Intravenous alteplase versus oral aspirin for acute central retinal artery occlusion within 4·5 h of severe vision loss (THEIA): a multicentre, double-dummy, patient-blinded and assessor-blinded, randomised, controlled, phase 3 trial

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Summary

Background Central retinal artery occlusion (CRAO) is a subtype of ischaemic stroke that results in acute monocular vision loss. Although open-label studies and meta-analyses have suggested that early intravenous thrombolysis might improve visual acuity, no randomised controlled trials have yet confirmed this benefit. We aimed to compare the safety and efficacy of intravenous alteplase with oral aspirin in patients with CRAO treated within 4·5 h of onset of severe vision loss.

Methods THEIA was a multicentre, double-dummy, patient-blinded, assessor-blinded, randomised, controlled, phase 3 trial conducted across 16 hospitals with stroke units in France. Adults (aged ≥18 years) presenting with sudden, severe, and persistent monocular vision loss (Snellen <20/400) due to suspected non-arteritic acute CRAO were eligible for inclusion. Participants were randomly assigned (1:1), stratified by centre, to receive either 0·9 mg/kg of bodyweight intravenous alteplase and oral placebo (alteplase group) or 300 mg oral aspirin and intravenous saline placebo (aspirin group) within 4·5 h of symptom onset. Patients, outcome assessors, and the study sponsor were masked to treatment allocation; treating nurses and neurologists were unmasked. The primary efficacy outcome was improvement in visual acuity of at least 0·3 logarithm of the minimum angle of resolution (LogMAR) from baseline to 1 month, analysed in the full analysis set, which included all patients who received the complete intervention and a visual acuity assessment at baseline. Safety outcomes included serious adverse events, particularly intracranial and extracranial bleeding, analysed in all randomly assigned participants. This study is registered at ClinicalTrials.gov (NCT03197194) and is completed.

Findings Between June 8, 2018, and Oct 2, 2023, 70 patients (mean age 70 years [SD 9]; 25 [36%] women and 45 [64%] men) were enrolled and randomly assigned to either the alteplase group (35 [50%]) or the aspirin group (35 [50%]). In total, 65 (93%) patients received the allocated treatment: 34 (97%) in the alteplase group and 31 (89%) in the aspirin group. Mean time from symptom onset to treatment initiation was 232·4 min (SD 43·6) . Among 56 patients with available data on the primary endpoint, 19 (66%) of 29 patients in the alteplase group and 13 (48%) of 27 patients in the aspirin group showed an improvement in visual acuity of at least 0·3 LogMAR at 1 month (unadjusted risk difference 17·4 [95% CI −1·8 to 46·5]; adjusted odds ratio 1·0 [95% CI 0·07 to 18·39]; p=0·95) . One asymptomatic intracranial haemorrhage related to study treatment was reported in the alteplase group. 14 serious adverse events unrelated to treatment occurred in 11 patients overall (six [17%] in the aspirin group and five [14%] in the alteplase group). No symptomatic haemorrhages or major bleeding related to study treatment were reported.

Interpretation Intravenous alteplase administered within 4·5 h of CRAO onset was not associated with a significant improvement in visual acuity compared with aspirin, despite a higher rate of improvement in the alteplase group. However, the study was likely underpowered to detect a statistical difference. Although no safety concerns related to alteplase were identified, the overall modest recovery rates underscore the need for individual patient-level data meta-analyses with forthcoming randomised controlled trials to clarify the potential benefit of thrombolysis or aspirin in patients with acute CRAO.

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Introduction

Acute non-arteritic central retinal artery occlusion (CRAO) causes sudden, severe, and painless vision loss due to an abrupt interruption of blood flow to the inner retinal layers. The condition is considered to be an infarction within the internal carotid artery territory.

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See **Online** for appendix

Research in context

Evidence before this study

Acute non arteritic central retinal artery occlusion (CRAO) is a type of ischaemic stroke affecting the carotid artery territory, causing sudden, painless, and severe loss in visual acuity. The prognosis for CRAO is generally poor, with most patients experiencing permanent monocular blindness, and treatment in the acute phase is currently controversial. We searched PubMed for articles published in English investigating the benefi of alteplase in patients with acute CRAO from database inception to Jan 1, 2025, using the following terms: "central retinal artery occlusion" OR "retinal stroke" AND "thrombolysis" OR "alteplase" Key criteria for quality assessment included time to treatment, randomised controlled trials, and sample size. Two trials assessing the efficacy of intravenous or intra arterial alteplase compared with conservative measures or placebo were prematurely terminated due to difficulties in patient enrolment. Neither trial found a signifi ant benefi of alteplase, but reported an increased risk of severe bleeding events. Notably, these studies involved treatment delays of more than 12 h. Subsequent meta analyses suggest that intravenous thrombolysis administered within a 4 5 h window from symptom onset could improve visual acuity outcomes, with functional visual recovery (defi ed as Snellen ≥20/100) reported in over a third of patients, compared with conservative management. In 2021, the American Heart Association, in collaboration with the North American Neuro Ophthalmology Society, published a scienti statement recommending early screening for patients with acute CRAO and considering intravenous alteplase as a potential treatment option.

Added value of this study

The THEIA trial is the fi st published phase 3 randomised controlled trial directly comparing the efficacy and safety of intravenous alteplase with oral aspirin in patients with acute CRAO treated within 4 5 h of vision loss. This study did not find a signifi ant benefit of intravenous alteplase over oral aspirin in improving visual acuity when administered within the first 4 5 h of symptom onset. However, an increased (albeit non signifi ant) rate of improvement in visual acuity was observed among patients in the alteplase group. Our fi dings support the feasibility of treating patients with CRAO within 4 5 h of symptom onset and indicate that intravenous thrombolysis does not signifi antly increase the risk of intracranial and extracranial bleeding.

