Ultra-early tranexamic acid after subarachnoid haemorrhage (ULTRA) a randomised controlled trial

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Ultra-early tranexamic acid after subarachnoid haemorrhage (ULTRA): a randomised controlled trial

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Lancet 2021; 397: 112–18

Published Online December 21, 2020 https://doi.org/10.1016/S0140-6736(20)32518-6

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Summary

Background In patients with aneurysmal subarachnoid haemorrhage, short-term antifibrinolytic therapy with tranexamic acid has been shown to reduce the risk of rebleeding. However, whether this treatment improves clinical outcome is unclear. We investigated whether ultra-early, short-term treatment with tranexamic acid improves clinical outcome at 6 months.

Methods In this multicentre prospective, randomised, controlled, open-label trial with masked outcome assessment, adult patients with spontaneous CT-proven subarachnoid haemorrhage in eight treatment centres and 16 referring hospitals in the Netherlands were randomly assigned to treatment with tranexamic acid in addition to care as usual (tranexamic acid group) or care as usual only (control group). Tranexamic acid was started immediately after diagnosis in the presenting hospital (1 g bolus, followed by continuous infusion of 1 g every 8 h, terminated immediately before aneurysm treatment, or 24 h after start of the medication, whichever came first). The primary endpoint was clinical outcome at 6 months, assessed by the modified Rankin Scale, dichotomised into a good (0–3) or poor (4–6) clinical outcome. Both primary and safety analyses were according to intention to treat. This trial is registered at ClinicalTrials.gov, NCT02684812.

Findings Between July 24, 2013, and July 29, 2019, we enrolled 955 patients; 480 patients were randomly assigned to tranexamic acid and 475 patients to the control group. In the intention-to-treat analysis, good clinical outcome was observed in 287 (60%) of 475 patients in the tranexamic acid group, and 300 (64%) of 470 patients in the control group (treatment centre adjusted odds ratio 0·86, 95% CI 0·66–1·12). Rebleeding after randomisation and before aneurysm treatment occurred in 49 (10%) patients in the tranexamic acid and in 66 (14%) patients in the control group (odds ratio 0·71, 95% CI 0·48–1·04). Other serious adverse events were comparable between groups.

Interpretation In patients with CT-proven subarachnoid haemorrhage, presumably caused by a ruptured aneurysm, ultra-early, short-term tranexamic acid treatment did not improve clinical outcome at 6 months, as measured by the modified Rankin Scale.

Funding Fonds NutsOhra.

Introduction

In patients with aneurysmal subarachnoid haemorrhage, rebleeding from the ruptured aneurysm increases the risk of poor clinical outcome and all-cause mortality.[1] Rebleeding can be prevented by endovascular or neurosurgical obliteration of the ruptured aneurysm and therefore aneurysm treatment as early as possible is recommended;[2,3] however, because the majority of all rebleedings in aneurysmal subarachnoid haemorrhage occur within the first 24 h, overall rebleeding rates remain high.[4]

Although previous trials investigating long-term (ie, throughout the hospital admission) antifibrinolytic treatment in patients with subarachnoid haemorrhage showed a reduction in rebleeding, they failed to show a beneficial effect on clinical outcome.[5] This lack of effect on clinical outcome is probably because in most clinical trials, the potentially positive effect of a reduction in rebleeding was negated by a concomitant rise in delayed cerebral ischaemia.[5] Shortening the duration (to a maximum of 72 h) of tranexamic acid treatment also showed a reduction in the risk of rebleeding, without an increase in delayed cerebral ischaemia. Nonetheless, the effect of tranexamic acid on clinical outcome remained unclear.[6]

We did the ULTRA trial to investigate whether ultra-early, short-term treatment with tranexamic acid improves clinical outcome at 6 months.

