Tranexamic Acid After Aneurysmal Subarachnoid Hemorrhage: Post-Hoc Analysis of the ULTRA Trial

Author(s):
Maud A. Tjerkstra, BSc; Rene Post, MD; Menno R. Germans, MD PhD; Mervyn D.J. Vergouwen, PhD; Korné Jellema, MD PhD; Radboud W. Koot, MD PhD; Nyika D. Kruyt, MD PhD; Peter W.A. Willems, MD PhD; Jasper F.C. Wolfs, MD PhD; Frits C. de Beer, MD; Hans Kieft, MD PhD; Dharmin Nanda, MD PhD; Bram van der Pol, MD PhD; Gerwin Roks, MD PhD; Frank de Beer, MD PhD; Patricia H.A. Haikkes, MD PhD; Loes J.A. Reichman, MD; Paul J.A.M. Brouwers, MD PhD; Renske M Van den Berg - Vos, MD PhD; Vincent I.H. Kwa, MD PhD; Taco C. van der Ree, MD PhD; Irene Bronner, MD PhD; Henri P. Bienfait, MD PhD; Hieronymus Boogaarts, PhD; Catharina JM. Klijn, MD; René van den Berg, PhD; Bert A. Coert, MD PhD; Janneke Horn, MD, PhD; Charles B.L.M. Majoie, MD, PhD; Gabriël J.E. Rinkel, FRCP, Professor; Yvo B.W.M. Roos, MD, PhD; William Vandertop, PhD, Professor; Dagmar Verbaan, PhD on behalf of ULTRA investigators

Corresponding Author:
Maud A. Tjerkstra, m.a.tjerkstra@amsterdamumc.nl

Neurology® Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes.
Affiliation Information for All Authors: 1 Department of Neurosurgery, Amsterdam Neuroscience Research Institute, Amsterdam University Medical Centres, Amsterdam, the Netherlands 2 Department of Neurosurgery, Clinical Neuroscience Centre, University Hospital Zurich, Zurich, Switzerland 3 Department of Neurology and Neurosurgery, UMC Utrecht Brain Centre, University Medical Centre Utrecht, Utrecht University, Utrecht, the Netherlands 4 Department of Neurology, Haaglanden Medical Centre, The Hague, the Netherlands 5 Department of Neurosurgery, Leids University Medical Centre, the Netherlands 6 Department of Neurology, Leids University Medical Centre, the Netherlands 7 Department of Neurosurgery, Haaglanden Medical Centre, The Hague, the Netherlands 8 Department of Neurosurgery, Isala Hospital, Zwolle, the Netherlands 9 Department of Intensive Care, Isala Hospital, Zwolle, the Netherlands 10 Department of Neurosurgery, Elisabeth Tweesteden ziekenhuis, Tilburg, the Netherlands 11 Department of Neurology, Spaarne Gasthuis, Haarlem, the Netherlands 12 Department of Neurology, Noordwest Ziekenhuis, Almelo, the Netherlands 13 Department of Neurology, Medisch Spectrum Twente, Enschede, the Netherlands 14 Department of Neurology, OLVG, Amsterdam, the Netherlands 15 Department of Neurology, Amsterdam University Medical Centres, location AMC, Amsterdam, the Netherlands 16 Department of Neurology, Dijklander Hospital, Hoorn, the Netherlands 17 Department of Neurology, Gelre Hospital, Apeldoorn, The Netherlands 18 Department of Neurosurgery, Radboud University Medical Centre, Nijmegen, the Netherlands 19 Department of Neurology, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Centre, Nijmegen, the Netherlands 20 Department of Radiology and Nuclear Medicine, Amsterdam University Medical Centres, location AMC, Amsterdam, the Netherlands 21 Department of Neurology, Medisch Spectrum Twente, Enschede, the Netherlands 22 Department of Neurology, Dijklander Hospital, Hoorn, the Netherlands 23 Department of Neurology, Spaarne Gasthuis, Haarlem, the Netherlands 24 Department of Neurology, Noordwest Ziekenhuis, Almelo, the Netherlands 25 Department of Neurosurgery, Radboud University Medical Centre, Nijmegen, the Netherlands 26 Department of Neurology, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Centre, Nijmegen, the Netherlands 27 Department of Radiology and Nuclear Medicine, Amsterdam University Medical Centres, location AMC, Amsterdam, the Netherlands