Implications of all the available evidence

Given that the THEIA trial was underpowered to detect a significant difference in improvement to visual acuity at 1 month between both treatment groups, investigation of intravenous thrombolysis administration within the first 4 5 h of symptom onset in other phase 3 trials is warranted. Two phase 3 randomised controlled trials, the TenCRAOS study (NCT04526951) and the REVISION trial (NCT04965038), are currently underway to establish whether intravenous thrombolysis administration within the first 4 5 h of symptom onset improves the prognosis of visual acuity loss in patients with acute CRAO. Subsequent individual participant level meta analyses should provide conclusive level 1 evidence for the use of early intravenous thrombolysis for this patient group.

Among older adults, the annual incidence of acute non arteritic CRAO ranges from 2 to 10 cases per 100 000 people worldwide.[1] Prognosis is poor; over 90% of patients experience permanent functional loss of visual acuity and the condition carries a high risk of subsequent ischaemic events. To date, no established treatment has shown meaningful improvement in visual outcomes.[1–5]

Intravenous thrombolysis has long been established as a level 1 evidence based therapy for improving functional outcomes in patients with acute ischaemic stroke.[6] Given that acute non arteritic CRAO is a subtype of ischaemic stroke,[7] restoring retinal perfusion through arterial recanalisation is an appealing strategy. Animal studies suggest the retina has a particularly low tolerance to ischaemia, with irreversible damage occurring after 240 min in primate models.[8] A 2007 systematic review of open label studies found that intravenous thrombolysis or local intra arterial thrombolysis improved visual acuity in roughly a third to half of patients with acute CRAO, despite long and variable treatment delays (mean 16 h [range 1 h to 10 days]).[9]

Two randomised controlled trials were subsequently conducted: one compared intra arterial alteplase with conservative treatment[10] and the other compared intravenous alteplase with placebo.[11] Both trials were prematurely terminated due to futility and safety concerns, with symptomatic intracranial haemorrhage reported in 5 2% of patients treated with thrombolysis. Neither trial reached their expected recruitment target (84 of 200 participants[10] and 16 of 50 participants[11]). In both trials, mean time from symptom onset to treatment initiation exceeded 12 h, with only one patient in one trial treated within 4 5 h. However, a time dependent benefit of intravenous thrombolysis was later supported by a meta analysis of these trials and other retrospective studies, showing that 17 (50%) of 34 patients treated within 4 5 h showed an improvement in visual acuity of up to and including 0 7 logarithm of the minimum angle of resolution (LogMAR; Snellen ≥20/100), compared with only 70 (18%) of 396 untreated patients.[5] Further observational data indicated that early administration of intravenous alteplase, when respecting standard contraindications, seemed safe.[12] A 2020 individual participant data meta analysis involving 67 patients treated within 4 5 h found a final improvement in visual acuity of up to and including 0 7 LogMAR (≥20/100) in 25 (37%) of 67 patients, compared with 70 (18%) of

396 untreated controls, with a low incidence of bleeding complications.[13]

As a result, in 2021, the American Heart Association, in collaboration with the North American Neuro-Ophthalmology Society, issued a scientific statement recommending urgent evaluation and suggesting that early intravenous alteplase might be effective for patients with acute non-arteritic CRAO, based on existing literature and meta-analyses.[2] However, to date, no randomised controlled trial has specifically assessed intravenous thrombolysis within the critical 4·5 h window. To address this gap, we aimed to compare the safety and efficacy of intravenous alteplase with oral aspirin administered to adults within 4·5 h of onset of severe vision loss due to acute non-arteritic CRAO.

Methods

Study design

THEIA was a multicentre, double-dummy, patient-blinded, assessor-blinded, randomised, controlled, phase 3 trial conducted across 16 hospitals with stroke units in France (appendix p 64). The study protocol[14] and amendments were approved by the Ile-de-France I Ethics Committee (number 17.00370.014608) and the French National Agency of Safety and Medicinal Device (Agence Nationale de Sécurité du Médicament et des Produits de Santé; EudraCT 2017-002061-22). An independent data and safety monitoring board oversaw the trial and conducted annual safety reviews. This study is registered at ClinicalTrials.gov (NCT03197194) and is completed.

Participants

Eligible patients were adults (aged ≥18 years) presenting with sudden, severe, and persistent monocular vision loss due to suspected non-arteritic acute CRAO, who could receive treatment within 4·5 h of symptom onset. Key inclusion criteria were a diagnosis of acute CRAO confirmed by a trained ophthalmologist based on fundoscopic examination or non-mydriatic retino-photography, showing characteristic signs (eg, diffuse retinal pallor, a macular cherry red spot, attenuation of retinal vessels, or visible arteriolar emboli) in association with an ipsilateral relative afferent pupillary defect, after exclusion of other causes of acute painless monocular vision loss; visual acuity of more than 1·3 LogMAR (Snellen 20/400); absence of clinical or laboratory evidence of giant cell arteritis; and no clinical or radiological signs of stroke in the past 3 months, except for asymptomatic punctate or small lesions on diffusion-weighted imaging. Clinical examination and brain imaging (CT scan or MRI) were required for inclusion. Before randomisation, eligible patients were assessed by a stroke physician to confirm all criteria were met and to authorise study enrolment and treatment. Study treatment had to be initiated by a trained and experienced stroke neurologist within 4·5 h of symptom onset, with a maximum inaccuracy of 15 min to account for the emergency context. Key exclusion criteria included minor visual acuity deficits or rapid improvement before treatment initiation; unknown or uncertain time of symptom onset; isolated branch retinal artery occlusion without clinically significant vision loss; CRAO with foveal sparing due to a cilioretinal artery (ie, CRAO without foveal ischaemia); and current use of anticoagulant medication.

A full list of inclusion and exclusion criteria is available in the appendix (p 68). Data on sex were collected from medical records. All patients provided written informed consent before enrolment, as approved by the ethics committee.

Randomisation and masking

Patients were randomly assigned (1:1) to receive either intravenous alteplase (alteplase group) or oral aspirin (aspirin group) within 4·5 h of onset of visual loss. Randomisation was performed with Ennov software,[15] connected to a dedicated website, based on a pre-established randomisation list created at the coordinating centre before the first participant was included. The list was generated by a methodologist (AG) who was not involved in determining patient eligibility or outcome assessment. Randomisation was stratified by centre for logistical purposes.

