ORIGINAL ARTICLE

A Randomized Trial of Tenecteplase in Acute Central Retinal Artery Occlusion

S.J. Ryan,[1-3] .K. J rstad,[2,4] M. Skjelland,[1,2] M. Pesonen,[5] C.Z. Simonsen,[6] T. Bek,[7] R.A. Blauenfeldt,[6] P. Ij s,[8,9] A. Laitinen,[10] A. Khanevski,[11] J. Krohn,[12,13] E. R dahl,[12,13] R. Lemmens,[14] J. Demeestere,[14,15] C. Cassiman,[16] I. Nakstad,[17] K. Evensen,[17] T. Sandell,[18] S. Hamann,[19,20] T.C. Truelsen,[21] L.M. Christensen,[20,22] S. Rosenbaum,[22] V. Matijošaitis,[23,24] R. Žemaitienė,[24,25] H. Ellekj r,[26,27] E. Almaas,[28] D. Austeng,[27,28] M.V. Mazya,[29,30] F. Tra sk,[31] P. Ylikotila,[32,33] U. Salmi,[34] K.N. Jenssen,[35] H. Lisether,[35] C. Breivik,[36] K. Devik,[37] L.-M.E. Honningsv g,[38] J. Valaikienė,[39] A. Cimbalas,[40,41] V.N. Malmberg,[42] E. Anderson,[43] A. Roy,[1] T.H. Skatt r,[1,2,44] K.L. Kraglund,[1] C. Kefaloykos,[1] I.C. Olsen,[45] P. Vanacker,[46-48] D. Strbian,[8] M.C. Moe,[2,4] and A.H. Aamodt,[1,26,49] for the TenCRAOS Investigators*

ABSTRACT

BACKGROUND

Central retinal artery occlusion can result in permanent vision loss. Effective treatment is lacking.

METHODS

We conducted a phase 3, double-blind, double-dummy, randomized, controlled trial involving adults with acute, nonarteritic central retinal artery occlusion who had symptom onset within 4.5 hours before treatment. Patients were assigned, in a 1:1 ratio, to receive intravenous tenecteplase (at a dose of 0.25 mg per kilogram of body weight) and oral placebo or intravenous placebo and oral aspirin (at a dose of 300 mg). The primary end point was vision recovery, defined as a best corrected visual acuity (BCVA) in the affected eye at 30 days of up to 0.7 logMAR (logarithm of the minimum angle of resolution; equivalent to ≥20/100). Key secondary visual end points were a BCVA of up to 0.5 logMAR (equivalent to ≥20/63), mean improvement in BCVA, and perimetry score at 30 days. Key safety end points included symptomatic intracranial hemorrhage, major bleeding, and death.

RESULTS

A total of 78 patients at 16 sites in six countries underwent randomization, with 40 assigned to receive tenecteplase and 38 to receive aspirin. At 30 days, 8 patients (20%) in the tenecteplase group and 9 patients (24%) in the aspirin group had vision recovery (risk difference, −3.7 percentage points; 95% confidence interval, −22.0 to 14.7; P=0.69). The outcomes with regard to the secondary visual end points did not differ substantially between the groups. There was a greater incidence of adverse events in the tenecteplase group, including one fatal intracranial hemorrhage.

CONCLUSIONS

Intravenous tenecteplase administered within 4.5 hours after onset of central retinal artery occlusion did not result in significantly greater vision recovery at 30 days than oral aspirin but was associated with serious safety concerns. (Funded by Oslo University Hospital and others; TenCRAOS ClinicalTrials.gov number, NCT04526951; EU Clinical Trials number, 2024-517606-29-00.)

The authors full names, academic degrees, and affiliations are listed at the end of the article. Anne Hege Aamodt can be contacted at a.h.aamodt@medisin.uio.no or at the Department of Neurology, Oslo University Hospital, P.O. Box 4950 Nydalen, 0424 Oslo, Norway.

*A full list of the TenCRAOS Investigators is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2026;394:442-50.
DOI: 10.1056/NEJMoa2508515

CME

Central retinal artery occlusion is an ophthalmologic emergency that carries a high risk of permanent blindness if prompt reperfusion is not achieved.[1] Patients typically present with sudden, painless monocular vision loss and an afferent pupillary defect.[1] Funduscopy usually shows signs of acute retinal ischemia, including retinal pallor, a cherry-red spot, segmented blood flow, and attenuated retinal arteries, although the fundus may appear normal.[2] In the acute phase, optical coherence tomography (OCT) usually shows inner retinal hyperreflectivity and thickening, which can aid in the diagnosis.[3] Central retinal artery occlusion is typically caused by embolism from a carotid plaque or a cardiac thrombus, but it can result from any type of ischemic event.[4]

Although central retinal artery occlusion is considered a cerebrovascular event, key differences between retinal and cerebral vascular anatomy limit the extrapolation of treatment effects from acute ischemic stroke therapies. Despite various attempted interventions, no therapy has been shown to have clear efficacy in the initial treatment of the condition. Although thrombolysis is the cornerstone of treatment in acute ischemic stroke, its role in treating patients with central retinal artery occlusion remains uncertain.