Equal Author Contribution:

Contributions:
Maud A Tjerkstra: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Rene Post: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Menno R Germans: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Mervyn D.I. Vergouwen: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Korné Jellema: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Radboud W Koot: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Nyka D Kruyt: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Peter W.A. Willems: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Jasper F.C. Wolfs: Major role in the acquisition of data
Frits C de Beer: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Hans Kieft: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Dharmin Nanda: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Bram van der Pol: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Gerwin Roks: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data
Frank de Beer: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the
Acknowledgment:
Foremost, we thank the patients participating in this trial, without whom this trial would have not been possible. We also thank the research teams in all participating centers who contributed to the data collection.

Study Funding:
Fonds Ohra (project number 1202-031).

Disclosures:
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 Organisation 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 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 minor stock holder of Nico-Lab. The other authors report no relevant disclosures.

Preprint DOI:

Received Date:
2021-11-19

Accepted Date:
2022-07-11

Handling Editor Statement:
Submitted and externally peer reviewed. The handling editor was Brad Worrall, MD, MSc, FAAN.
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 six months. An expected proportion of the included patients had non-aneurysmal 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 six 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 non-contrast computer tomography, 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 six months, assessed by the modified Rankin Scale, dichotomized into good (0-3) and poor (4-6) outcome.

**Results** Of the 813 ULTRA-trial patients who had 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% confidence interval (C.I.) 0.69 to 1.24). None of the secondary outcomes showed significant differences between the treatment groups: excellent clinical outcome (mRS 0-2) aOR 0.76, 95% C.I. 0.57-1.03, all-cause mortality at 30 days aOR 0.91, 95% C.I. 0.65-1.28), all-cause mortality at six months aOR 1.10 (95% C.I. 0.80-1.52).
Discussion  Ultra-early and short-term tranexamic acid treatment did not improve clinical outcome at six months in patients with aneurysmal subarachnoid hemorrhage and therefore, cannot be recommended.

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

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

Introduction  Aneurysmal subarachnoid hemorrhage is a disease with high morbidity and mortality. The main causes of poor outcome 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 anti-fibrinolytic treatment.\(^5,6\) Recently, the ULTRA-trial showed that ultra-early and short-term tranexamic acid did not improve clinical outcome at six months.\(^7\) As a result of the pragmatic design of the trial, in which tranexamic acid was administered immediately after non-contrast head computed tomography (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 non-aneurysmal 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: does ultra-early and short-term tranexamic acid treatment in patients with aneurysmal subarachnoid hemorrhage improve clinical outcome at six months.

Methods

Standard Protocol Approvals, Registrations and Patient Consents

The protocol of the ULTRA-trial has been published previously. In brief, the ULTRA-trial was a randomized, controlled, multicenter, open label trial with blinded outcome assessment. The trial was conducted in eight 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 published previously.

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 non-contrast 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 neurological 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 the current 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).

**Randomization, masking and procedures**

Immediately after confirmation of subarachnoid hemorrhage by a non-contrast 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 health-care providers were not blinded for the randomization results. As soon as possible after randomization, patients of the tranexamic group received a bolus of one gram of tranexamic acid intravenously, followed by continuous intravenous infusion of one gram every eight hours. Tranexamic acid administration was continued until the start of aneurysm treatment, or for a maximum of 24 hours, whichever came first. 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 six 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. Secondary outcomes included excellent clinical outcome (mRS score 0-2) and ordinal shift analysis of the mRS scores at six months (sensitivity analyses) and all-cause mortality at 30 days and six months after the initial hemorrhage.