Due to differences in appearance between alteplase and its placebo (alteplase required reconstitution, but the placebo did not), the pharmacist, nurses administering treatments, and treating neurologists were aware of treatment allocation. These individuals were not otherwise involved in the trial. Patients; outcome assessors, including clinicians (eg, neurologists and ophthalmologists) and paramedics (eg, orthoptists); and the sponsor were masked to treatment allocation. Other physicians and nurses in the stroke unit were also masked to treatment allocation. A double-dummy approach was implemented to ensure masking. Patients in the alteplase group received oral placebo, whereas those in the aspirin group received a saline infusion as placebo. Intravenous alteplase and its saline placebo were administered by use of the same procedure, and aspirin and placebo tablets were matched in appearance and number. Study investigators and the statistician analysing the data remained masked to group assignment until unmasking at database lock (June 24, 2024). The success of masking procedures was not formally assessed.

Procedures

Patients in the alteplase group received intravenous alteplase at the recommended stroke dose of 0·9 mg/kg of bodyweight (maximum dose 90·0 mg), with 10% of the dose administered as a bolus and the remainder infused over 1 h. These participants also received one oral dose of placebo. In the aspirin group, patients were given a 300 mg oral dose of aspirin and an intravenous saline

placebo (10 mL of saline in a syringe administered over 1 min, followed by 50 mL as an infusion over 1 h). All other treatments followed standard care protocols for acute ischaemic stroke. Anticoagulants, additional thrombolytic agents, and antiplatelet drugs were not permitted during the first 24 h after study treatment (with the exception of the assigned investigational product), but could be started thereafter at the discretion of the local team, guided by the results of initial investigations into the mechanism of CRAO. All patients received standard stroke unit care, which included investigations to identify the cause of CRAO and secondary prevention measures based on European Stroke Organisation guidelines.[16]

Scheduled study visits occurred at day 1, day 7 (within 2 days of this date), 1 month (within 7 days of this date), and 3 months (within 7 days of this date) after randomisation. At the first visit, patients underwent laboratory tests, including assessments of haemostasis, blood chemistry, inflammatory markers, and pregnancy tests for women of reproductive age. Brain imaging (CT or MRI) was conducted at baseline (before inclusion) and at day 1. Neurological evaluations, including National Institutes of Health Stroke Scale (NIHSS) score, were performed at each visit. Visual acuity was assessed at each visit with the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, positioned 4 m from the patient (or 1 m if needed). ETDRS scores were recorded in LogMAR, where LogMAR 0 corresponds to normal vision (Snellen 20/20), with higher values indicating worse vision. For patients unable to read any letters on the ETDRS chart (ie, off-chart patients), with visual acuity worse than 1·7 LogMAR (Snellen 20/1000), semi-quantitative measures were used. These measures, assessed at a distance of 30 cm, included counting fingers, hand motion, light perception, and no light perception. Each measure was assigned a LogMAR value based on the Freiburg Visual Acuity Test: counting fingers LogMAR + 2·01, hand motion LogMAR + 2·35, light perception LogMAR + 2·65, and no light perception LogMAR + 2·91.[17] The corresponding visual acuity equivalences from LogMAR to Snellen values and semi-quantitative measures for patients unable to read any letters on the ETDRS chart are presented in appendix (p 70).

On day 1, patients underwent an ophthalmological examination, including visual function testing. A more comprehensive ophthalmological evaluation was performed at day 7 (or discharge), 1 month, and 3 months. This evaluation included visual function testing, ophthalmoscopy or non-mydriatic retinophotography, visual field assessments, and slit-lamp iris examination to monitor for neovascular complications starting at 1 month. Neurological examinations were conducted at day 1 (including NIHSS score), day 7, and 3 months. Follow-up brain imaging was performed on day 1 (20–36 h) to detect any intracranial haemorrhage. The neurological assessment at 3 months focused on classifying the ischaemic event by use of Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification,[18] assessing global disability by use of the modified Rankin Scale (mRS), and evaluating vision-related quality of life with the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25; version 2000).[19] The mRS score ranges from 0 (no disability) to 6 (death).[20] The NEI-VFQ-25 assesses quality of life related to visual function, with higher scores indicating better functioning, and each item is converted to a 0–100 scale.

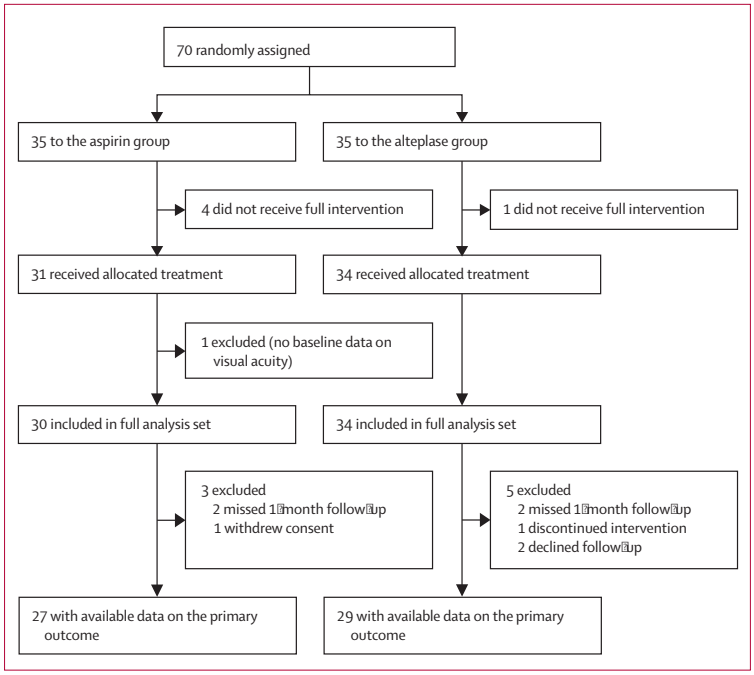

Figure 1: **Trial profile**

Outcomes

The primary outcome was improvement in visual acuity from baseline to 1 month, defined as a gain of at least three Snellen lines (15 letters) on the ETDRS chart, equivalent to an improvement of at least 0·3 LogMAR. For patients with visual acuity corresponding to counting fingers, hand motion, light perception, or no light perception, a change between categories was considered to be an improvement of at least 0·3 LogMAR in visual acuity. The primary outcome was locally assessed.

