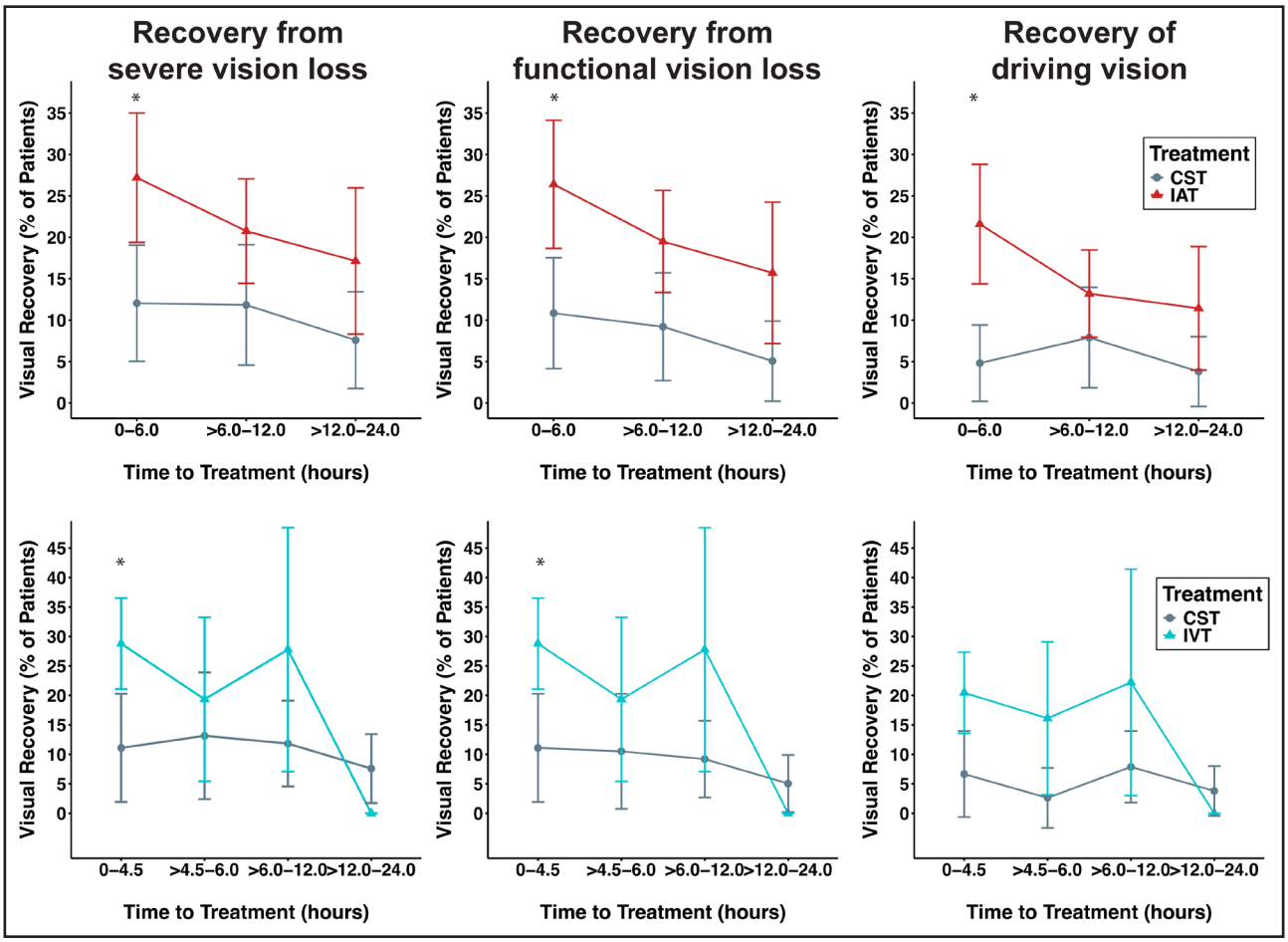

Figure 3. Rates of visual recovery based by thrombolysis modality compared with conservative standard treatment (CST) and clinically relevant time points.

A, Rate of visual recovery of intra-arterial thrombolysis (IAT) compared with CST for eyes treated within 6 hours of symptom onset, between 6 and 12 hours, and 12 and 24 hours. Data is represented as mean±95% CI. **B**, Rate of visual recovery of intravenous thrombolysis (IVT) compared with CST for eyes treated within 4.5 hours of symptoms onset, between 4.5 and 6 hours, between 6 and 12 hours, and 12 and 24 hours.

trials, THEIA (n=70 total) and TenCRAOS (n=78 total), are under the sample size threshold, and only REVISION (n=422), scheduled for completion in 2026, is adequately powered. Ultimately, a meta-analysis of IPD from these RCTs will be critical to determine whether IVT within 4.5 hours of symptom onset is effective.

