RESEARCH ARTICLE

Tranexamic Acid After Aneurysmal Subarachnoid Hemorrhage

Post Hoc Analysis of the ULTRA Trial

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Neurology® 2022;99:e2605-e2614. doi:10.1212/WNL.0000000000201160

Abstract

Background and Objectives

The ULTRA trial showed that ultra-early and short-term tranexamic acid treatment after subarachnoid hemorrhage did not improve clinical outcome at 6 months. An expected proportion of the included patients experienced nonaneurysmal subarachnoid hemorrhage. In this post hoc study, we will investigate whether ultra-early and short-term tranexamic acid treatment in patients with aneurysmal subarachnoid hemorrhage improves clinical outcome at 6 months.

Methods

The ULTRA trial is a multicenter, prospective, randomized, controlled, open-label trial with blinded outcome assessment, conducted between July 24, 2013, and January 20, 2020. After confirmation of subarachnoid hemorrhage on noncontrast CT, patients were allocated to either ultra-early and short-term tranexamic acid treatment with usual care or usual care only. In this post hoc analysis, we included all ULTRA participants with a confirmed aneurysm on CT angiography and/or digital subtraction angiography. The primary endpoint was clinical outcome at 6 months, assessed by the modified Rankin scale (mRS), dichotomized into good (0–3) and poor (4–6) outcomes.

Results

Of the 813 ULTRA trial patients who experienced an aneurysmal subarachnoid hemorrhage, 409 (50%) were assigned to the tranexamic acid group and 404 (50%) to the control group. In the intention-to-treat analysis, 233 of 405 (58%) patients in the tranexamic acid group and 238 of 399 (60%) patients in the control group had a good clinical outcome (adjusted odds ratio [aOR] 0.92; 95% CI 0.69–1.24). None of the secondary outcomes showed significant

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

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ULTRA coinvestigators are listed at links.lww.com/WNL/C392.

Glossary

IQR = interquartile range; **mRS** = modified Rankin scale; **mRS** = odds ratio.

differences between the treatment groups: excellent clinical outcome (mRS 0–2) (aOR 0.76; 95% CI 0.57–1.03), all-cause mortality at 30 days (aOR 0.91; 95% CI 0.65–1.28), and all-cause mortality at 6 months (aOR 1.10; 95% CI 0.80–1.52).

Discussion

Ultra-early and short-term tranexamic acid treatment did not improve clinical outcomes at 6 months in patients with aneurysmal subarachnoid hemorrhage and therefore cannot be recommended.

Trial Registration Information

ClinicalTrials.gov (NCT02684812; submission date February 18, 2016, first patient enrollment on July 24, 2013).

Classification of Evidence

This study provides Class II evidence that tranexamic acid does not improve outcomes in patients presenting with aneurysmal subarachnoid hemorrhage.

Aneurysmal subarachnoid hemorrhage is a disease with high morbidity and mortality. The main causes of poor outcomes include the initial bleeding with subsequent early brain injury and rebleeding of the aneurysm.[1,2] The most effective way to prevent rebleeding is early obliteration of the aneurysm. Unfortunately, most rebleedings occur within the first few hours following the initial hemorrhage before aneurysm obliteration can logistically be performed.[3,4] Further prevention of rebleeding could be achieved by antifibrinolytic treatment.[5,6] Recently, the ULTRA trial showed that ultra-early and short-term tranexamic acid did not improve clinical outcome at 6 months.[7] Because of the pragmatic design of the trial, in which tranexamic acid was administered immediately after noncontrast head CT–confirmed spontaneous subarachnoid hemorrhage, 15% of the included patients did not have an aneurysm on vascular imaging, as expected. As it is well known that the clinical course in patients with nonaneurysmal subarachnoid hemorrhages is more benign and rebleedings rarely occur,[8,9] this might have diluted the effect of tranexamic acid. The primary research question of this post hoc analysis of the ULTRA trial is as follows: does ultra-early and short-term tranexamic acid treatment in patients with aneurysmal subarachnoid hemorrhage improve clinical outcomes at 6 months.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