We assessed several secondary efficacy outcomes. First, we evaluated the proportion of patients who exceeded the threshold for monocular blindness at 1 month, defined as visual acuity of up to and including 1·3 LogMAR (Snellen 20/400) according to WHO's revised visual impairment categories.[21] Second, we assessed the proportion of patients with functional visual recovery allowing reading at 1 month, defined as visual acuity of up to and including

0·5 LogMAR (Snellen 20/63). Third, we evaluated the effect of treatments on visual field at 3 months, particularly focusing on mean visual field deficit, with more negative values indicating a greater deficit, and the foveal threshold, where higher values indicate better vision. Fourth, we considered the change in visual acuity from baseline to any follow-up visit, from day 1 to 3 months. Finally, we assessed the effect of time to treatment on visual acuity progression, along with the effect of treatment on global disability and vision-related quality of life at 3 months, measured with the mRS and the NEI-VFQ-25.

Post-hoc analyses focused on the proportion of patients able to read the ETDRS chart with visual acuity of up to 1·7 LogMAR (ie, on-chart patients), as well as improvements in visual acuity from baseline to 1 month (ie, difference in visual acuity) in each group. Additionally, we analysed the association between improvement in visual acuity at 1 month and time to treatment administration in each group.

All serious adverse events, particularly any intracranial haemorrhage or extracranial bleeding related to study treatment, were reported to the data safety and monitoring board. Symptomatic intracranial haemorrhage was defined according to criteria used in the ECASS II study.[22]

Statistical analysis

Based on previous studies, we hypothesised that an improvement of 0·3 LogMAR (a gain of three lines on the ETDRS chart or one category for patients unable to read any letters) would occur in 10% of patients in the aspirin group and 40% in the alteplase group.[5,9,11] With a target power of 80%, an alpha level of 5%, and an estimated dropout rate of 10%, a total of 70 patients was required. The significance level for all statistical tests was set at 5%.

For continuous variables, summary statistics included number (n) and mean (SD) values. For categorical variables, frequency and percentage (n [%]) were reported. The primary outcome was analysed with a generalised linear mixed model with a logit link function for repeated measures. The model accounted for the fixed effects of treatment, visit (baseline, day 1, day 7, 1 month, and 3 months), and the interaction between treatment group and visit. Random effects included a participant-specific intercept and slope to account for variation in treatment response between individuals. Estimation was performed with maximum likelihood by use of the Laplace approximation. Model diagnostics, including singularity and final gradient checks, confirmed model stability. Given that the main analysis was based on a longitudinal model, no data imputation was performed.[23,24] Treatment effects at the 1-month follow-up visit were reported as adjusted odds ratios (ORs) and 95% CIs for categorical outcomes, derived from the generalised linear mixed model.

Regarding secondary outcomes, the rate of participants with no monocular blindness at 1 month and change in visual acuity over time were analysed with the same generalised linear mixed model for repeated measures as the primary endpoint. Due to small sample sizes and convergence issues, some tests were adapted. The rates of functional visual recovery at 1 month (≤0·5 LogMAR) were compared with Fisher's exact test; global disability (mRS) was analysed with the Chi-squared test. The effect of time to treatment administration on visual acuity progression, categorised as 0·0–3·0 h, 3·0–4·5 h, or 4·5–5·0 h, was tested with the Cochran–Mantel–Haenszel

	Total (n=70)	Aspirin group (n=35)	Alteplase group (n=35)
Age, years	70·2 (9·4)	71·8 (9·0)	68·6 (9·6)
Sex			
Female	25 (36%)	8 (23%)	17 (49%)
Male	45 (64%)	27 (77%)	18 (51%)
Cardiovascular risk factors and comorbidities			
Arterial hypertension	51 (73%)	28 (80%)	23 (66%)
Hypercholesterolaemia	32 (46%)	23 (66%)	9 (26%)
Diabetes	14 (20%)	10 (29%)	4 (11%)
Current smoker	20 (29%)	10 (29%)	10 (29%)
Data missing	1 (1%)	0	1 (3%)
BMI >30 kg/m²	18 (26%)	8 (23%)	10 (29%)
Sleep apnoea	4 (6%)	1 (3%)	3 (9%)
Coronary artery disease	16 (23%)	7 (20%)	9 (26%)
Atrial fibrillation	3 (4%)	1 (3%)	2 (6%)
Stroke or transient ischaemic attack	9 (13%)	6 (17%)	3 (9%)
Current use of antiplatelet therapy at study entry	18 (26%)	11 (31%)	7 (20%)
Ophthalmological data			
Visual acuity at presentation, LogMAR*	2·4 (0·3)	2·3 (0·3)	2·4 (0·3)
Data missing	1 (1%)	1 (3%)	0
Off-chart visual acuity at presentation†	65 (94%)	31 (91%)	34 (97%)
Funduscopic data†			
Normal fundoscopy†	1 (1%)	1 (3%)	0
Retinal whitening	51 (76%)	27 (82%)	24 (71%)
Cherry red spot	47 (70%)	23 (70%)	24 (71%)
Attenuated arteries	45 (67%)	20 (61%)	25 (74%)
Slow segmental blood flow	16 (24%)	9 (27%)	7 (21%)
Arteriolar embolism	16 (24%)	10 (29%)	6 (18%)
Data missing	3 (3%)	2 (3%)	1 (3%)
Biological data			
Glucose, mmol/L	6·6 (2·0)	6·6 (1·6)	6·7 (2·5)
Data missing	6 (9%)	1 (3%)	5 (14%)
HbA1c, %	6·0 (0·9)	6·0 (0·7)	5·9 (1·1)
Data missing	10 (14%)	6 (17%)	4 (11%)
LDL, g/dL	1·2 (0·5)	1·3 (0·6)	1·1 (0·4)
Data missing	9 (13%)	4 (11%)	5 (14%)
Platelet count, G/L	247·0 (62·1)	239·3 (54·1)	254·7 (69·1)
C-reactive protein ≤5 mg/L	52 (77·6)	26 (78·8)	26 (76·5)
Data missing	3 (4%)	2 (6%)	1 (3%)