Observational studies suggest a potential benefit of intravenous thrombolysis.[5,6] In contrast, a phase 2, placebo-controlled trial of intravenous alteplase administered within 24 hours after symptom onset showed a negative result but only included 16 patients.[7] In the larger (70 patients) THEIA (Thrombolysis [Alteplase] in Patients with Acute Central Retinal Artery Occlusion) trial, patients who received alteplase within 4.5 hours after symptom onset had improvement in vision acuity by an average of 0.62 logMAR (logarithm of the minimum angle of resolution) as compared with 0.44 logMAR in the aspirin group, a difference that did not reach statistical significance.[8] Intraarterial thrombolysis for central retinal artery occlusion has also been evaluated in the European Assessment Group for Lysis in the Eye (EAGLE) trial, which was discontinued after enrolling 82 of 200 patients owing to similar efficacy in the treatment groups and more adverse events in the fibrinolysis group. The treatment window was broad, with time from symptom onset to intraarterial thrombolysis ranging from 4.75 to 23.43 hours.[9]

Tenecteplase, a genetically modified tissue plasminogen activator, offers pharmacologic advantages over alteplase, including greater fibrin specificity, longer half-life, and ease of administration as a single intravenous bolus.[10] Tenecteplase is an established treatment for myocardial infarction and acute ischemic stroke but has not been evaluated in central retinal artery occlusion.[11-14] Owing to the limited evidence for effective therapy in central retinal artery occlusion, we conducted the Tenecteplase in Central Retinal Artery Occlusion Study (TenCRAOS) to assess the efficacy and safety of intravenous tenecteplase administered within 4.5 hours after symptom onset.[15]

A Quick Take is available at NEJM.org

Methods

Trial Design and Oversight

TenCRAOS was a phase 3, investigator-initiated, double-dummy, double-blind, parallel-group, randomized, controlled trial that assessed treatment with intravenous tenecteplase at a dose of 0.25 mg per kilogram of body weight plus oral placebo as compared with intravenous placebo plus oral aspirin at a dose of 300 mg administered within 4.5 hours after the onset of central retinal artery occlusion symptoms.[15] The trial was coordinated by Oslo University Hospital and sponsored by the Norwegian Program for Clinical Therapy Research in the specialist health service (Klinbeforsk), the South-Eastern Norway Regional Health Authority, and Odd Fellow. The cost of tenecteplase was covered by an unconditional grant from Boehringer Ingelheim Norway. The trial involved close collaboration between ophthalmologic departments and stroke units[15] (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The protocol (available at NEJM.org) was approved by the relevant ethics committees and regulatory authorities in all participating countries. The trial was conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation and the principles of the Declaration of Helsinki.

The trial design, analyses, and data collection were overseen by a steering committee (see the Supplementary Appendix). Site investigators gathered the data, and the trial statistician (the fourth author) conducted the data analyses. The first, second, and last authors wrote the first draft of

the manuscript. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The sponsors had no role in designing the trial; collecting, monitoring, analyzing, or interpreting the data; or drafting the manuscript. There were no confidentiality agreements between the manufacturer and the investigators.

PATIENTS

The target population consisted of patients in whom central retinal artery occlusion had been diagnosed and who had a best corrected visual acuity (BCVA) of 1.0 logMAR or greater in the affected eye, corresponding to a decimal BCVA of 0.1 or lower or a fraction BCVA of 20/200 or less.[16]

Adults who were at least 18 years of age and who had central retinal artery occlusion and could receive trial treatment within 4.5 hours after symptom onset were eligible. All eligible patients were first assessed by an ophthalmologist. The diagnosis was based on a typical history and findings from the acute ophthalmologic examination. Given the 4.5-hour treatment window, arteritic central retinal artery occlusion could not be ruled out by laboratory or imaging studies and was assessed clinically. Patients were then assessed by an acute-stroke team. A neurologic examination (which included assigning a score on the National Institutes of Health Stroke Scale) and neuroimaging (in accordance with the standard stroke protocol at each participating hospital) were performed to rule out a concomitant intracranial vascular event. Written informed consent was obtained from all the patients before administration of the investigational medicinal product; proxy consent was not permitted.