The protocol of the ULTRA trial has been previously published (links.lww.com/WNL/C394).[7,10] In brief, the ULTRA trial was a randomized, controlled, multicenter, open-label trial with blinded outcome assessment. The trial was conducted in 8 treatment centers and 16 referral hospitals between July 24, 2013, and January 20, 2020. The study was performed in accordance with the principles of the Declaration of Helsinki and International Conference of Harmonization guidelines for Good Clinical Practice and was registered on ClinicalTrials.gov (NCT02684812). The ethics committee of the Amsterdam University Medical Center (Amsterdam UMC, Amsterdam, the Netherlands) approved the trial protocol (2012_160#2012370). A description of the informed consent procedure has been previously published.[7]

Patients

Inclusion criteria of the ULTRA trial were adult patients admitted to one of the participating referring hospitals or treatment centers. Patients were included if they presented within 24 hours of symptoms indicating subarachnoid hemorrhage, with noncontrast CT–confirmed subarachnoid hemorrhage. Exclusion criteria were no proficiency of the Dutch or English language; a perimesencephalic bleeding pattern on CT in combination with a Glasgow coma scale score of 13–15 without focal neurologic deficit on admission or loss of consciousness; traumatic subarachnoid hemorrhage pattern on CT; ongoing treatment for deep vein thrombosis or pulmonary embolism; a history of a hypercoagulability disorder; pregnancy; severe renal failure (serum creatinine >150 μmol/L), or imminent death within 24 hours. For this post hoc analysis, we additionally excluded patients without a confirmed causative intracranial aneurysm on CT angiography and/or digital subtraction angiography. The definition of a subarachnoid bleeding pattern is described in the supplementary appendix (page 3, links.lww.com/WNL/C393).

Randomization, Masking, and Procedures

Immediately after confirmation of subarachnoid hemorrhage by a noncontrast head CT scan, patients were randomly assigned (in a 1:1 ratio) to either tranexamic acid (cyklokapron, Pfizer) treatment with usual care (tranexamic acid group) or usual care only (control group). Randomization was performed with a secured web-based system that stratified

according to permuted blocks (random block sizes; maximum of 12) by treatment center. Patients, investigators, and healthcare providers were not blinded for the randomization results. As soon as possible after randomization, patients of the tranexamic group received a bolus of 1 g of tranexamic acid intravenously, followed by continuous intravenous infusion of 1 g every 8 hours. Tranexamic acid administration was continued until the start of aneurysm treatment or for a maximum of 24 hours, whichever came first.[7] Tranexamic acid treatment was stopped when patients, or their legally authorized representatives, refused further participation in the ULTRA trial.

Outcomes

The primary outcome was the modified Rankin scale (mRS) score of 0–3 at 6 months after subarachnoid hemorrhage. A research nurse, who was trained according to a standard procedure and blinded to the randomization results, assessed the mRS by a standardized and validated telephone interview.[11-13] Secondary outcomes included excellent clinical outcome (mRS score 0–2) and ordinal shift analysis of the mRS scores at 6 months (sensitivity analyses) and all-cause mortality at 30 days and 6 months after the initial hemorrhage.

Suspected rebleeding after randomization and before treatment of the aneurysm(s) was defined as sudden neurologic deterioration with change in vital parameters suggestive for recurrent bleeding not confirmed by CT or a sudden increase of fresh blood production from an external ventricular drain. CT-confirmed rebleeding was defined as an increase in the amount of subarachnoid hemorrhage on CT compared with a previous investigation. Delayed cerebral ischemia was defined according to the criteria of a multidisciplinary research group.[14] Per-procedural thromboembolic events were defined as reduced passage or stasis of contrast in an artery or slowed venous outflow without the aspect of vascular spasm and were scored by the treating intervention neuroradiologist. The definitions of other serious adverse events are listed in the supplementary appendix (page 3–6, links.lww.com/WNL/C393).