(Table 1 continues on next page)

	Total (n=70)	Aspirin group (n=35)	Alteplase group (n=35)
(Continued from previous page)			
Haemodynamic constants at admission			
Systolic blood pressure, mm Hg	154·4 (22·3)	156·8 (18·1)	152·0 (25·9)
Diastolic blood pressure, mm Hg	79·5 (15·2)	80·4 (15·7)	78·6 (14·9)
Data missing	18 (26%)	9 (26%)	9 (26%)
Treatment window			
Onset-to-treatment time, min	232·4 (43·6)	231·7 (43·8)	233·0 (44·0)
Onset-to-treatment time category, h			
≤3·0	8 (12%)	4 (13%)	4 (11%)
>3·0 and ≤4·5	53 (79%)	24 (75%)	29 (83%)
>4·5 and ≤5·0	6 (9%)	4 (13%)	2 (6%)
Data missing	3 (4%)	3 (9%)	0

Data are n (%) or mean (SD). LogMAR=logarithm of the minimum angle of resolution. *LogMAR visual acuity values ranged from 0·0 to 2·9, with higher scores indicating poorer vision. Off-chart visual acuity ranged from 2·0 to 2·9 LogMAR (appendix p 70). †Off-chart refers to patients who were unable to read any letters on the Early Treatment Diabetic Retinopathy Study chart. ‡Diagnosis was confirmed at subsequent ophthalmological visits based on the appearance of retinal oedema.

Table 1: **Baseline participant characteristics**

test. The effect of treatment on visual field at 3 months and quality of life related to vision (NEI-VFQ-25) were compared with the Mann-Whitney-Wilcoxon test.

Adverse events were analysed with descriptive statistics, with the frequency of participants experiencing at least one adverse event and the number of events categorised by severity and relationship to treatment. Given that randomisation was stratified by centre due to a small study population, centre effects were not adjusted in the analysis.[25]

The primary analysis population was the full analysis set, defined as all patients who received full intervention (bolus, infusion, and tablet) and had undergone a visual acuity assessment at baseline. The generalised linear mixed model for repeated measures used to analyse the primary endpoint incorporated all measurement occasions per individual, including participants with missing data. A per-protocol population analysis was also performed alongside an intention-to-treat analysis, which involved multiple imputation for missing data in the post-hoc analyses. The per-protocol population was defined during data review before unmasking and included all patients in the full analysis set who had no major protocol deviations (eg, treatment delays exceeding 4 h 35 min or unmet inclusion criteria), did not withdraw consent, and had available primary outcome measurements at the 1-month follow-up visit. The same statistical model as the main analysis was applied. The intention-to-treat population included all randomly assigned patients. Missing data were handled with multiple imputation, including variables such as treatment group, baseline visual acuity, baseline participant characteristics significantly associated with the primary endpoint, the presence of missing data on the primary endpoint, and treatment group. The number of imputations corresponded to the percentage of missing data. Analyses were conducted with a generalised linear model to assess the association between the primary outcome and treatment group. All patients who were randomly assigned were included in the safety analysis.

For additional post-hoc analyses, the change in visual acuity from baseline to 1 month (difference in visual acuity) in each group was assessed with a paired Student's *t* test. The proportion of patients able to read the ETDRS chart (with visual acuity <1·7 LogMAR) was assessed with a Chi squared test. Simple linear regressions were used to assess the association between improvement in visual acuity at 1 month and time to treatment initiation in each group. All statistical analyses were performed with R (version 4.4.1; lme4 package), with superiority testing performed at a two-sided alpha level of 0·05.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The funder was given the opportunity to review the manuscript for medical and scientific accuracy given that it relates to Boehringer Ingelheim substances, as well as intellectual property considerations.

Results

Between June 8, 2018, and Oct 2, 2023, 70 patients were enrolled across 16 centres, of whom 35 (50%) were randomly assigned to the alteplase group and 35 (50%) to the aspirin group. In total, 65 (93%) patients received the allocated treatment: 34 (97%) in the alteplase group and 31 (89%) in the aspirin group. The number of participants enrolled at each centre is provided in the appendix (p 64). Six (9%) patients were excluded from the full analysis set: one (1%) in the alteplase group did not receive the placebo; three (4%) in the aspirin group received alteplase instead of aspirin; one (1%) in the aspirin group discontinued the full intervention after being diagnosed with giant cell arteritis and initiating high-dose corticosteroids; and one (1%) in the aspirin group had missing baseline data on visual acuity. Consequently, 64 (91%) patients were included in the full analysis set (34 in the alteplase group and 30 in the aspirin group) and all 70 participants were included in the safety analysis (figure 1). Primary outcome data were unavailable for eight (12%) patients: four (6%) missed the 1-month follow-up visit (but had an available primary outcome data at the 3-month assessment), one discontinued treatment early due to a serious adverse event, one withdrew consent, and two declined further follow-up. Thus, the primary endpoint was available for 56 (88%) patients.