Suspected rebleeding after randomization and before treatment of the aneurysm(s) was defined as sudden neurological deterioration with change in vital parameters suggestive for recurrent bleeding not confirmed by CT, or 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 to a previous investigation. Delayed cerebral ischemia was defined according to the criteria of a multidisciplinary research group. Per-procedural thrombo-embolic events were defined as reduced passage or stasis of contrast in an artery or slowed venous outflow without the aspect of vascular spasm and was scored by the treating intervention neuro-radiologist. The definitions of other serious adverse events are listed in the supplementary appendix (page 3-4).

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 spontaneous subarachnoid hemorrhage patients 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 non-aneurysmal 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 means with standard deviations and non-normally distributed variables as medians with interquartile range (IQR). Group differences were analyzed by the Chi-Square, independent T-test, Fisher’s 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 (OR) 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 refer to the published statistical analysis plan.15

Statistical analyses were performed using the IBM SPSS Statistics version 25 software (IBM Corporation, Armonk, NY, USA).
Data availability

The authors have reported all relevant data used to conduct the research. All data requests should be submitted to the Principal Investigator (DV) 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 the current post-hoc analysis, we included 813 patients (85.1%) who had an aneurysm confirmed by either CT-angiography or digital subtraction angiography. The majority of excluded patients (135 of 142, 95.1%) had non-aneurysmal hemorrhage. In four moribund patients additional angiographic imaging was not performed and in three patients the CT-angiography was uninterpretable due to insufficient cerebral perfusion as a result of high intracranial pressure following the SAH. 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 SAH to treatment was 14.0 hours (IQR 5.0 to 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). Within the tranexamic acid group 16 (3.9%) patients did not receive tranexamic acid and in the control group two patients (0.5%) received tranexamic acid (figure 1). In one 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 page 8-9). Tranexamic acid was administered 195 minutes (IQR 130 to 340; n=367) after ictus and 74 minutes (IQR 49 to 132; n=369) after confirmation of SAH on non-contrast 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 to 3.1).

Outcomes

The modified Rankin Scale score six 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 to 1.22). After adjustment for treatment center and Fisher grade on initial non-contrast CT-scan, the adjusted OR was 0.92, 95% CI 0.69 to 1.24. None of the secondary outcomes showed significant differences between the treatment groups (figure 2, 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).

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 of the control group (OR 0.66, 95% CI 0.44 to 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 to 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 to 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 to 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% CI 0.72 to 1.36), thrombo-embolic events during endovascular aneurysm treatment (OR 0.81, 95% CI 0.48 to 1.38), extra-cranial thrombosis (OR 0.70, 95% CI 0.22 to 2.23; table 3), nor any other serious adverse event (eTable 5, supplementary appendix page 12-13). The as-treated analyses also showed no significant differences in any 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 outcome after six months.