Enrolled patients were admitted and treated in stroke units according to local thrombolysis protocols for ischemic stroke. Etiologic evaluations were conducted in accordance with national guidelines. After discharge, patients were reexamined by an ophthalmologist and a stroke physician as outpatients at a mean (±SD) of 30±5 days.

RANDOMIZATION AND BLINDING

Block randomization with a computer-generated random assignment sequence was used to assign the patients, in a 1:1 ratio, to receive one of two treatment kits intravenous tenecteplase plus dummy comedication (oral placebo capsule) or dummy treatment (intravenous placebo) plus active comedication (oral aspirin capsule at a dose of 300 mg). Each treatment kit was assigned a unique kit number on the basis of the assignment sequence. Once a patient was assigned to a treatment group, trained site personnel authorized the treatment kit with the lowest kit number to be prepared and administered.

END POINTS

The primary end point was a BCVA of 0.7 logMAR or lower in the affected eye at 30 days after treatment, equivalent to a decimal BCVA of at least 0.2 or a fraction BCVA of at least 20/100. Because a BCVA of at least 1.0 logMAR was an inclusion criterion, the primary end point reflected an improvement in on-chart BCVA of at least 0.3 logMAR, equivalent to at least 15 letters on the Early Treatment Diabetic Retinopathy Study chart, a change that is widely regarded as a clinically meaningful improvement in visual acuity.[17]

Key secondary end points were a BCVA of 0.5 logMAR or lower at 30 days (equivalent to a decimal BCVA of at least 0.32 or a fraction BCVA of at least 20/63), a mean change in BCVA from baseline to 30 days, the monocular Esterman perimetry score at 30 days, and scores on the National Institutes of Health Stroke Scale and modified Rankin scale at discharge and at 30 days. Follow-up assessment also included patient-reported end-point measures of health-related quality of life as measured with the EuroQol Group 5-Dimension 5-Level questionnaire and visual function and vision-related quality of life as measured with the National Eye Institute Visual Function Questionnaire at 30 days (see the Supplementary Appendix).

STATISTICAL ANALYSIS

The sample size was estimated on the basis of the 2015 meta-analysis by Schrag et al. and its primary end point, defined as the proportion of patients with central retinal artery occlusion who had an initial BCVA of at least 1.0 logMAR and recovered to 0.7 logMAR or lower at 30 days.[18] Assuming that the percentage of patients who met the primary end-point criterion was 20% in the aspirin group and 50% in the tenecteplase group, we calculated that a total of 78 patients (39 per group) would be required to provide the trial with 80% power to detect a 30 percentage-point risk difference (i.e., the difference in the percentage of patients with vision recovery) at a two-sided significance level of 0.05. No replace-

ments were made for patients lost to follow-up (see the statistical analysis plan, available with the protocol).

The primary analyses were performed in the full analysis population, which included all the patients who had received the assigned trial treatment within 4.5 hours after symptom onset. The primary end point was analyzed with a logistic regression model with the treatment group as a covariate. Because there were multiple trial sites that enrolled only one or two patients, the trial site was not included as a covariate in the primary model, but robustness analyses were performed with adjustment for the trial site as a fixed effect. The treatment effect on the primary end-point event was defined as the population-averaged marginal risk difference in the proportion of patients in the combined groups who had a BCVA of up to 0.7 logMAR; the treatment effect was reported with a 95% confidence interval and P value of the null hypothesis of no treatment effect (two-sided significance level, 0.05) calculated from a logistic-regression model with a marginal-effects package by R software, version 4.5.0 (R Foundation for Statistical Computing). A sensitivity analysis involving all the patients (the intention-to-treat population) was also performed.

For the primary end point, subgroup analyses were conducted on the basis of the time from symptom onset to treatment administration (within 3 hours vs. 3 to 4.5 hours) and the cause of central retinal artery occlusion. We imputed missing values for the primary end point using the results of the 90-day follow-up visit, if available; otherwise, worst-case imputation (>0.7 logMAR) was applied. Sensitivity analyses for the primary end point were performed with complete case data, worst-case imputation, and best-case imputation (≤0.7 logMAR). Because no adjustments were made for multiple testing for secondary analyses, results are reported as point estimates with 95% confidence intervals, from which causal inferences should not be drawn. All statistical analyses were performed using R software.