Methods

Study design

We did a prospective, randomised, controlled, open-label trial with masked outcome assessment in eight treatment

Research in context

Evidence before this study

Treatment with antifibrinolytic medication (ie, tranexamic acid or epsilon aminocaproid acid) has been shown to reduce the risk of rebleeding in patients with an aneurysmal subarachnoid haemorrhage. Previous randomised controlled trials of antifibrinolytic therapy after aneurysmal subarachnoid haemorrhage throughout the length of hospital stay showed a reduced risk of rebleeding, but no improvement in clinical outcome. We searched ClinicalTrials.gov and PubMed up to Nov 1, 2020, with the terms ("subarachnoid haemorrhage" OR "subarachnoid hemorrhage") AND "antifibrinolytic" AND "clinical trial" with no date or language restrictions. A 2013 updated Cochrane review identified one trial that compared the efficacy of short-term (<72 h) tranexamic acid in aneurysmal subarachnoid haemorrhage, but this study was powered on the reduction of rebleedings and not on clinical outcome. We found no new trials done after the updated Cochrane review. Current international guidelines differ in their recommendations on whether or not to treat patients with antifibrinolytic treatment after aneurysmal subarachnoid haemorrhage.

Added value of this study

Despite weak evidence for a reduction in rebleeds in the tranexamic acid treatment group compared with the control group in our study, this did not result in improved clinical outcome. Even ultra-early initiation of tranexamic acid (immediately after CT confirmation) was not early enough to prevent a considerable proportion of rebleedings. Early aneurysm treatment (<24 h) as current practice seems to outweigh the reduction in rebleeding by tranexamic acid.

Implications of all the available evidence

This study provides evidence that tranexamic acid treatment in spontaneous subarachnoid haemorrhage, started immediately after CT diagnosis and continued until start of the aneurysm treatment as early as possible, does not improve clinical outcome. In the absence of reliable evidence that treatment with tranexamic acid improves clinical outcome, standard use cannot be recommended. Future studies should focus on other means to improve clinical outcome in subarachnoid haemorrhage.

centres (for patients with subarachnoid haemorrhage) and 16 referring hospitals in the Netherlands. The study was done in accordance with the principles of the Declaration of Helsinki and International Conference of Harmonization guidelines for Good Clinical Practice. The trial rationale and design, and the statistical analysis plan, have been published.[7,8]

The study protocol was approved by the institutional review board of the Academic Medical Centre (Amsterdam, the Netherlands; appendix pp 12–70). The institutional review board of each participating centre also approved the conduct of the study in that centre.

Patients

Adult patients (age ≥18 years) were eligible for inclusion if they were admitted to one of the participating referring hospitals or treatment centres, had signs and symptoms (ictus) for less than 24 h indicating subarachnoid haemorrhage, and had a non-contrast CT confirming subarachnoid haemorrhage. Exclusion criteria were a perimesencephalic bleeding pattern on CT in combination with a Glasgow Coma Scale score of 13–15, and without loss of consciousness directly after ictus or focal neurological deficit on admission; traumatic subarachnoid haemorrhage 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 h. A full list of inclusion and exclusion criteria and their definitions are provided in the appendix (p 5).

Because of the necessity of urgent administration of tranexamic acid and incapability of the vast majority of patients with subarachnoid haemorrhage to provide informed consent at short notice, the trial was done using deferred consent, under the exception from informed consent requirements for emergency research.[9,10] As soon as the informed consent dialogue no longer interfered with proper and rapid diagnosis and aneurysm treatment, patients or their legally authorised representatives were notified about enrolment into the trial by the research team and asked to provide written informed consent for continued tranexamic acid treatment (if applicable) and data collection until the end of the trial.

Randomisation and masking

Patients were randomly assigned (1:1), as soon as possible after a non-contrast CT-proven diagnosis of spontaneous subarachnoid haemorrhage, to receive either ultra-early tranexamic acid treatment in addition to usual care (tranexamic acid group), or care as usual only (control group). Tranexamic acid was subsequently started as soon as possible, if assigned to the tranexamic acid group. Randomisation was done with a secured web-based system that stratified according to permuted blocks (random block sizes; maximum of 12) by treatment centre. Health-care providers in the treatment centres enrolled the patient using the Alea tool (TENALEA-MV, 2003–05) for clinical trials. Alea assigned participants to the trial groups. Health-care providers report on adverse events but had no further involvement in the rest of the trial. Patients, investigators, and health-care providers were not masked to study drug assignment.