Anti-fibrinolytic 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 four weeks showed no improvement in clinical outcome due to an increase in ischemic complications\textsuperscript{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.\textsuperscript{6} Recently, the results of the ULTRA-trial showed no significant differences in clinical outcome in patients with ultra-early and short-term tranexamic acid in addition to standard treatment compared to patients with standard treatment only.\textsuperscript{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. Even though 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 the current study, 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 SAH management without tranexamic acid, which was based on our own data\textsuperscript{19} (all rebleedings 16%, CT-proven rebleedings 12%) and supported by another (at that time) recent
study of Guo et al (bleeding rate 21.5% in aneurysmal SAH).\textsuperscript{20} Compared to previous studies on ultra-early anti-fibrinolytic treatment after SAH, which showed bleeding rates of approximately 12% in the control group, the determined bleeding rate in our calculation may be considered overestimated.\textsuperscript{6,21} The results of this post-hoc analysis of the ULTRA-trial show a bleeding rate in the control group of 16% (CT-proven bleedings 14%), which is slightly lower than the bleeding rate used in our sample size calculation. This might have contributed to the lack of difference found between the treatment groups. However as the difference in bleeding rate between our sample size calculation and our results is very subtle, we think the influence of the determined bleeding 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 towards 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 SAH on non-contrast 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 to 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 bleeding is 180 minutes, a substantial proportion of bleedings might have been unavoidable.\textsuperscript{19} The only way to avoid these very early bleedings would be to administer tranexamic acid in a pre-hospital 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 bleedings that can be prevented by our study’s treatment strategy shrinks considerably. Due to this relatively small proportion of bleedings 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 six months did not improve. Specifically, the point estimate of clinical outcome showed a trend towards worse outcomes in patients treated with tranexamic acid. In other words, even though the occurrence of rebleeding is associated with poor outcome, a tranexamic acid-induced reduction of rebleeding did not lead to an improved clinical outcome. Since patients randomized to tranexamic acid were not at increased risk of delayed cerebral ischemia or thrombo-embolic complications, other, perhaps yet unknown, pathophysiological 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. One of the pathophysiological mechanisms involved in early brain injury is microthrombosis, and in half of the patients with aneurysmal subarachnoid hemorrhage ischemic lesions can be seen on diffusion-weighted MR-imaging within 72 hours after ictus and prior to aneurysm treatment. The use of ultra-early tranexamic acid may result in a decreased degradation of microthrombi and, as a consequence, may lead to more severe injury or a 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 non-significant beneficial effect on clinical outcome in SAH patients with a normal level of consciousness, but a non-significant disadvantageous effect on clinical outcome in patients with an impaired level of consciousness.

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
amongst 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 study is the largest study on the effect of tranexamic acid on clinical outcome 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 six months. Our data do not recommend tranexamic acid treatment in patients with subarachnoid hemorrhage.

**ULTRA trial collaborators**


WNL-2022-201089_eapp --[http://links.lww.com/WNL/C393](http://links.lww.com/WNL/C393)

References


Figure Legends

Figure 1. Trial allocation profile (CONSORT)

TXA = tranexamic acid
Figure 2. Distribution of modified Rankin Scale score at six 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 carry out 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 odds ratio, 0.78; 95% CI, 0.59-1.03), as well as after adjustment for treatment center and Fisher grade (adjusted common odds ratio, 0.83; 95% CI 0.64-1.07).
Table 1. Baseline characteristics of 813 patients with an aneurysmal subarachnoid hemorrhage

<table>
<thead>
<tr>
<th></th>
<th>Tranexamic acid group</th>
<th>Control group</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=409</td>
<td>N=404</td>
<td>p-value</td>
</tr>
<tr>
<td><strong>Age (years), mean (SD)</strong></td>
<td>58.4 (12.7)</td>
<td>58.4 (12.3)</td>
<td>0.99</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>297 (73)</td>
<td>281 (70)</td>
<td>0.35</td>
</tr>
<tr>
<td><strong>WFNS(^a)</strong></td>
<td></td>
<td></td>
<td>0.78</td>
</tr>
<tr>
<td>I</td>
<td>132 (33)</td>
<td>142 (36)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>77 (19)</td>
<td>75 (19)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>23 (6)</td>
<td>16 (4)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>89 (22)</td>
<td>91 (23)</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>81 (20)</td>
<td>77 (19)</td>
<td></td>
</tr>
<tr>
<td><strong>Fisher Grade Score(^b)</strong></td>
<td></td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>II</td>
<td>24 (6)</td>
<td>12 (3)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>101 (25)</td>
<td>122 (30)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>284 (69)</td>
<td>270 (67)</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment modality(^\text{a})</strong></td>
<td></td>
<td></td>
<td>0.65</td>
</tr>
<tr>
<td>Endovascular</td>
<td>272 (67)</td>
<td>258 (64)</td>
<td></td>
</tr>
<tr>
<td>Clipping</td>
<td>86 (21)</td>
<td>89 (22)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>50 (12)</td>
<td>57 (14)</td>
<td></td>
</tr>
</tbody>
</table>

Data presented as n (%), unless noted otherwise. Percentages may not total 100 because of rounding. Standard deviation (SD), World Federation of Neurosurgical Societies (WFNS)

\(^a\) WFNS score: could not be assessed in 10 patients (1.2%). Treatment modality: one patient with two potentially causative aneurysms, of which one was clipped and one was treated endovascularly
Analyses for each Fisher grade separately showed no significant differences between the treatment groups (grade 2, p=0.06; grade 3, p=0.08; grade 4, p=0.45).