RESULTS

PATIENTS

Between November 8, 2020, and March 16, 2025, a total of 81 patients were enrolled at 16 sites across six European countries. Patients were randomly assigned to receive either intravenous tenecteplase and oral placebo or intravenous placebo and oral aspirin. Before the trial treatments were unblinded, three patients who had undergone randomization were excluded from the full analysis population because they did not meet the inclusion criteria. One patient received the trial treatment outside the 4.5-hour time window, 1 had a cilioretinal artery supplying the macula that preserved BCVA, and 1 subsequently received a diagnosis of retinal vasospasm rather than central retinal artery occlusion. Unblinding of the trial treatments that had been assigned to the 3 patients revealed that all 3 were in the tenecteplase group. A total of 78 patients were included in the full analysis population 40 in the tenecteplase group and 38 in the aspirin group.

Baseline visual acuity in the affected eye was severely reduced in both groups. In the tenecteplase group, 3 patients (8%) had on-chart visual acuity, 8 (20%) could count fingers, 13 (32%) perceived hand motion, 13 (32%) had light perception, and 3 (8%) had no light perception. In the aspirin group, 2 patients (5%) had on-chart visual acuity, 5 (13%) could count fingers, 18 (47%) perceived hand motion, 9 (24%) had light perception, and 4 (11%) had no light perception.

Other baseline characteristics were similar in the tenecteplase group and the aspirin group, except for carotid artery disease, which was more prevalent in the aspirin group, and diabetes mellitus, which was more prevalent in the tenecteplase group (Table 1). Of the 78 patients included in the analysis, 54 (69%) received the trial medication within 3 hours after symptom onset 31 of 40 patients (78%) in the tenecteplase group and 23 of 38 patients (61%) in the aspirin group.

EFFICACY END POINTS

At 30 days, eight patients (20%) in the tenecteplase group and nine patients (24%) in the aspirin group had a BCVA of 0.7 logMAR or lower (the primary end point) in the affected eye (risk difference, −3.7 percentage points; 95% confidence interval [CI], −22.0 to 14.7; P=0.69) (Table 2 and Fig. S1 in the Supplementary Appendix). Results of the primary end-point analysis in the intention-to-treat population were similar to those in the full analysis population (Table S3).

The secondary BCVA end-point outcomes aligned with that of the primary end point, showing no substantial differences between the treatment groups for any of the assessed end points

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Tenecteplase (N=40)	Aspirin (N=38)
Age yr	71±10	72±9
Female sex no. (%)	15 (38)	12 (32)
Weight kg	82±19	84±19
Mean NIHSS score	0	0
Modified Rankin scale score no. (%)		
0	32 (80)	32 (84)
1	5 (12)	4 (11)
2	3 (8)	2 (5)
Current smoker or history of smoking no. (%)	9 (22)	5 (13)
Hypertension no. (%)	31 (78)	25 (66)
Cardiac valvular disease no. (%)	3 (8)	1 (3)
Heart failure no. (%)	3 (8)	1 (3)
Coronary artery disease no. (%)	10 (25)	6 (16)
Carotid artery disease no. (%)	2 (5)	9 (24)
Atrial fibrillation no. (%)	1 (2)	1 (3)
Diabetes mellitus no. (%)	6 (15)	0
Dyslipidemia no. (%)	24 (60)	19 (50)
Previous transient ischemic attack or stroke no. (%)	4 (10)	4 (11)
Cause no. (%)		
Carotid-artery atherosclerosis	16 (40)	17 (45)
Small-vessel disease	6 (15)	5 (13)
Cardioembolism	3 (8)	2 (5)
Other	5 (12)	1 (3)
Unknown	10 (25)	13 (34)

* Plus minus values are means ±SD.
Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating greater neurologic deficit.
Scores on the modified Rankin scale measure the degree of disability or functional dependence in daily activities, ranging from 0 (no symptoms) to 6 (death).
Carotid-artery atherosclerosis data specifically refer to previously diagnosed carotid artery disease at baseline, as recorded in the case-report forms. The etiologic classification of central retinal artery occlusion (not included here) reflects the final adjudicated cause of the index event, determined post hoc after a full diagnostic workup including carotid imaging.

(Table 2 and Fig. S2). The proportion of patients who had a BCVA of 0.5 logMAR or lower at 30 days was 8 of 40 (20%) in the tenecteplase group and 7 of 38 (18%) in the aspirin group (risk difference, 1.6 percentage points; 95% CI, –15.9 to 19.1). In the subgroup of 54 patients who received treatment within 3 hours after symptom onset, 7 of 31 patients (23%) in the tenecteplase group and 5 of 23 patients (22%) in the aspirin group had a BCVA of 0.7 logMAR or lower (risk difference, 0.8 percentage points; 95% CI, –21.5 to 23.2), and 7 of 31 patients (23%) in the tenecteplase group and 4 of 23 patients (17%) in the aspirin group had a BCVA of 0.5 logMAR or lower at 30 days (risk difference, 5.2 percentage points; 95% CI, –16.2 to 26.6) (Table 2). Furthermore, the mean change in logMAR from baseline to 30 days was –0.73±0.92 in the tenecteplase group and –0.60±0.91 in the aspirin group, results that indicate improvement in BCVA. In addition, there were no substantial between-group differences in visual field as assessed with monocular Esterman perimetry and patient-reported end-point measures at 30 days. The primary end point reflected an improvement in on-chart BCVA of 0.3 logMAR or more. However, some patients had an improvement of 0.3 logMAR despite remaining off-chart for example, improving from counting fingers to perceiving hand motion. When these patients were also included, 25 of 40 patients (62%) in the tenecteplase group and 19 of 38 (50%) in the aspirin group had an improvement in BCVA of at least 0.3 logMAR (Table S4).