Procedures

Once patients were randomly assigned to treatment, patients in the intervention group were immediately

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See Online for appendix

administered an intravenous bolus of 1 g tranexamic acid, directly followed by 1 g continuous intravenous infusion of tranexamic acid every 8 h. Treatment was continued until the start of endovascular or surgical treatment of the aneurysm or until a maximum of 24 h (ie, a maximum of 4 g tranexamic acid in total), whichever came first. Tranexamic acid treatment was stopped if no aneurysm was seen after the diagnostic workup (CT angiography or digital subtraction angiography), when other intracranial pathology was responsible for the subarachnoid haemorrhage, or when patients or their legally authorised representatives refused further treatment with tranexamic acid.

Outcomes

The primary endpoint was clinical outcome, assessed with the modified Rankin Scale (mRS) by a standardised and validated telephone interview, at 6 months after randomisation.[11–13] Assessments were done by trained research nurses who were masked to treatment allocation. Research nurses were trained, according to a standard operating procedure, how to perform the structured telephone interview to assess the mRS score. Because no universally accepted threshold for dichotomising a good versus a poor outcome on the mRS score exists, the scores were subsequently dichotomised into a good (mRS 0–3) or poor (mRS 4–6) clinical outcome.[14] Secondary outcomes included excellent clinical outcome (mRS 0–2) at 6 months, ordinal shift analysis of the mRS scores at 6 months (sensitivity analyses) and all-cause mortality at 30 days and after 6 months.

Serious adverse events reported after randomisation were defined as: rebleeding after randomisation and before treatment of the aneurysm, hydrocephalus, delayed cerebral ischaemia, complications of treatment of the aneurysm (per-procedural thromboembolic, per-procedural rupture, cerebral infarction related to clipping); other complications (extracranial thrombosis, deep venous thrombosis, pulmonary embolism, intracranial and extracranial haemorrhagic complications, severe hyponatraemia, pneumonia, infectious meningitis, urinary tract infection, seizures, delirium, and Terson's syndrome); suspected unexpected serious adverse drug reactions or other serious adverse events during hospital admission. Definitions of the aforementioned serious adverse events are listed in the appendix (pp 6–7).

	Tranexamic acid group (n=480)	Control group (n=475)
Age, years	58·4 (12·6)	58·4 (12·3)
Sex		
Female	332 (69%)	312 (66%)
Male	148 (31%)	163 (34%)
WFNS[15]*		
I	170 (36%)	188 (40%)
II	95 (20%)	94 (20%)
III	24 (5%)	16 (3%)
IV	93 (20%)	94 (20%)
V	88 (19%)	80 (17%)
Fisher Grade Score[16]		
II	36 (8%)	20 (4%)
III	126 (26%)	151 (32%)
IV	318 (66)%	304 (64%)
Medication use†		
Platelet inhibitor	61 (13%)	61 (13%)
Anticoagulation	15 (3%)	19 (4%)
Antihypertensive drugs	113 (24%)	110 (23%)
None of the above	326 (69%)	325 (69%)
Location of aneurysm‡		
Anterior circulation	332 (70%)	327 (69%)
Posterior circulation	76 (16%)	77 (16%)
None	66 (14%)	69 (15%)
Treatment modality§		
Endovascular	272 (67%)	258 (64%)
Clipping	86 (21%)	89 (22%)
None	51 (13%)	57 (14%)

Data are mean (SD) or n (%). Percentages might not total 100 because of rounding. WFNS=World Federation of Neurosurgical Societies. *WFNS score could not be assessed in 13 (1%) patients. †Patients had none, or one or more of the listed medications before subarachnoid haemorrhage, resulting in percentages that do not total 100. In all categories, data for five (<1%) patients were missing. Reversal of anticoagulation either with prothrombin complex or platelet transfusion was done according to local hospital treatment protocols. ‡In eight (<1%) patients this could not be assessed, therefore scored as missing. §In 142 patients, no ruptured aneurysm was found.

Table 1: **Characteristics of participants at baseline**

Statistical analysis

The power calculation was based on the assumption that a good clinical outcome would occur in 69·0% of the patients in the control group and in 77·1% of the patients in the tranexamic acid group (through a reduction of the rate of rebleeding from 17% to 3·9%).[7] The defined sample size of 950 participants provided a power of 80% to detect an absolute 8·1% difference in good clinical outcome between groups with a type 1 error rate of 0·05 and included correction for withdrawals.

An independent data and safety monitoring board assessed the safety of the trial participants, and efficacy and overall progress of the study and did a masked interim analysis after half of the patients (n=475) were enrolled.