Statistical Analysis

The power calculation of the original ULTRA trial was based on a tranexamic acid–induced reduction of the rate of rebleeding from 17% to 3.9% and on the assumption that a good clinical outcome would occur in 77.1% of patients with spontaneous subarachnoid hemorrhage treated with tranexamic acid and in 69.0% of patients with standard treatment. The required sample size, with a power of 80% with a type 1 error rate of 0.05, taking nonaneurysmal subarachnoid hemorrhage and some withdrawals into account, was 950 patients.

An independent data and safety monitoring board assessed the safety of participants, the progress of the trial, and the efficacy of the intervention. A blinded interim analysis after enrolment of half of the patients (n = 475) was performed.

We analyzed the data according to the intention-to-treat principle. Normality of data was explored by a normal Q-Q plot and tested by the Shapiro-Wilk test (statistic test threshold 0.9). Baseline characteristics and data concerning the tranexamic dosage are summarized by descriptive statistics. Categorical variables are reported as percentages, normally distributed continuous variables as mean values with SDs, and non-normally distributed variables as medians with interquartile ranges (IQRs). Group differences were analyzed by the χ^2 test, independent T test, Fisher exact test, or Mann-Whitney *U* test, depending on the distribution of the data. For the primary outcome and main secondary outcomes, multivariable logistic regression was used to calculate odds ratios (ORs) and adjusted OR (aOR) for the influence of treatment centers and potential differences ($p < 0.2$) in baseline characteristics. We additionally performed as-treated analyses. For more detailed information, we referred to the published statistical analysis plan.[15] Statistical analyses were performed using the IBM SPSS Statistics software, version 25 (IBM Corporation, Armonk, NY).

Data Availability

The authors have reported all relevant data used to conduct the research. All data requests should be submitted to the principal investigator (D.V.) for consideration. Access to anonymized data may be granted following review.

Results

Patients

The ULTRA trial enrolled 955 participants between July 24, 2013, and July 29, 2019. The last follow-up was performed on January 20, 2020. For this post hoc analysis, we included 813 patients (85.1%) who had an aneurysm confirmed by either CT angiography or digital subtraction angiography. Most of the excluded patients (135 of 142, 95.1%) had nonaneurysmal hemorrhage. In 4 moribund patients, additional angiographic imaging was not performed, and in 3 patients, the CT angiography was uninterpretable due to insufficient cerebral perfusion because of high intracranial pressure following the subarachnoid hemorrhage. The mean age of the included patients was 58.4 years (SD 12.5), and 71.1% was female. The ruptured aneurysm was treated in 706 of 813 (87%) patients. The median time from confirmation of subarachnoid hemorrhage to treatment was 14.0 hours (IQR 5.0–20.0).

Intervention

Of the 813 patients, 409 (50.3%) were assigned to the tranexamic acid group and 404 (49.7%) to the control group (Table 1, eTable 1, links.lww.com/WNL/C393). Within the tranexamic acid group, 16 (3.9%) patients did not receive tranexamic acid, and in the control group, 2 patients (0.5%) received tranexamic acid (Figure 1). In 1 patient, allocated to the tranexamic group, it was uncertain whether tranexamic acid was administered and this patient was therefore excluded from the as-treated analysis (eTable 2, supplementary appendix pages

Table 1 Baseline Characteristics of 813 Patients With an Aneurysmal Subarachnoid Hemorrhage

	Tranexamic acid group (N = 409)	Control group (N = 404)	Significance *p* Value
Age (yr), mean (SD)	58.4 (12.7)	58.4 (12.3)	0.99
Female	297 (73)	281 (70)	0.35
WFNS[24,a]			0.78
I	132 (33)	142 (36)	
II	77 (19)	75 (19)	
III	23 (6)	16 (4)	
IV	89 (22)	91 (23)	
V	81 (20)	77 (19)	
Fisher grade score[25,b]			0.04
II	24 (6)	12 (3)	
III	101 (25)	122 (30)	
IV	284 (69)	270 (67)	
Treatment modality[a]			0.65
Endovascular	272 (67)	258 (64)	
Clipping	86 (21)	89 (22)	
None	50 (12)	57 (14)	

Abbreviations: WFNS = World Federation of Neurosurgical Societies.
Data presented as n (%), unless noted otherwise. Percentages may not total 100 because of rounding.
[a] WFNS score: could not be assessed in 10 patients (1.2%). Treatment modality: one patient with 2 potentially causative aneurysms, of which one was clipped and the other was treated endovascularly.
[b] Analyses for each Fisher grade separately showed no significant differences between the treatment groups (grade 2, $p = 0.06$; grade 3, $p = 0.08$; and grade 4, $p = 0.45$).