SAFETY END POINTS

A total of 30 adverse events among 19 participants were reported in the tenecteplase group, and 19 adverse events among 13 participants were reported in the aspirin group. A similar trend was observed for serious adverse events, with 10 events among 8 patients in the tenecteplase group and 4 events among 4 patients in the aspirin group (Table 3). One serious adverse event that was reported in the tenecteplase group was considered by the investigators and the data and safety monitoring board to be related to the trial medication. This event was fatal, involving ongoing cerebral ischemia that was not apparent clinically or on computed tomography of the head. Multiple intracerebral hemorrhages caused by reperfusion of damaged brain tissue subsequently developed.

DISCUSSION

In this trial, intravenous tenecteplase at a dose of 0.25 mg per kg administered within 4.5 hours after symptom onset did not lead to better visual outcomes than oral aspirin at a dose of 300 mg

Table 2. Efficacy End Points at 30 Days.*

End Point	Tenecteplase (N = 40)	Aspirin (N = 38)	Risk Difference (95% CI)
Primary end point: BCVA of ≤0.7 logMAR no. of patients/total no. (%)	8/40 (20)	9/38 (24)	−0.04 (−0.22 to 0.15)
Secondary end points			
BCVA of ≤0.5 logMAR no. of patients/total no. (%)	8/40 (20)	7/38 (18)	0.02 (−0.16 to 0.19)
Mean change in BCVA from baseline logMAR	−0.73±0.92	−0.60±0.91	−0.12 (−0.53 to 0.28)
Mean number of test points seen on Esterman perimetry no. out of 100	35±36	37±38	−1.71 (−13.37 to 9.96)
Mean NIHSS score at discharge	0.1±0.3	0±0.2	
Mean NIHSS score at 30 days	0.2±0.5	0	
Mean mRs score at discharge	1.3±1.1	1.3±0.8	
Mean mRs score at 30 days	1.4±0.3	1.4±1.0	
Mean EQ-5D-5L index value at 30 days	0.84±0.25	0.87±0.13	
Mean VFQ-25 score at 30 days‖	74.6±20.3	74.1±18.6	
Neovascularization in the affected eye at 30 days no. (%)	1 (2)	1 (3)	
Subgroup treated ≤3 hr after onset no./total no. (%)			
Patients with BCVA of ≤0.7 logMAR	7/31 (23)	5/23 (22)	0.01 (−0.22 to 0.23)
Patients with BCVA of ≤0.5 logMAR	7/31 (23)	4/23 (17)	0.05 (−0.16 to 0.27)

* The percentages in the treatment-group columns have been rounded to the nearest whole number; however, the values in the Risk Difference column are based on the actual values. BCVA denotes best-corrected visual acuity and mRs modified Rankin scale.
The logarithm of the minimum angle of resolution (logMAR) is a linear scale of visual acuity, in which higher values indicate worse vision. Each 0.1 increment represents a one-line change on the five-letters-per-line Early Treatment Diabetic Retinopathy Study visual acuity chart. A logMAR of 0.0 corresponds to 20/20 vision.
The differences and 95% confidence intervals for the secondary end points have not been adjusted for multiplicity.
Monocular Esterman perimetry is a standardized, single-eye variant of the binocular Esterman visual field test. It evaluates the full visual field using suprathreshold stimuli.
The EuroQol 5-Dimension 5-Level (EQ-5D-5L) questionnaire assesses health-related quality of life across five domains. Scores are converted into an index value and range from −0.594 (indicating worst health) to 1.00 (indicating full health).
‖ The National Eye Institute Visual Function Questionnaire (VFQ-25) evaluates vision-related quality of life, with scores ranging from 0 (worst possible function) to 100 (best possible function).

in patients with central retinal artery occlusion. This finding was consistent across all visual efficacy end points, including in patients treated within 3 hours after symptom onset a subgroup that comprised two thirds of the trial population. However, safety concerns emerged, with a higher frequency of serious adverse events in the tenecteplase group, including one incident of fatal intracranial bleeding. Although we concluded that there was no significant difference between the groups, the 95% confidence interval for the primary end point includes a risk difference of up to 14.7 percentage points in favor of tenecteplase. Thus, a modest treatment effect cannot be ruled out; however, the effect may be insufficient to justify the risks of systemic thrombolysis.