Analyses were based on the intention-to-treat principles. Differences between treatment groups are listed with odds ratio (OR) and 95% CI. For the primary outcome and secondary outcomes, multivariable logistic regression was used to calculate adjusted odds ratios (aORs) for the influence of treatment centre and potential differences in baseline characteristics. Additionally, we did per-protocol and as-treated analyses. More detailed information is given in the statistical analysis plan.[8]

Statistical analyses were done using IBM SPSS Statistics, version 25.

This trial is registered at ClinicalTrials.gov, NCT02684812.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript. RP, MAT, BAC, and DV had full access to all the data in the study. RP, WPV, and DV had final responsibility for the decision to submit for publication.

Results

We enrolled 955 participants between July 24, 2013, and July 29, 2019. The mean age was 58·4 years (SD 12·4), and 644 (67%) of 955 participants were female (table 1). The median time from ictus to first CT was 93 min (IQR 65–165; n=866). In 66 (14%) of 480 patients in the tranexamic acid group, and 69 (15%) of 475 patients in the control group no causative aneurysm was found. The median time to start aneurysm treatment after CT diagnosis was 14 h (IQR 5–20; n=708). Other time intervals are listed in the appendix (p 8).

480 (50%) patients were assigned to the tranexamic acid group and 475 (50%) patients to the control group. One patient received tranexamic acid after allocation to the control group on request of the family (figure 1). The main reasons for tranexamic acid discontinuation was treatment of the aneurysm in 255 (53%) of 480 patients, or expiration of 24 h after start of tranexamic acid in 74 (15%) of 480 patients (according to the study protocol). Other reasons are listed in the appendix (p 8). The median time between first signs and symptoms suggestive of subarachnoid haemorrhage and start of tranexamic acid treatment (n=390) was 185 min (IQR 130–333).

The primary outcome was obtained in 945 (99%) of 955 patients; five patients in each group were lost to follow-up (figure 1). In the intention-to-treat analysis, 287 (60%) of 475 patients in the tranexamic acid group and 300 (64%) of 470 patients in the control group had a good clinical outcome (mRS 0–3; OR 0·87, 95% CI 0·67–1·13; figure 2). After adjustment for treatment centre, the aOR was 0·86 (95% CI 0·66–1·12; table 2). The results of the as-treated and per-protocol analyses showed no significant difference in clinical outcome between treatment groups (appendix pp 8–9).

Ordinal shift analysis showed no differences between treatment groups (OR 0·80, 95% CI 0·64–1·01), which remained after adjustment for treatment centre (aOR 0·80, 95% CI 0·63–1·01; figure 2). Excellent clinical outcome (mRS 0–2) was significantly lower in the tranexamic acid group than in the control group (OR 0·74, 95% CI 0·57–0·96), which remained after adjustment for treatment centre (aOR 0·73, 95% CI 0·57–0·95). All-cause mortality at 30 days and 6 months did not differ between the two groups (table 2). The results of the as-treated analysis and per-protocol analysis were consistent with those of the intention-to-treat analysis (appendix pp 8–9).

Predefined serious adverse events including disease-related complications and other serious adverse events reported during hospital admission are listed in table 3. Rebleeding after randomisation, but before aneurysm treatment, occurred in 49 (10%) of 480 patients in the tranexamic acid group and 66 (14%) of 475 patients in the control group (OR 0·71, 95% CI 0·48–1·04). CT-proven rebleeding before aneurysm treatment occurred in 42 (9%) of 480 patients in the tranexamic acid group and