Table 2. Primary outcome (modified Rankin Scale score at six months) and secondary outcomes

<table>
<thead>
<tr>
<th></th>
<th>Intention-to-treat analysis^a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tranexamic acid group (N=409)</td>
</tr>
<tr>
<td>Good clinical outcome^b (mRS 0-3)</td>
<td>233 (58)</td>
</tr>
</tbody>
</table>

Secondary outcomes

<table>
<thead>
<tr>
<th></th>
<th>Tranexamic acid group</th>
<th>Control group</th>
<th>OR (95% CI)</th>
<th>aOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent clinical outcome^b (mRS 0-2)</td>
<td>182 (45)</td>
<td>204 (51)</td>
<td>0.78 (0.59-1.03)</td>
<td>0.76 (0.57-1.03)</td>
</tr>
<tr>
<td>All-cause mortality at 30 days</td>
<td>95 (23)</td>
<td>98 (24)</td>
<td>0.95 (0.68-1.31)</td>
<td>0.91 (0.65-1.28)</td>
</tr>
<tr>
<td>All-cause mortality at six months</td>
<td>117 (29)</td>
<td>107 (27)</td>
<td>1.11 (0.82-1.51)</td>
<td>1.10 (0.80-1.52)</td>
</tr>
</tbody>
</table>

Data presented as n (%), unless noted otherwise. Percentages may not total 100 because of rounding. Odds ratio (OR), adjusted odds ratio (aOR), 95% confidence interval (95% CI)

^a nine patients lost to follow up (tranexamic acid group N=405, control group N=399)
Table 3. Complications during hospital admissions

<table>
<thead>
<tr>
<th>Complication</th>
<th>Tranexamic acid group (N=409)</th>
<th>Control group (N=404)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All(^a) rebleedings before aneurysm treatment</td>
<td>46 (11)</td>
<td>65 (16)</td>
<td>0.66 (0.44-0.99)</td>
</tr>
<tr>
<td>CT-proven rebleedings</td>
<td>39 (10)</td>
<td>56 (14)</td>
<td>0.66 (0.42-1.01)</td>
</tr>
<tr>
<td>Delayed cerebral ischemia(^b)</td>
<td>104 (25)</td>
<td>103 (26)</td>
<td>0.99 (0.72-1.36)</td>
</tr>
<tr>
<td>Thrombo-embolic complications during endovascular treatment</td>
<td>29 (11)</td>
<td>33 (13)</td>
<td>0.81 (0.48-1.38)</td>
</tr>
<tr>
<td>Extra-cranial thrombosis</td>
<td>5 (1)</td>
<td>7 (2)</td>
<td>0.70 (0.22-2.23)</td>
</tr>
<tr>
<td>- Deep venous thrombosis</td>
<td>0 (0)</td>
<td>2 (0)</td>
<td>0.20 (0.01-4.11)</td>
</tr>
<tr>
<td>- Pulmonary embolism</td>
<td>4 (1)</td>
<td>5 (1)</td>
<td>0.79 (0.21-2.96)</td>
</tr>
</tbody>
</table>

Data presented as n (%), unless noted otherwise. Odds ratio (OR), adjusted odds ratio (aOR), 95% confidence interval (95% CI), severe adverse event (SAE), severe unexpected serious adverse events (SUSARs)

\(^a\) Both suspected (not CT-proven) and CT-proven

\(^b\) data missing in one patient in the control group
Tranexamic Acid After Aneurysmal Subarachnoid Hemorrhage: Post-Hoc Analysis of the ULTRA Trial
Maud A Tjerkstra, Rene Post, Menno R Germans, et al.

Neurology published online October 20, 2022
DOI 10.1212/WNL.0000000000201160

This information is current as of October 20, 2022