The results of our trial are consistent with findings from the French multicenter THEIA trial, which evaluated intravenous alteplase administered within 4.5 hours after symptom onset,[8] as well as those from the EAGLE trial, which investigated intraarterial thrombolysis.[9] Because earlier trials have used longer time windows, uncertainty remained about whether earlier reperfusion treatment within the first few hours after symptom onset might yield better outcomes. With both the THEIA and TenCRAOS trials now completed, there is so far no evidence that intravenous systemic thrombolysis is more effective than aspirin in treating central retinal artery occlusion within 4.5 hours after symptom onset. However, the ongoing REVISION (Early Reperfusion Therapy with Intravenous Alteplase for Recovery of Vision in Acute Central Retinal Artery Occlusion) trial will contribute more data.[19]

Despite having pathophysiologic mechanisms that are similar to those of cerebral ischemia, central retinal artery occlusion appears resistant

Table 3. Safety End Points.

End Point	Tenecteplase (N=40)	Aspirin (N=38)
	no. of patients (%)	
Death at 30 days	1 (2)	0
Symptomatic intracranial hemorrhage*	1 (2)	0
Any intracranial hemorrhage at 24 hr	2 (5)	0
Any systemic bleeding at 30 days	1 (2)	2 (5)
Ischemic stroke	1 (2)	1 (3)
Reocclusion of central retinal artery	1 (2)	
Giant-cell arteritis	1 (2)	0
Carotid endarterectomy or stenting	3 (8)	2 (5)
Hypotension or syncope	1 (2)	1 (3)
Adverse events‖	19 (48)	13 (34)
Mild	12 (30)	11 (29)
Moderate	13 (32)	3 (8)
Severe	3 (8)	5 (13)
Life-threatening	1 (2)	0
Death	1 (2)	0

* The patient who had a symptomatic intracerebral hemorrhage was the same patient who died.
One patient in the tenecteplase group had reduced visual function in the affected eye 25 days after enrollment and was diagnosed with retinal bleeding at the 30-day follow-up, although the visual acuity had normalized (a score of 89 on the Early Treatment Diabetic Retinopathy Study visual acuity chart). The two cases of systemic bleeding in the aspirin group involved rectal bleeding and epistaxis. Only the incident of retinal bleeding was classified as a serious adverse event.
The patient in the tenecteplase group died. The patient in the aspirin group had ipsilateral ischemic stroke one day after enrollment and had partial recovery. Carotid emboli were considered the cause of both central retinal artery occlusion and ischemic stroke.
One patient had reduced visual function 7 days after enrollment, and reocclusion of the central retinal artery was diagnosed on the same day, but the patient s visual function improved as of the 30-day follow-up, when the score on the Early Treatment Diabetic Retinopathy Study visual acuity chart was 70. The patient met the criteria for enrollment, with a normal sedimentation rate and no headache. However, 3 weeks after enrollment, leg pain and elevated inflammatory markers developed, leading to a diagnosis of polymyalgia rheumatica.
‖ Adverse events are classified and graded in accordance with *Common Terminology Criteria for Adverse Events* of the U.S. National Cancer Institute and range from grade 1 (mild) to grade 5 (death related to the adverse event).

to the same reperfusion strategies. Effective therapy for central retinal artery occlusion remains elusive, and alternative approaches warrant investigation in future trials. Whether the use of intravenous thrombolysis in the treatment of this disorder may be beneficial within an even shorter time window remains uncertain. The central retinal artery is effectively an end artery with limited collateral circulation, making early intervention theoretically important.[1] Nevertheless, no benefit was observed in the two thirds of the total trial population who were treated within a 3-hour window.