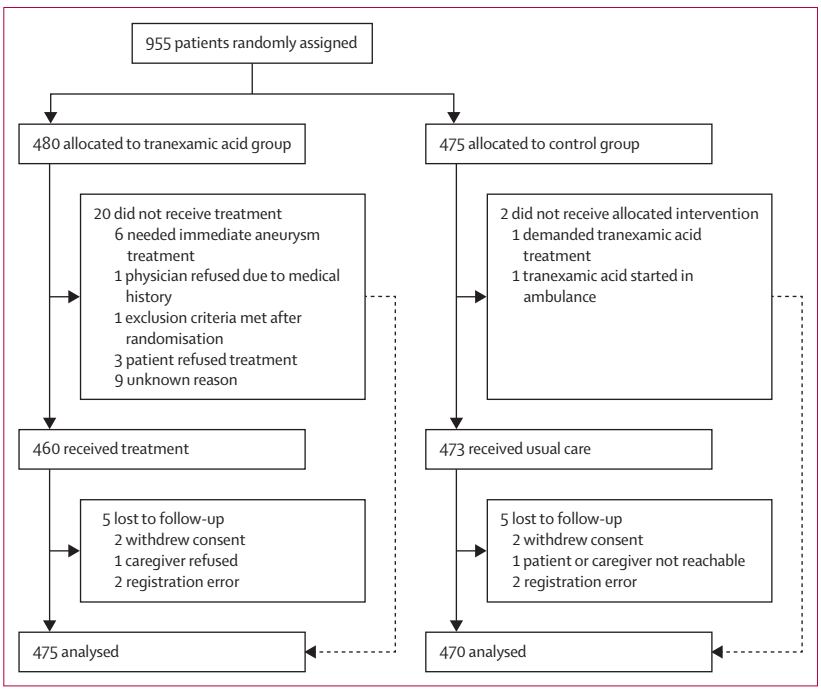

Figure 1: **Trial allocation profile**

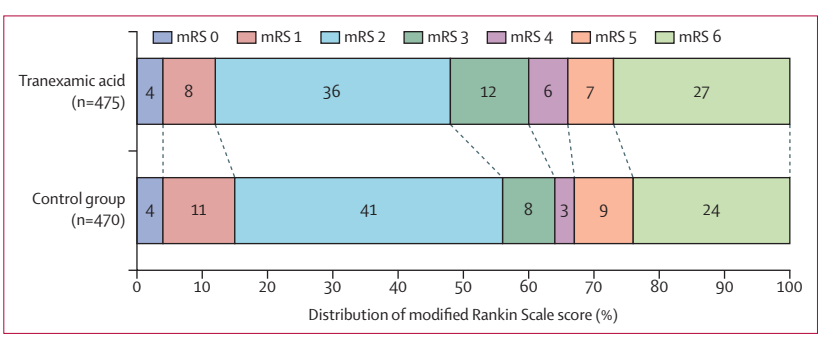

Figure 2: **Distribution of modified Rankin Scale score at 6 months in the intention-to-treat analysis**
Ten patients were lost to follow-up. Stacked bar chart of scores on the modified Rankin Scale (0–6). A score of 0 indicates no symptoms, 1 no clinically significant disability, 2 slight disability (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 univariable ordinal shift analysis (common odds ratio [OR], 0·80; 95% CI, 0·64 to 1·01), as well as after adjustment for treatment centre (adjusted common OR 0·80 (95% CI 0·63–1·01).

	Tranexamic acid group (n=480)	Control group (n=475)	OR (95% CI)	aOR (95% CI)
Primary outcome				
Good clinical outcome (mRS 0–3)*	287 (60%)	300 (64%)	0·87 (0·67–1·13)	0·86 (0·66–1·12)
Secondary outcomes				
Excellent clinical outcome (mRS 0–2)*	229 (48%)	262 (56%)	0·74 (0·57–0·96)	0·73 (0·57–0·95)
Shift analysis (ordinal)*	NA	NA	0·80 (0·64–1·01)	0·80 (0·63–1·01)†
mRS 0	17 (4%)	20 (4%)	NA	NA
mRS 1	39 (8%)	51 (11%)	NA	NA
mRS 2	173 (36%)	191 (41%)	NA	NA
mRS 3	58 (12%)	38 (8%)	NA	NA
mRS 4	26 (6%)	15 (3%)	NA	NA
mRS 5	34 (7%)	41 (9%)	NA	NA
mRS 6	128 (27%)	114 (24%)	NA	NA
All-cause mortality at 30 days	103 (22%)	104 (22%)	0·98 (0·72–1·33)	0·98 (0·72–1·33)
All-cause mortality at 6 months*	128 (27%)	114 (24%)	1·15 (0·86–1·54)	1·15 (0·86–1·55)

Data are n (%), unless stated otherwise. OR=odds ratio. aOR=adjusted odds ratio. mRS=modified Rankin Scale. NA=not applicable. *Ten patients lost to follow-up (tranexamic acid group n=475; control group n=470). †The proportional odds assumption was violated after correcting for treatment centre. After excluding six patients from the treatment centre with the smallest number of inclusions, the proportional odds assumption was not violated. aORs were equal in both the violated (0·80, 95% CI 0·63–1·01) and the unviolated analysis (0·81, 0·64–1·02).