8–9). Tranexamic acid was administered 195 minutes (IQR 130–340; n = 367) after ictus and 74 minutes (IQR 49–132; n = 369) after confirmation of subarachnoid hemorrhage on noncontrast CT. Tranexamic acid was most frequently discontinued because aneurysm treatment was started (252 of 409 patients, 61.6%; eTable 3, supplementary appendix page 10). Patients received a median dosage of 2.0 grams (IQR 1.4–3.1).

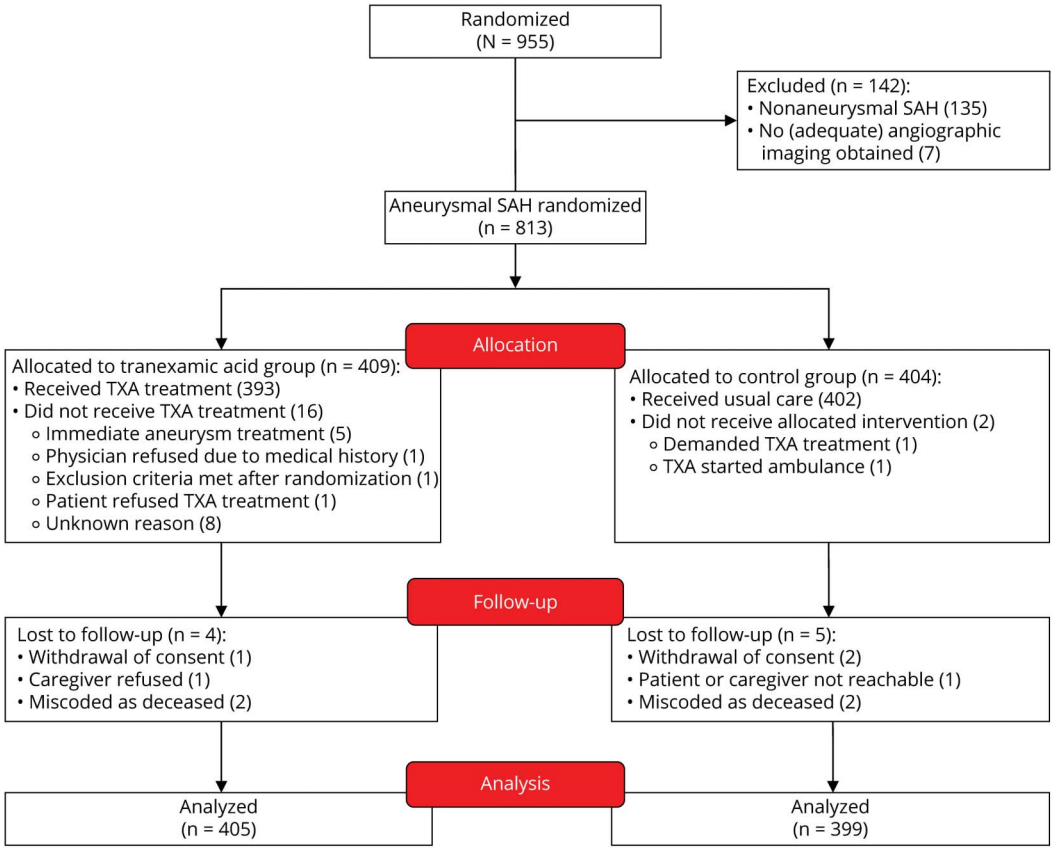
Outcomes

The mRS score 6 months after subarachnoid hemorrhage was assessed in 405 of 409 patients (99.0%) in the tranexamic group and in 399 of 404 patients (98.8%) in the control group (Figure 1). In the intention-to-treat analysis, 233 of 405 (57.5%) patients in the tranexamic acid group and 238 of 399 (59.6%) patients in the control group had a good clinical outcome (mRS score 0–3; OR 0.92, 95% CI 0.77–1.22). After adjustment for treatment center and Fisher grade on initial noncontrast CT scan, the adjusted OR was 0.92 and 95% CI 0.69–1.24. None of the secondary outcomes showed significant differences between the treatment groups (Figure 2 and Table 2). The results of the as-treated analyses were in line with the results of the intention-to-treat analyses (eTable 4, supplementary appendix page 11, links.lww.com/WNL/C393).

Serious Adverse Events