Safety concerns particularly the increased risk of intracranial hemorrhage remain irrespective of the treatment window. Any modest treatment effect may be insufficient to justify the risks associated with systemic thrombolysis, particularly given that most patients retain vision in the unaffected eye. However, the single fatal event observed in our trial should be interpreted in a broader context. Symptomatic intracerebral hemorrhage occurred in 2 of 42 patients (5%) in the EAGLE trial who were treated with intraarterial fibrinolysis, which allowed a broader treatment window, whereas one meta-analysis showed no such cases among 89 patients treated with intravenous fibrinolysis within 4.5 hours after symptom onset and two cases among patients in whom treatment was initiated later.[5,9] Because 20 to 30% of patients with central retinal artery occlusion have concurrent cerebral ischemia detectable on diffusion-weighted magnetic resonance imaging,[20,21] data on bleeding risk in stroke also provide important context. In minor stroke, the reported rate of fatal intracranial hemorrhage is approximately 0.9%, which is similar to the percentage observed in our trial.[22]

The population in our trial reflects real-world clinical presentation and aligns well with known demographic and etiologic patterns of central retinal artery occlusion in Europe (Table S2). The main limitation of the trial was its relatively small sample size of 78 patients, which provided statistical power to detect a difference in clinically meaningful improvement in vision of 30 percentage points in favor of tenecteplase, but the trial was not powered to detect smaller differences. Although the trial was powered on the basis of previous meta-analytic data that suggested a relatively large treatment effect,[18] our results are consistent with those of a later observational cohort study of intravenous thrombolysis in central retinal artery occlusion, which showed no evidence of superiority of thrombolysis over conservative treatment.[23] Another limitation is that the mean change in BCVA from baseline to 30 days, a secondary end point, required the conversion of no light perception or light perception to a logMAR value, which is inherently inaccurate.[16] Moreover, inclusion of patients with central retinal artery occlusion within 4.5 hours after

symptom onset relied solely on the patient s report of the time of onset.

In patients with central retinal artery occlusion, intravenous tenecteplase administered within 4.5 hours after symptom onset did not improve visual outcomes more than oral aspirin at a dose of 300 mg and was associated with an increased risk of serious adverse events. These findings do not support the routine use of thrombolytic therapy to treat central retinal artery occlusion.

Supported by Oslo University Hospital, the Norwegian Program for Clinical Therapy Research in the specialist health service (Klinbeforsk), the South-Eastern Norway Regional Health Authority, and the International Order of Odd Fellows and by an unconditional grant from Boehringer Ingelheim Norway for the purchase of tenecteplase.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank Prof. Dan Atar and Prof. Eivind Berge (Oslo University Hospital) for consultation regarding the design of the trial.

AUTHOR INFORMATION

Stephen J. Ryan, M.D.,[1-3] ystein Kalsnes J rstad, M.D., Ph.D.,[2,4] Mona Skjelland, M.D., Ph.D.,[1,2] Maiju Pesonen, Ph.D.,[5] Claus Z. Simonsen, M.D., Ph.D.,[6] Toke Bek, M.D., Ph.D.,[7] Rolf Ankerlund Blauenfeldt, M.D., Ph.D.,[6] Petra Ij s, M.D., Ph.D.,[8,9] Arja Laitinen, M.D., Ph.D.,[10] Andrej Khanevski, M.D., Ph.D.,[11] J rgen Krohn, M.D., Ph.D.,[12,13] Eyvind R dahl, M.D., Ph.D.,[12,13] Robin Lemmens, M.D., Ph.D.,[14] Jelle Demeestere, M.D., Ph.D.,[14,15] Catherine Cassiman, M.D., Ph.D.,[16] Ingvild Nakstad, M.D.,[17] Kristin Evensen, M.D., Ph.D.,[17] Tiril Sandell, M.D., Ph.D.,[18] Steffen Hamann, M.D., Ph.D.,[19,20] Thomas C. Truelsen, M.D., Ph.D.,[21] Louisa M. Christensen, M.D., Ph.D.,[20,22] Sverre Rosenbaum, M.D., Ph.D.,[22] Vaidas Matijošaitis, M.D., Ph.D.,[23,24] Reda Žemaitienė, M.D., Ph.D.,[24,25] Hanne Ellekj r, M.D., Ph.D.,[26,27] Erlend Almaas, M.D.,[28] Dordi Austeng, M.D., Ph.D.,[27,28] Michael V. Mazya, M.D., Ph.D.,[29,30] Frank Tra sk, M.D., Ph.D.,[31] Pauli Ylikotila, M.D.,[32,33] Ulpu Salmi, M.D., Ph.D.,[34] Kristian N. Jenssen, M.D.,[35] H vard Lisether, M.D.,[35] Cathrine Breivik, M.D., Ph.D.,[36] Kristina Devik, M.D.,[37] Lasse-Marius Elden Honningsv g, M.D.,[38] Jurgita Valaikienė, M.D., Ph.D.,[39] Andrius Cimbalas, M.D., Ph.D.,[40,41] Vetle Nilsen Malmberg, M.D.,[42] Espen Anderson, M.D.,[43] Ansar Roy, B.S.N.,[1] Thor H kon Skatt r, M.D.,[1,2,44] Kristian Lundsgaard Kraglund, M.D., Ph.D.,[1] Christina Kefaloykos, B.S.N.,[1] Inge Christoffer Olsen, Ph.D.,[45] Peter Vanacker, M.D., Ph.D.,[46-48] Daniel Strbian, M.D., Ph.D.,[8] Morten C. Moe, M.D., Ph.D.,[2,4] and Anne Hege Aamodt, M.D., Ph.D.[1,26,49]