Table 2. Effect of Time to Treatment on Recovery From Severe Vision Loss

Outcome	Comparison	Sample size		Time to treatment	Mean difference or odds ratio	95% CI	*P* value*
Recovery from severe vision loss (VA better than 20/200)	IAT vs CST	n_{IAT}=125	n_{CST}=83	≤6 h	2.72	1.02–7.28	0.05†
	IAT vs CST	n_{IAT}=159	n_{CST}=76	6–12 h	1.96	0.85–4.49	0.11
	IAT vs CST	n_{IAT}=70	n_{CST}=79	12–24 h	2.55	0.72–9.01	0.15
	IVT vs CST	n_{IVT}=132	n_{CST}=45	≤4.5 h	3.32	1.24–8.92	0.02†
	IVT vs CST	n_{IVT}=31	n_{CST}=38	4.5–6 h	2.46	0.72–8.43	0.15
	IVT vs CST	n_{IVT}=18	n_{CST}=76	6–12 h	2.72	0.76–9.71	0.12
	IVT vs CST	n_{IVT}=10	n_{CST}=79	12–24 h	…	…	…
	IAT vs IVT	n_{IAT}=125	n_{IVT}=132	≤6 h and ≤4.5 h	0.90	0.42–1.91	0.77
	IAT vs IVT	n_{IAT}=159	n_{IVT}=49	6–12 h and 4.5–12 h	0.82	0.32–2.10	0.68
	IAT vs IVT	n_{IAT}=70	n_{IVT}=10	12–24 h	…	…	…

CST indicates conservative standard treatment; IAT, intraarterial thrombolysis; IVT, intravenous thrombolysis; and VA, visual acuity.
*Mixed effects, 1-stage logistic regression.
†Significant results.

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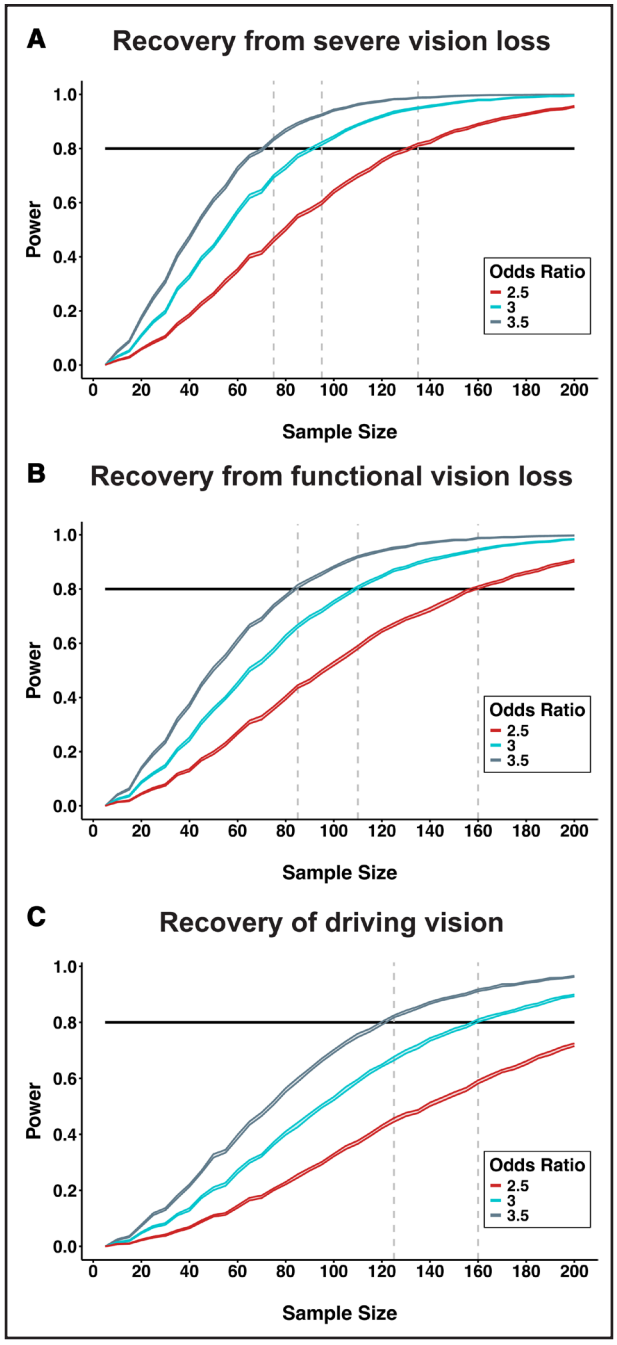

Figure 4. Sample size required to achieve a statistical power of 80% in randomized controlled trials (RCTs) for central retinal artery occlusion (CRAO).
A–**C**, 95% CIs of the proportion of simulations (25 000 for each combination of outcome, effect size, and sample size) achieving statistical significance at α=0.05 at sample sizes ranging from 5 to 200 to detect odds ratios of 2.5, 3, and 3.5 for (**A**) recovery from severe vision loss, (**B**) recovery from functional vision loss, (**C**) recovery of driving vision. Horizontal black line denotes the power threshold of 80%. The conservative standard treatment group data were used as the population for sampling, and logistic regression models were used as the statistical test.