Analyzed by intention-to-treat, rebleeding after randomization and before aneurysm treatment occurred in 46 of 409 (11.2%) patients in the tranexamic group and in 65 of 404 (16.1%) patients in the control group (OR 0.66, 95% CI 0.44–0.99), whereas CT-proven rebleeding before aneurysm treatment occurred in 39 of 409 (9.5%) patients in the tranexamic group and 56 of 404 (13.9%) patients in the control group (OR 0.66, 95% CI 0.42–1.01). No association between rebleeding rate after randomization and before aneurysm treatment and treatment with tranexamic acid was seen in the as-treated analyses (OR 0.71, 95% CI 0.48–1.07). In patients without aneurysm treatment, rebleeding after randomization and before aneurysm treatment occurred in 45 of 107 (42.1%) patients and CT-proven rebleeding before aneurysm treatment occurred in 33 of 107 (30.8%) patients. The proportion of patients without aneurysm treatment and with rebleeding was lower, though not significantly, in the tranexamic acid group compared with that in the control group (all rebleedings: 18 of 49 [36.7%] and 27 of 58 [46.6%] patients, $p = 0.31$; CT-proven rebleedings: 12 of 49 [24.5%] and 21 of 58 [36.2%] patients, $p = 0.19$). The intention-to-treat analyses showed no significant association between tranexamic acid treatment and delayed cerebral ischemia (OR 0.99, 95%

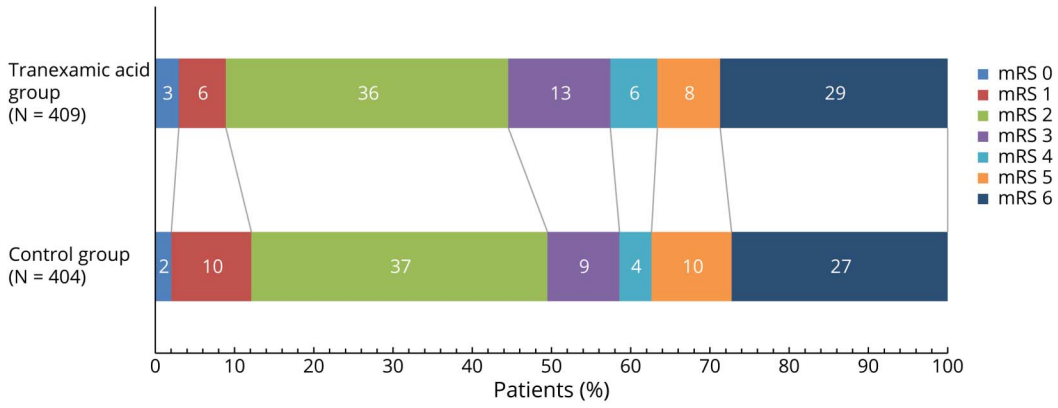
Figure 1 Trial Allocation Profile (CONSORT)



TXA = tranexamic acid.