Table 2: **Primary outcome (mRS score at 6 months) and secondary outcomes in the intention-to-treat group***

57 (12%) of 475 patients in the control group (OR 0·70, 95% CI 0·46–1·07). Delayed cerebral ischaemia occurred in 108 (23%) of 480 patients in the tranexamic acid group and 106 (22%) of 475 patients in the control group (OR 1·01, 95% CI 0·74–1·37). Thromboembolic complications during endovascular treatment occurred in 29 (11%) of 272 patients in the tranexamic acid group and in 33 (13%) of 258 patients in the control group (OR 0·81, 95% CI 0·48–1·38). All other serious adverse events were comparable between groups. The results of the as-treated analysis were consistent with those of the intention-to-treat analysis (appendix pp 9–10).

Discussion

In patients with a spontaneous, CT-proven subarachnoid haemorrhage, presumably caused by a ruptured aneurysm, ultra-early tranexamic acid treatment initiated immediately after diagnosis in the primary hospital, with a maximum treatment duration of 24 h, did not improve clinical outcome at 6 months.

In 1984, the beneficial effect of long-term (throughout the hospital admission) tranexamic acid on rebleeding was shown to be offset by an increased risk of delayed cerebral ischaemia and therefore failed to show a beneficial effect on clinical outcome.[17] In 2000, long-term tranexamic acid combined with standard nimodipine treatment and maintenance of normovolaemia (so-called anti-ischaemic treatments) was shown to reduce the risk of rebleeding without a concomitant increased risk in delayed cerebral ischaemia.[18] However, despite plasma volume expansion and induced hypertension when delayed cerebral ischaemia occurred, delayed cerebral ischaemia was more often the cause of poor clinical outcome in the antifibrinolytic treatment group.[18] In 2002, a randomised clinical multicentre trial[6] showed that short-term (<72 h) treatment with antifibrinolytic therapy reduced the occurrence of rebleeding with no statistically significant increase in delayed cerebral ischaemia and showed a tendency towards improved clinical outcome. Unfortunately, that trial was not powered to show any effect on clinical outcome.

For optimal reduction of the rate of rebleeding, we initiated ultra-early tranexamic acid treatment as soon as the diagnosis has been made—ie, immediately after CT confirmation of subarachnoid haemorrhage and randomisation, if applicable, when patients were still in the referring hospital. Because the majority of recurrent bleedings occurs within 24 h, tranexamic acid treatment was continued for only a short period of time (ie, until the aneurysm had been obliterated), with a maximum of 24 h, thereby optimally reducing the increased risk of delayed cerebral ischaemia. In addition, we powered our trial not on the rate of rebleeding, but on the clinical outcome at 6 months, because long-term clinical outcome is what matters most to patients.[4]

In our study, the median interval between the first signs and symptoms suggestive of aneurysmal subarachnoid haemorrhage and the actual start of the tranexamic acid infusion was 3 h; thus, even ultra-early start of tranexamic acid infusion is too late to prevent a considerable proportion of rebleedings, considering that half of all rebleedings occurs within 3 h.[4] Although ultra-early administration of tranexamic acid did reduce the rate of rebleedings somewhat, this reduction in rebleeds did not meet the predefined threshold for statistical significance, and the proportion of rebleedings in the control group was also low in our trial, which could explain the lack of significant difference between groups. A contributing factor might also be that usual practice is to obliterate the aneurysm as early as possible, preferably within 24 h, reflected in the median time from diagnosis to aneurysm treatment of 14 h in our trial. In contrast with previous tranexamic acid trials, this early aneurysm treatment now possibly outweighs the reduction in rebleeding by tranexamic acid. In the trial by Hillman and colleagues,[6] in which short-term (<72 h) treatment with antifibrinolytic therapy was used with almost comparable dose regimens, the rate of rebleeds was substantially lower than in our study. This difference could be explained by the fact that the first hospital contact after subarachnoid haemorrhage in their study was more than 4 h, as compared with 1·5 h in our trial.