[1] Department of Neurology, Oslo University Hospital, Oslo; [2] Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo; [3] Department of Technology and E-health, st-fold Hospital Trust, Sarpsborg, Norway; [4] Department of Ophthalmology, Oslo University Hospital, Oslo; [5] Oslo Center for Biostatistics and Epidemiology, Oslo University Hospital, Oslo; [6] Department of Neurology, Aarhus University Hospital, Aarhus, Denmark; [7] Department of Ophthalmology, Aarhus University Hospital, Aarhus, Denmark; [8] Neurology, Helsinki University Hospital, Helsinki; [9] University of Helsinki, Helsinki; [10] Department of Ophthalmology, Helsinki University Hospital, Helsinki; [11] Department of Neurology, Haukeland University Hospital, Bergen, Norway; [12] Department of Ophthalmology, Haukeland University Hospital, Bergen, Norway; [13] Department of Clinical Medicine, University of Bergen, Bergen, Norway; [14] Department of Neurosciences, Experimental Neurology, University Hospitals Leuven, Department of Neurology, Leuven, Belgium; [15] KU Leuven, Leuven Brain Institute, Department of Neurosciences, Experimental Neurology, Leuven, Belgium; [16] Department of Ophthalmology, UZ Leuven, Leuven, Belgium; [17] Department of Neurology, Vestre Viken Hospital Trust Drammen Hospital, Drammen, Norway; [18] Department of Ophthalmology, Drammen Hospital, Drammen, Norway; [19] Department of Ophthalmology, Copenhagen University Hospital, Rigshospitalet, Glostrup, Denmark; [20] Department of Clinical Medicine, University of Copenhagen, Copenhagen; [21] Department of Neurology, Rigshospitalet, University of Copenhagen, Copenhagen; [22] Department of Neurology, Bispebjerg Hospital Copenhagen, Copenhagen; [23] Department of Neurology, Hospital of Lithuanian University of Health Sciences, Kauno Klinikos, Kaunas, Lithuania; [24] Lithuanian University of Health Sciences, Kaunas, Lithuania; [25] Department of Ophthalmology, Hospital of Lithuanian University of Health Sciences, Kauno klinikos, Kaunas, Lithuania; [26] Department of Medicine, Stroke Unit, St. Olav University Hospital, Trondheim University Hospital, Trondheim, Norway; [27] Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology, Trondheim, Norway; [28] Department of Ophthalmology, St. Olav University Hospital, Trondheim University Hospital, Trondheim, Norway; [29] Department of Neurology, Karolinska University Hospital, Stockholm; [30] Department of Clinical Neuroscience, Karolinska Institutet, Stockholm; [31] Department of Neuro-ophthalmology, St. Erik Eye Hospital, Department of Neuroscience, Karolinska Institute, Stockholm; [32] Clinical Neurosciences, University of Turku, Turku, Finland; [33] Neurocenter, Turku University Hospital, Turku, Finland; [34] Department of Ophthalmology, Turku University Hospital, Turku, Finland; [35] Department of Neurology, Vestfold Hospital Trust, T nsberg, Norway; [36] Department of Ophthalmology, Vestfold Hospital Trust, T nsberg, Norway; [37] Department of Neurology, Nord Tr ndelag Hospital Trust, Namsos, Norway; [38] Department of Ophthalmology, Nord Tr ndelag Hospital Trust, Namsos, Norway; [39] Center of Neurology, Vilnius University, Vilnius, Lithuania; [40] Department of Ophthalmology, Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania; [41] Clinic of Ear, Nose, Throat and Eye Diseases, Vilnius University Faculty of Medicine, Vilnius, Lithuania; [42] Department of Neurology, Telemark Hospital Trust, Skien, Norway; [43] Department of Ophthalmology, Betanien Hospital, Skien, Norway; [44] Department of Radiology, Oslo University Hospital, Oslo; [45] Department of Research Support for Clinical Trials, Oslo University Hospital, Oslo; [46] Department of Neurology, Antwerp University Hospital, Edegem, Belgium; [47] Department of Neurology, Algemeen Ziekenhuis Groeninge, Kortrijk, Belgium; [48] Department of Translational Neuroscience, University of Antwerp, Antwerp, Belgium; [49] Institute of Population Health, Faculty of Health and Life Sciences, University of Liverpool, Liverpool, United Kingdom.

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