Mean age of participants at baseline was 70 years (SD 9; table 1). 25 (36%) participants were women and 45 (64%) were men. There were more female participants in the alteplase group than in the aspirin group. Cardiovascular

	Aspirin group (n=30)		Alteplase group (n=34)		Adjusted OR or mean difference (95% CI)	p value
	Number of participants with available data	Mean (SD) or median (IQR)	Number of participants with available data	Mean (SD) or median (IQR)		
Primary outcome						
Visual acuity improvement ≥0·3 L ogMAR at 1 month	13/27 (48%)		19/29 (66%)		1·10 (0·37 to 18·39)	0·95*
Secondary outcomes						
Visual acuity ≤1·3 L ogMAR at 1 month	7/27 (26%)		7/29 (24%)		0·76 (0·21 to 11·33)	0·91*
Visual acuity ≤0·5 LogMAR at 1 month	2/27 (7%)		4/29 (14%)		NA	0·67
Change in visual acuity over time						
1 day	26	−0·26 (0·59)	29	−0·40 (0·60)	1 (reference)	
7 days	26	−0·25 (0·71)	31	−0·38 (0·77)	−0·07 (−0·34 to 0·20)	0·62*
1 month	27	−0·44 (0·70)	29	−0·62 (0·85)	−0·09 (−0·37 to 0·18)	0·51*
3 months	26	−0·40 (0·76)	28	−0·67 (0·95)	−0·19 (−0·46 to 0·09)	0·19*
Effect of CRAO on visual fi d at 3 months						
De fi it, dB	14	−2·59 (3·01 to −1·20)	15	−2·02 (−2·46 to −1·29)		0·35
Foveal threshold, dB	12	0·0 (0·0 to 7·2)	16	6·0 (0·0 to 20·2)		0·17
Patients reaching the primary endpoint according to time to treatment						
Total	25		29			
≤3·0 h	1/3 (33%)		3/3 (100%)			0·35
>3·0 h and ≤4·5 h	9/19 (47%)		14/24 (58%)			
>4·5 h	3/3 (100%)		2/2 (100%)			
Modi fi d Rankin Scale score 0–1 at 3 months	16/28 (57%)		17/24 (71%)			0·46
Mean NEI-VFQ-25 score	24	80·0 (6·65 to 83·7)	23	72·5 (61·2 to 81·4)		0·32
Post-hoc outcomes						
Visual acuity ≤0·7 L ogMAR at 1 month	4/27 (15%)		4/29 (14%)			1·00

Data are n/N (%), mean (SD), or median (IQR), unless otherwise indicated. NA=not available. OR=odds ratio. NEI-VFQ-25=National Eye Institute Visual Function Questionnaire-25. *Analysed with a generalised linear mixed model for repeated measures accounting for treatment, visit (baseline, day 1, day 7, 1 month, and 3 months), and interactions between treatment group and visit as fi ed effects. †Fisher's exact test. ‡Mann-Whitney Wilcoxon test. §Cochran-Mantel-Haenszel test. ¶Chi squared test.

Table 2: **Primary, secondary, and post-hoc outcome measures**

risk factors and comorbidities were common across both groups, but an imbalance in the prevalence of hypercholesterolaemia was noted, which was more frequent in the aspirin group than in the alteplase group (table 1). Mean visual acuity at baseline was 2·4 LogMAR (SD 0·3) in the alteplase group and 2·3 LogMAR (SD 0·3) in the aspirin group, with 65 (94%) of 69 patients with baseline data on visual acuity classi fi d as off-cha rt patients (visual acuity >1·7 LogMAR). A central retinal artery embolus was present at admission in 16 (24%) patients. One (1%) patient with branch retinal artery occlusion, associated with visual acuity of more than 1·3 LogMAR (Snellen 20/400), was also included in the full analysis set.

Mean time from symptom onset to treatment initiation (ie, onset-to-trea tment time) was 232·4 min (SD 43·6). Of the 70 patients, eight (11%) were treated within 3·0 h; 53 (76%) between 3·0 h and 4·5 h; and six (9%) between 4·5 h and 5·0 h (figure 1; appendix p 65). Onset-to-treatment time was missing from three (4%) patients in the aspirin group (time of bolus injection not documented in two and no bolus administration in one). According to TOAST classification, cause of CRAO remained undetermined in 34 (49%) patients overall, while large vessel atherosclerosis was identified in 23 (33%; appendix p 71). Patients with missing data on cause of CRAO (six [17%] in the alteplase group and two [6%] in the aspirin group) were categorised as undetermined.

In the full analysis set, 19 (66%) of 29 patients in the alteplase group and 13 (48%) of 27 patients in the aspirin group showed an improvement in visual acuity of at least 0·3 LogMAR at 1 month (unadjusted risk difference 17·4 [95% CI −11·8 to 46·5]; adjusted OR 1·10 [95% CI 0·07 to 18·39]; p=0·95; table 2). Per-protocol and

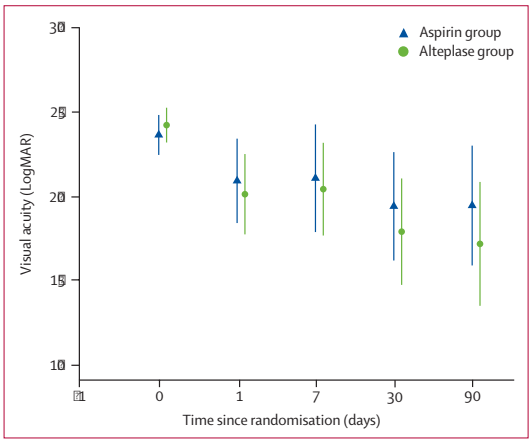

Figure 2: **Change in visual acuity over time**
Visual acuity is shown on a LogMAR scale, ranging from 1·0 (Snellen equivalent 20/200) to 2·9 (no light perception). Mean values are shown for each visit, with error bars representing SD. LogMAR=logarithm of the minimum angle of resolution.

	Aspirin group (n=35)	Alteplase group (n=35)
Related to study treatment		
Any intracranial haemorrhage	0	1 (3%)*
Symptomatic intracranial haemorrhage	0	0
Fatal intracranial haemorrhage	0	0
Retinal haemorrhage	0	0
Major extracranial bleeding	0	0
Hypersensitivity reaction	0	0
After acute phase		
Serious adverse event	6 (17%)†	5 (14%)†
Retinal neovascularisation	1 (3%)‡	2 (6%)‡
Death	0	0

Data are n (%). One bleeding complication was related to study treatment and 14 serious adverse events occurred in 11 patients. *Asymptomatic intracranial haemorrhage detected on CT scan on day 1. †Carotid endarterectomy in five patients and pyelonephritis in one patient. ‡Carotid endarterectomy in one patient, neoplasia in two patients, manic episode in one patient with bipolar disorder, and melena related to colon polyps at 30 days requiring one red blood cell transfusion in one patient. ‡Rubeosis iridis detected at 1 month in two patients and vitreous haemorrhage at 3 months in one patient.