Although tranexamic acid treatment did not have a positive effect on good clinical outcome (mRS 0–3 at 6 months), treatment with tranexamic acid was associated

with a lower rate of excellent clinical outcome (mRS 0–2 at 6 months). There were no differences in the serious adverse events nor baseline differences in our study; thus, we surmise that other factors—eg, early brain injury, or not-predefined complications—might have played a role in accounting for poor outcome, either alone or in combination.

The pragmatic design of our trial accurately represents day-to-day usual practice. More importantly, our study represents current practice to treat the aneurysm as early as possible. Because the timing of tranexamic acid treatment in our trial was not soon enough to prevent a considerable number of rebleedings, it might be worth considering whether tranexamic acid treatment should be administered by ambulant caregivers (first responders). However, because tranexamic acid could lead to complications in other diagnoses that might present with acute headache, such as cerebral venous sinus thrombosis, it is preferably only given once the diagnosis of a subarachnoid haemorrhage has been confirmed by CT.

Future studies should focus on other strategies to improve clinical outcome in these patients—eg, emergency aneurysm repair within hours.[19] However, the numbers needed to treat to prevent poor clinical outcome due to rebleeding was shown to be 59 for aneurysm occlusion within 1 h, and 250 for aneurysm occlusion within 4 h.[20] In addition, the logistics and burden on health-care systems to ensure around-the-clock availability of intervention teams is probably not feasible in most centres and countries. Furthermore, many patients with aneurysmal subarachnoid haemorrhage are initially presented to a secondary care hospital and need to be transferred to a tertiary care hospital after diagnosis of subarachnoid haemorrhage, making emergency aneurysm repair almost impossible. Besides the logistic considerations, emergency aneurysm repair might lead to an increase in periprocedural aneurysm rerupture due to clot instability in the first hours after initial ictus.[15,16] Another strategy to reduce the risk of rebleeding might be blood pressure control between CT diagnosis and aneurysm obliteration.[21] This treatment could be initiated in the prehospital phase by paramedical caregivers. However, randomised trials for these strategies have not yet been done and the effect on outcome is therefore unclear. Because the majority of patients in our trial had either a disease-related, or other serious adverse events occurring during the course of their disease—which is very common in patients after aneurysmal subarachnoid haemorrhage—future strategies could focus on interventions to reduce, or mitigate, this large proportion of in-hospital complications to eventually improve clinical outcome.

Our trial has some limitations. Treatment with tranexamic acid was not masked, so patients and treating physicians could have been aware of group allocation, leading to possible treatment bias. The primary outcome assessment at 6 months was done by specialised trained nurses, who were unaware of the treatment group allocation. Although masked assessment was applied to the primary outcome, there was no masking for the all-cause mortality and reporting on serious adverse events. The high proportion of patients without underlying aneurysm (so-called angiogram-negative subarachnoid haemorrhages) in our study might have diluted the effects of tranexamic acid treatment, because recurrent bleedings in this group of patients are uncommon. However, due to our pragmatic design to randomly assign patients as soon as possible after CT confirmation of the diagnosis, the inclusion of angiogram-negative patients was unavoidable. Excluding non-aneurysmal patients before randomisation would cause a delay in the ultra-early start of tranexamic acid, because additional investigations are needed for confirmation of absence or presence of an aneurysm. We therefore accounted for this group in our sample size calculation, when estimating the effect sizes of rebleeding and clinical outcome.

In conclusion, our trial shows that tranexamic acid treatment, initiated immediately after CT confirmation of