Based on previous RCTs and IPD-MAs on CRAO, the major complication rates after IAT and IVT are 2.2%[12] and 1.6% to 3.4%,[12–14] respectively; for minor complications, these rates are 2.6%[12] and 0.4%.[12–14] We found similar rates of adverse events: major complications (1.4% IAT, 3.1% IVT, 1.7% CST) and minor complications (3.7% IAT, 0.5% IVT, and 3.4% CST). Given the ease of IVT administration relative to IAT, these findings argue for consideration of IVT as first-line therapy, with IAT reserved for patients ineligible for IVT, in line with AHA recommendations. Ultimately, the risk-benefit calculation regarding whether to proceed with thrombolysis will be specific to each individual patient's needs. For this reason, we provide information on outcomes important to patients and clinicians (ie, monocular thresholds for legal blindness, functional vision, and driving vision).

This study has several limitations. First, single-armed studies were the predominant data sources, which are subject to inherent selection bias and confounding.[29] There was a limited number of multiarm studies, and most of them were nonrandomized; thus, subgroup analysis restricted to comparative studies was underpowered and could not reproduce the findings from the main analysis. Second, studies differed in methodological design, eligibility criteria, patient characteristics, clinical practice patterns, definitions of time to treatment (eg, how nocturnal occurrence of CRAO is interpreted), and treatment protocols. Despite heterogeneity in the IVT and CST groups, sensitivity analyses revealed our findings were robust (Figures S3 and S4; Tables S7, S12, and S13). Third, reversibility of CRAO depends on disease stage, with only incomplete rather than subtotal or total CRAO likely to benefit from IAT.[43] Given that central BCVA is poorly correlated with disease stage, it may not be the most sensitive measure to evaluate treatment efficacy. Formal assessment of visual field loss with automated perimetry may provide more accurate information,[44] but risks delaying treatment. With these considerations in mind, comparisons of IAT and IVT with CST should be interpreted with caution, and at best as estimates of plausible effect sizes to be tested in RCTs.

Given the rarity of CRAO and the paucity of RCTs, IPD analyses remain the highest level of evidence for thrombolytic treatments. We made several efforts to increase the robustness of data synthesis, including formal consultation with statisticians (D.Z. and L.K.), exclusion of studies with <5 participants to limit selection bias, leave-one-out and missing data sensitivity analyses, and definition of patient-level inclusion criteria to decrease heterogeneity. Over several years of outreach and data acquisition, we formed an international, multidisciplinary collaboration for CRAO. We make the code used for our analyses available to the scientific community to facilitate reproducibility efforts and aim to expand this IPD-MA as data accumulates. Thus, in addition to providing a foundation to inform clinical trial design, this study advocates for open data sharing and collaboration as the field advances towards consensus on CRAO management.

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This IPD-MA demonstrated that earlier administration of thrombolysis and CST in acute CRAO results in better visual outcomes. Thrombolysis with rtPA is superior to CST in promoting recovery from severe vision loss, functional vision loss, and rDRV in early but not late time windows. IAT may have a longer efficacy window than IVT, but it is not superior to IVT when administered early. These findings warrant investigation with RCTs enrolling a minimum of 95 patients per group, which is significantly exceeded by the currently ongoing REVISION trial. Concurrently, systems of care should leverage telemedicine and point-of-care technologies to facilitate rapid diagnosis and management of CRAO.

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Author Contributions

Drs Zaslavsky and Margolin conceptualized the study. Drs Xie, Zaslavsky, Chaban, Kaur, Motekalem, Zeraatkar, Margolin, and A. Lusterio developed a methodology. Drs Xie, Zaslavsky, Chaban, Kaur, Motekalem, and A. Lusterio were responsible for data curation. Drs Xie and Zaslavsky performed data analyses and produced visualizations of results. Drs Xie, Zaslavsky, and Margolin wrote the original draft. Drs Popovic, Althaus, Malbin, Nolte, Scheitz, Khrlobyan, Sangha, Jurado, Arnold, Mattle, Heldner, Nedelmann, Cordonnier, Spitzer, Poli, Hametner, Baumgartner, Wegener, Kook, Shahjouei, Dumitrascu, and Margolin reviewed and edited the article. Dr Margolin supervised the project.

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Supplemental Material

Supplemental Materials S1–S2
Tables S1–S20
Figures S1–S4
MOOSE Checklist
PRISMA-IPD Checklist

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