Table 3: **Serious adverse events related to study treatment and occurring after the acute phase of central retinal artery occlusion**

intention-to-treat analyses showed similar non-significant results (appendix pp 72–73). At 1 month, seven (24%) patients in the alteplase group and seven (26%) in the aspirin group had a visual acuity of less than or equal to 1·3 LogMAR (Snellen ≥20/400; adjusted OR 0·76 [95% CI 0·01 to 113·33]; p=0·91). An improvement in visual acuity of less than or equal to 0·5 LogMAR (Snellen ≥20/63) was observed in four (14%) patients in the alteplase group and two (7%) patients in the aspirin group (p=0·67) at 1 month. Both groups showed an initial improvement in visual acuity of approximately three Snellen lines at day 1, plateauing between 1 and 3 months (figure 2). Final improvement at 3 months was 6·7 lines (mean visual acuity 0·67 [SD 0·95]) in the alteplase group and 4·0 lines (0·4 [0·76]) in the aspirin group (adjusted OR 0·19 [95% CI 0·46 to 0·09]; p=0·19; table 2). No significant association was found between onset-to-treatment time and visual acuity recovery in the alteplase group.

In the post-hoc analysis, a significant association between onset-to-treatment time and improvement in visual acuity at 1 month was observed in the aspirin group (p=0·01 4; appendix p 66). Mean improvement in visual acuity was significant in both treatment groups: 0·62 LogMAR (95% CI 0·29–0·94; p<0·0001) in the alteplase group and 0·44 LogMAR (0·16–0·72; p=0·0032) in the aspirin group (appendix p 74). At 1 month, 14 (48%) patients in the alteplase group and seven (26%) in the aspirin group were able to read the ETDRS chart, with visual acuity up to 1·7 LogMAR; however, this difference was not significant (p=0·15; appendix p 67).

Among the 54 patients who completed the follow-up visit at 3 months, 29 (54%) had sufficient visual acuity to undergo visual field testing. Mean deficit and foveal threshold values were slightly better in the alteplase group but did not differ significantly from the aspirin group: median deficit was 20·2 dB in the alteplase group versus 25·9 dB in the aspirin group (p=0·35) and median foveal threshold was 6·0 versus 0·0 (p=0·17; table 2). No significant difference was observed in global disability outcomes: a mRS score of 0–1 at 3 months was observed in 17 (71%) patients in the alteplase group and 16 (57%) patients in the aspirin group (p=0·46; table 2). Vision-related quality of life at 3 months, measured by the NEI-VFQ-25, also showed no significant difference between groups (median global score 72·5/1 00 in the alteplase group and 80·0/1 00 in the aspirin group; p=0·32).

No symptomatic haemorrhages or major bleeding related to study treatment were reported. An asymptomatic 15 mm right parietal haematoma was detected in one patient in the alteplase group on CT scan on day 1, with no lesion on initial MRI (table 3). Another patient with a history of bipolar disorder experienced a manic episode after administration of alteplase. The most common serious adverse event was extended hospitalisation for carotid endarterectomy in six patients. One patient required red blood cell transfusion due to gastrointestinal bleeding, likely linked to aspirin use for secondary cardiovascular prevention. Neovascular complications occurred in three (4%) of 70 patients, including one case of intravitreal haemorrhage at 3-month follow-up.

Discussion

The THEIA trial provides valuable insights into the management of patients with acute non-arteritic CRAO,

comparing the safety and efficacy of intravenous alteplase with oral aspirin. When administered within 4·5 h of symptom onset, intravenous alteplase did not result in a significant improvement in visual acuity compared with aspirin. Although both groups showed mean improvements in visual acuity, visual acuity remained above 1·3 LogMAR (Snellen 20/400) in most patients, indicating persistent monocular blindness. From a functional perspective, beyond the standard criterion of a three-line gain in visual acuity, only four (14%) patients in the alteplase group and two (7%) in the aspirin group had an improvement in visual acuity of up to and including 0·5 LogMAR (Snellen 20/63), representing a meaningful recovery from severe vision impairment or blindness to a level of functional vision.

Previous meta-analyses of individual participant-level data have reported visual improvements of at least 0·3 LogMAR in 56–74% of patients treated with intravenous thrombolysis within 4·5 h,[13,26] compared with 36% among untreated patients.[13] Additionally, a final improvement in visual acuity of up to and including 0·7 LogMAR (Snellen ≥20/100) was observed in 37% of treated patients, whereas the spontaneous recovery rate among those who had not received treatment was 18%.[13]

The outcome measure of an improvement in visual acuity of at least 0·3 LogMAR might be less sensitive than more clinically relevant criteria, such as a final improvement in visual acuity of up to and including 0·7 LogMAR (Snellen ≥20/100), which better reflects functional visual recovery. This measure was selected for the THEIA trial because it had been used in previous randomised controlled trials[10,11] and has since been used in cohort studies.[13,27] The proportion of patients with a final improvement in visual acuity of at least 0·7 LogMAR (Snellen ≥20/100) in the THEIA trial, along with the two other published randomised controlled trials,[10,11] contrasts with data from cohort studies and patient-level meta-analyses, which report a functional recovery ranging from 25% to 50%.[5,13,26,28] This discrepancy might be attributed to biases inherent in non-randomised studies, such as publication, selection, and heterogeneity biases. By contrast, the current study provides robust, prospective, and randomised data, minimising such biases and offering a more accurate depiction of treatment outcomes for patients with CRAO.