CI 0.72–1.36), thromboembolic events during endovascular aneurysm treatment (OR 0.81, 95% CI 0.48–1.38), extracranial thrombosis (OR 0.70, 95% CI 0.22–2.23; Table 3, or any other serious adverse event (eTable 5, supplementary appendix page 12–13, links.lww.com/WNL/C393). The as-treated analyses also showed no significant differences in any

Figure 2 Distribution of Modified Rankin Scale Score at 6 Months in the Intention-to-Treat Analysis



*Nine patients lost to follow-up. Stacked bar chart of scores on the modified Rankin scale (0–6). A score of 0 indicates no symptoms, 1 no clinically significant disability, 2 slight disability (patient is able to look after own affairs without assistance but is unable to perform all previous activities), 3 moderate disability (patient requires some help but is able to walk unassisted), 4 moderately severe disability (patient is unable to attend to bodily needs without assistance and unable to walk unassisted), 5 severe disability (patient requires constant nursing care and attention), and 6 death. There was no statistically significant difference between the tranexamic acid group and the control group in the overall distribution of scores with univariate ordinal shift analysis (common OR, 0.78; 95% CI, 0.59–1.03) and after adjustment for treatment center and the Fisher grade (adjusted common OR, 0.83; 95% CI 0.64–1.07). OR = odds ratio.

Table 2 Primary Outcome (Modified Rankin Scale Score at 6 Months) and Secondary Outcomes

	Intention-to-treat analysis[a]			
	Tranexamic acid group (N = 409)	Control group (N = 404)	OR (95% CI)	aOR (95% CI)
Good clinical outcome[a] (mRS 0–3)	233 (58)	238 (60)	0.92 (0.69–1.21)	0.92 (0.69–1.24)
Secondary outcomes				
Excellent clinical outcome[a] (mRS 0–2)	182 (45)	204 (51)	0.78 (0.59–1.03)	0.76 (0.57–1.03)
All-cause mortality at 30 d	95 (23)	98 (24)	0.95 (0.68–1.31)	0.91 (0.65–1.28)
All-cause mortality at 6 months	117 (29)	107 (27)	1.11 (0.82–1.51)	1.10 (0.80–1.52)

Abbreviations: aOR = adjusted odds ratio; mRS = modified Rankin scale; OR = odds ratio.
Data presented as n (%), unless noted otherwise. Percentages may not total 100 because of rounding.
[a] Nine patients lost to follow up (tranexamic acid group N = 405, control group N = 399).

serious adverse event (eTable 6, supplementary appendix page 14–15).

Classification of Evidence

This study provides Class II evidence that tranexamic acid does not improve outcomes in patients presenting with aneurysmal subarachnoid hemorrhage.

Discussion

In this post hoc analysis of the ULTRA trial, ultra-early and short-term tranexamic acid treatment started immediately after diagnosis in patients with an aneurysmal subarachnoid hemorrhage did not result in improved clinical outcomes after 6 months.

Antifibrinolytic treatment in patients with subarachnoid hemorrhage has been a topic of debate for decades. Randomized controlled trials with prolonged administration of tranexamic acid up to 4 weeks showed no improvement in clinical outcome due to an increase in ischemic complications.[16-18] A trial on short-term tranexamic acid treatment for a maximum of 72 hours significantly reduced the occurrence of rebleeding, without a concurrent increased occurrence of delayed cerebral ischemia. The trial was, however, underpowered for clinical outcome analyses.[6] Recently, the results of the ULTRA trial showed no significant differences in clinical outcomes in patients with ultra-early and short-term tranexamic acid treatment in addition to standard treatment compared with patients with standard treatment only.[7] As expected, the pragmatic design of the ULTRA trial resulted in an unavoidable inclusion of a number of patients without an aneurysm on vascular imaging. Although this was taken into account in the initial power calculation, it may have led to a dilution of the effect of tranexamic acid. Therefore, we performed this post hoc subgroup analysis on only patients with aneurysmal subarachnoid hemorrhages.

In our power calculation, we assumed a relative risk reduction in the occurrence of rebleeding of at least 75%. In this study,

Table 3 Complications During Hospital Admissions

	Intention-to-treat analysis		
	Tranexamic acid group (N = 409)	Control group (N = 404)	OR (95% CI)
All[a] rebleedings before aneurysm treatment	46 (11)	65 (16)	0.66 (0.44–0.99)
CT-proven rebleedings	39 (10)	56 (14)	0.66 (0.42–1.01)
Delayed cerebral ischemia[b]	104 (25)	103 (26)	0.99 (0.72–1.36)
Thromboembolic complications during endovascular treatment	29 (11)	33 (13)	0.81 (0.48–1.38)
Extracranial thrombosis	5 (1)	7 (2)	0.70 (0.22–2.23)
Deep venous thrombosis	0 (0)	2 (0)	0.20 (0.01–4.11)
Pulmonary embolism	4 (1)	5 (1)	0.79 (0.21–2.96)

aOR = adjusted odds ratio; OR = odds ratio; SAE = severe adverse event; SUSARs = severe unexpected serious adverse events.
Data presented as n (%), unless noted otherwise.
[a] Both suspected (not CT-proven) and CT-proven.
[b] Data missing in 1 patient in the control group.

we found a relative risk reduction of 34%. In our sample size calculation, we determined a rebleeding rate of 17% in patients treated with state-of-the-art subarachnoid hemorrhage management without tranexamic acid, which was based on our own data[19] (all rebleedings 16%, CT-proven rebleedings 12%) and supported by another (then) recent study conducted by Guo et al.[20] (rebleeding rate 21.5% in aneurysmal subarachnoid hemorrhage). Compared with previous studies on ultra-early antifibrinolytic treatment after subarachnoid hemorrhage, which showed rebleeding rates of approximately 12% in the control group, the determined rebleeding rate in our calculation may be considered overestimated.[6,21] The results of this post hoc analysis of the ULTRA trial show a rebleeding rate in the control group of 16% (CT-proven rebleedings 14%), which is slightly lower than the rebleeding rate used in our sample size calculation. This might have contributed to the lack of difference found between the treatment groups. However, because the difference in rebleeding rate between our sample size calculation and our results is very subtle, we think the influence of the determined rebleeding rate used in our power calculation on the lack of difference between the groups is minimal. Besides, the point estimate of clinical outcome showed a trend toward worse outcomes in patients treated with tranexamic acid. Other explanations for the discrepancy in relative risk reduction are as follows: first, despite a rapid confirmation of subarachnoid hemorrhage on noncontrast CT and the strategy of ultra-early administration of tranexamic acid already in the referral centers, tranexamic acid was still administered after a median of 195 minutes after ictus. Compared with previous trials, the timing of tranexamic acid administration in our study is quite rapid. Nevertheless, as we have shown previously that the median time interval between ictus and rebleeding is 180 minutes, a substantial proportion of rebleedings might have been unavoidable.[19] The only way to avoid these very early rebleedings would be to administer tranexamic acid in a prehospital setting, which is not desirable, as long as subarachnoid hemorrhage cannot be distinguished from other (ischemic) stroke types before hospital arrival; second, because aneurysm obliteration was performed relatively early (median 14 hours), the proportion of rebleedings that can be prevented by our study's treatment strategy shrinks considerably. Owing to this relatively small proportion of rebleedings that could have been prevented in the ULTRA trial, the effect of tranexamic acid on clinical outcome might have been diluted.