The administration of intravenous alteplase within 4·5 h of CRAO onset seems to be safe. Unlike previous randomised controlled trials, no symptomatic intracranial haemorrhages were reported, and only one asymptomatic intracranial haemorrhage was identified incidentally on CT scan 24 h after onset. This prevalence of bleeding is much lower than that typically observed in patients with ischaemic stroke.[6] This observation likely reflects the absence or presence of only small or punctiform-associated ischaemic brain lesions. One patient with bipolar disorder experienced a manic episode shortly after receiving intravenous thrombolysis, although this is not a typical side-effect of alteplase. Other serious adverse events were primarily related to atherosclerotic stenosis, requiring endarterectomy, or delayed gastrointestinal bleeding associated with aspirin. Additionally, 4% of patients developed neovascularisation between the 1-month and 3-month follow-up visits, with one case of associated intraocular haemorrhage. This prevalence is slightly lower than the 6·1–16% typically observed in patients with CRAO;[29,30] however, an increased prevalence of neovascularisation beyond 3 months of follow-up cannot be excluded. This difference could potentially be explained by an increased rate of central retinal artery recanalisation due to antithrombotic therapy, although this hypothesis requires further investigation.

Our study has notable limitations. The study is likely to be underpowered to detect a significant difference between both groups in improvement in visual acuity of at least 0·3 LogMAR at 1-month follow-up. Sample size calculations were based on a 10% improvement hypothesis in the aspirin group, derived from available data at the time, including open-label studies, one randomised controlled trial on intravenous thrombolysis, and the first patient-level meta-analysis.[5,9,11] The unexpectedly high improvement among 48% patients in the aspirin group raises questions about the benefit of administering oral aspirin within 4·5 h of vision loss in patients with acute CRAO. Aspirin was chosen over placebo to avoid delaying antiplatelet therapy, given that at least a third of patients with acute CRAO show signs of concomitant acute cerebral ischaemia on diffusion-weighted imaging MRI.[31] However, no data exist on the efficacy of administering aspirin within a 4·5 h window in patients with either acute CRAO or acute ischaemic stroke. Furthermore, the impact of intensive stroke unit care on visual outcomes should not be underestimated. The structured and timely care in these settings might independently contribute to improved outcomes, warranting further exploration. There was an imbalance between treatment groups regarding participant sex and prevalence of hypercholesterolaemia at baseline; however, no evidence exists on the effects of these factors on the efficacy of alteplase and are, therefore, unlikely to have influenced the trial's results or conclusions. The study's double-dummy design, involving both oral aspirin or placebo and intravenous alteplase or saline, prevented the masking of treating neurologists and nurses, introducing potential behavioural bias, as evidenced by three patients in the aspirin group receiving alteplase. Additionally, the study faced challenges due to a smaller than expected sample size, with a dropout rate of 20%, which was higher than the anticipated 10%. Recruitment was hindered by the COVID-19 pandemic, the low incidence of CRAO, and the narrow therapeutic window. These challenges underscore the need for innovative strategies and partnerships to overcome such barriers, including the implementation of early recognition, triage, and management of CRAO through outreach campaigns;

the development of telemedicine and tele-expertise integrating fundus photography; the use of imaging techniques of retinal viability (eg, optical coherence tomography) to extend this therapeutic window in selected patients; the use of tenecteplase instead of alteplase; and the fostering of close collaboration among stroke teams, ophthalmologists (in both private and public settings), and emergency departments.

The low proportion of patients with functional recovery in both treatment groups raises questions about retinal ischaemic tolerance, with irreversible damage potentially occurring much earlier than previously thought.[8] Although no clear relationship between onset-to-treatment time and improvement in visual acuity was observed, only a few patients were treated within a 3–0 h window. The time threshold for permanent retinal ischaemia might have been overestimated;[1] complete CRAO could lead to rapid and irreversible retinal ganglion cell death within as little as 15 min.[32] These considerations highlight the need for further research to define the precise time limits for effective intervention in this patient group.

Although our findings differ from those of previous non-randomised studies and meta-analyses, they suggest that intravenous alteplase could improve visual outcomes compared with aspirin among patients with acute CRAO, with fewer patients in the alteplase group experiencing persistent severe visual impairment and no major safety concerns related to alteplase. Given the likely limited statistical power of our study, ongoing trials such as the TenCRAOS study (NCT04526951) and the large-scale REVISION trial (NCT04965038) are expected to provide more definitive evidence. A planned individual participant data meta-analysis might also help to define the role of thrombolysis with intravenous alteplase in the management of patients with acute CRAO.

In conclusion, intravenous alteplase administered within 4–5 h of symptom onset was not associated with a significant improvement in visual acuity compared with aspirin in patients with acute CRAO, despite a higher rate of improvement observed among those in the alteplase group. However, the non-significant difference might be due to the study being underpowered. Although no safety concerns related to alteplase were identified, the overall modest recovery rates underscore the need for potentially even earlier treatment and improvement in patient selection strategies.

Contributors

Data collection was carried out by the participating sites, with trial coordination led by the University Hospital of Nantes. CP, MO, CV, IM, JP, DS, MG, GR, GG, CU, GM, EM, SA, MB, SM, LM, TR, LC, SGD, PL, and BG were involved in investigation, data collection, validation, and manuscript review. CP, LB, PL, and BG conceptualised the study, validated and interpreted data, wrote the original draft, and revised the manuscript. CP drafted the original manuscript. AG was responsible for data curation, formal analysis, data interpretation, and drafting and revising the manuscript. CP, AG, LB, PL, and BG participated in data review meetings, accessed and verified the underlying data, and took responsibility for the decision to submit the manuscript. Other authors could access parts of the underlying data upon a well founded request. LB contributed to funding acquisition. BG supervised the study as coordinator. All authors had final responsibility for the decision to submit for publication.

Declaration of interests

LC reports receipt of grants from the French Ministry of Health and honoraria from Bristol-Myers Squibb and Pfizer. EM reports receipt of honoraria from Lundbeck, Medtronic, Teva, Pfizer, and Novartis. All other authors declare no competing interests.

Data sharing

The aggregated data analysed during the trial are available for scientific review upon reasonable request to the corresponding author. Personal participant data, which are under the responsibility of the sponsor, will be accessible for scientific review only under conditions defined by the EU General Data Protection Regulation (GDPR). A data transfer agreement will be signed with the sponsor, specifying the scope of data transfer (as required by GDPR) and including an obligation to use the data solely for scientific review purposes and to prohibit disclosure to third parties.

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