Despite the significant reduction in rebleedings in patients treated with tranexamic acid in the intention-to-treat analyses, clinical outcome at 6 months did not improve. Specifically, the point estimate of clinical outcome showed a trend toward worse outcomes in patients treated with tranexamic acid. In other words, although the occurrence of rebleeding is associated with poor outcome,[1] a tranexamic acid–induced reduction of rebleeding did not lead to an improved clinical outcome. Because patients randomized to tranexamic acid were not at an increased risk of delayed cerebral ischemia or thromboembolic complications, other, perhaps yet unknown, pathophysiologic pathways may have been adversely influenced by tranexamic acid, leading to secondary brain injury. A potential explanation may be an increase in, or delayed recovery from, early brain injury. Early brain injury, defined as the initial injury in the first 72 hours following a subarachnoid hemorrhage, is commonly graded by the World Federation of Neurological Surgeons or Hunt and Hess scale.[22] One of the pathophysiologic mechanisms involved in early brain injury is microthrombosis, and in in half of the patients with aneurysmal subarachnoid hemorrhage, ischemic lesions can be seen on diffusion-weighted MRI within 72 hours after ictus and before aneurysm treatment.[22,23] The use of ultra-early tranexamic acid may result in decreased degradation of microthrombi and, as a consequence, may lead to more severe injury or delayed recovery from early brain injury. This hypothesis is supported by a previous randomized controlled trial of the STAR study group, which showed that tranexamic acid had a nonsignificant beneficial effect on clinical outcomes in patients with subarachnoid hemorrhage with a normal level of consciousness, but a nonsignificant disadvantageous effect on clinical outcomes in patients with an impaired level of consciousness.[17]

Our study has several limitations. By selecting patients with confirmed aneurysmal subarachnoid hemorrhage only, the randomization is undone, which could lead to differences between treatment groups. However, the baseline characteristics were evenly distributed among the treatment groups, except for the Fisher score. The ULTRA trial was an investigator-initiated trial with minimal funding, which, in combination with the pragmatic design, hampered blinded treatment with tranexamic acid, potentially leading to treatment bias. For the same reason, assessment of safety outcomes was not blinded.

This is the largest study on the effect of tranexamic acid on clinical outcomes in patients with aneurysmal subarachnoid hemorrhage. Other strengths are the nation-wide participation in the study and the negligible number of patients who were lost to follow-up.

In conclusion, ultra-early and short-term treatment with tranexamic acid in patients with an aneurysmal subarachnoid hemorrhage did not result in an improved clinical outcome at 6 months. Our data do not recommend tranexamic acid treatment in patients with subarachnoid hemorrhage.

Acknowledgment

The authors thank the patients participating in this trial, without whom this trial would have not been possible. The authors also thank the research teams in all participating centers who contributed to the data collection.

Study Funding

Fonds Ohra (project number 1202-031).

Disclosure

M.D.I. Vergouwen reports a grant from the Dutch Heart Foundation (Clinical Established Investigator grant 2018T076). J.F.C. Wolfs reports personal fees from Consultant Nuvasive, personal fees from Zimmer Biomet, personal fees from Safe Orthopaedics, personal fees from EIT/Johnson and Johnson, outside the submitted work. H.D. Boogaarts reports consulting fees paid to the Department of Neurosurgery Radboud University Medical Center Nijmegen from Stryker neurovascular. C.J.M. Klijn reports grants from Clinical established investigator grant of the Dutch Heart Foundation (Grant Number 2012T077), grants from ASPASIA, grant from The Netherlands Organization for Health Research and Development, ZonMw (Grant Number 015008048), grants from Support of the Netherlands Cardiovascular Research Initiative, which is supported by the Dutch Heart Foundation, CVON2015–01: CONTRAST, and the support of the Brain Foundation Netherlands (HA2015 01·06), outside the submitted work. R. van den Berg reports consulting fees for unrelated research and teaching activities from Cerenovus Neurovascular. C.B.L.M. Majoie reports grants from CVON/Dutch Heart Foundation, grants from European Commission, grants from Dutch Health Evaluation Program, grants from TWIN Foundation, grants from Stryker, outside the submitted work and is a Shareholder of Nico-Lab, a company that focuses on the use of artificial intelligence for medical image analysis. G.J.E. Rinkel reports no disclosures relevant to the manuscript. Y.B.W.E.M. Roos is a minor stockholder of Nico-Lab. The other authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* November 19, 2021. Accepted in final form July 11, 2022. Submitted and externally peer reviewed. The handling editor was Brad Worrall, MD, MSc, FAAN.

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Appendix 1 *(continued)*

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Appendix 2 Coinvestigators

Coinvestigators are listed at links.lww.com/WNL/C392

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Neurology 2022;99;e2605-e2614 Published Online before print October 20, 2022
DOI 10.1212/WNL.0000000000201160