	Tranexamic acid group (n=480)	Control group (n=475)	OR (95% CI)
Any serious adverse event	386 (80%)	372 (78%)	1·14 (0·83–1·56)
All rebleedings before aneurysm treatment*	49 (10%)	66 (14%)	0·71 (0·48–1·04)
CT-proven rebleedings	42 (9%)	57 (12%)	0·70 (0·46–1·07)
Hydrocephalus	292 (61%)	262 (55%)	1·26 (0·98–1·63)
Delayed cerebral ischaemia†	108 (23%)	106 (22%)	1·01 (0·74–1·37)
Thromboembolic complications during endovascular treatment‡	29 (11%)	33 (13%)	0·81 (0·48–1·38)
Cerebral infarction related to clipping procedure§	22 (26%)	18 (21%)	1·34 (0·66–2·72)
Per-procedural rupture‡§			
Coiling	16 (6%)	12 (5%)	1·28 (0·59–2·76)
Clipping	17 (20%)	22 (25%)	0·75 (0·37–1·54)
Extracranial thrombosis	8 (2%)	7 (2%)	1·13 (0·41–3·15)
Deep venous thrombosis	0	2 (<1%)	0·20 (0·01–4·13)
Pulmonary embolism	6 (1%)	5 (1%)	1·19 (0·36–3·93)
Haemorrhagic complication¶	29 (6%)	34 (7%)	0·84 (0·50–1·40)
Severe hyponatraemia	12 (3%)	9 (2%)	1·33 (0·55–3·18)
Pneumonia	63 (13%)	67 (14%)	0·92 (0·64–1·33)
Infectious meningitis	37 (8%)	31 (7%)	1·20 (0·73–1·96)
Urinary tract infection	44 (9%)	45 (10%)	0·96 (0·62–1·49)
Seizure	59 (12%)	40 (8%)	1·52 (1·00–2·33)
Delirium	65 (14%)	60 (13%)	1·08 (0·74–1·58)
Terson's syndrome	18 (4%)	18 (4%)	0·99 (0·51– 1·93)
SUSARs	0	0	NA
Other	134 (28%)	126 (27%)	1·07 (0·81–1·43)

Data are n (%), unless stated otherwise. OR=odds ratio. aOR=adjusted odds ratio. SUSARs=severe unexpected serious adverse events. NA=not applicable. *Both suspected (not CT proven) and CT proven. †Data missing in one patient in the control group. ‡Tranexamic acid group n=272; control group n=258. §Tranexamic acid group n=86; control group n=88. ¶Data missing in one patient in the tranexamic acid group.

Table 3: **Serious adverse events in the intention-to-treat group**

a subarachnoid haemorrhage, did not improve clinical outcome at 6 months, as measured by mRS. Based on this trial and previous evidence, routine use of tranexamic acid in spontaneous subarachnoid haemorrhage cannot be recommended. Because a large proportion of rebleedings occurs before diagnosis, and many patients in the intervention arm still had rebleedings, despite ultra-early start of tranexamic acid therapy, other strategies to improve clinical outcome after aneurysmal subarachnoid haemorrhage should be explored, probably focusing on reducing other complications during the disease course.

Contributors

DV was the principal investigator. RP, MAT, MDIV, KJ, RWK, NDK, PWAW, JFCW, HK, DN, BvdP, GR, FdB, PHAH, LJAR, PJAMB, RMvdB-V, VIHK, TCvdR, IB, JvdV, HPB, and HDB contributed to trial conduct and data collection. DV provided the statistical expertise. RP, WPV and DV wrote the Article. RP, MAT, and DV accessed and verified the data. All authors read, commented on, and approved the final Article.

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Declaration of interests

RvdB reports grants from Cerenovus neurovascular, outside the submitted work; CBLMM reports grants from CVON/Dutch Heart Foundation, European Commission, Dutch Health Evaluation Program, TWIN Foundation, and 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. YBWEMR is a minor shareholder of Nico-Lab. CJMK reports funding from the Dutch Heart Foundation (clinical established investigator grant number 2012T077), and ASPASIA grant from The Netherlands Organisation for Health Research and Development, ZonMw (grant number 015008048), outside the submitted work. MDIV reports funding from the Dutch Heart Foundation (clinical established investigator grant number 2018T0769). All other authors declare no competing interests.

Data sharing

All data requests should be submitted to DV for consideration. Access to anonymised data may be granted following review.

Acknowledgments

This study was funded by the Fonds NutsOhra (project 1202–31). 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 centres who contributed to the data collection forms.

References

1 Stienen MN, Germans M, Burkhardt JK, et al. Predictors of in-hospital death after aneurysmal subarachnoid hemorrhage: analysis of a nationwide database (Swiss SOS [Swiss study on aneurysmal subarachnoid hemorrhage]). *Stroke* 2018; **49:** 333–40.

2 Connolly ES Jr, Rabinstein AA, Carhuapoma JR, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2012; **43:** 1711–37.

3 Steiner T, Juvela S, Unterberg A, Jung C, Forsting M, Rinkel G. European Stroke Organization guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage. *Cerebrovasc Dis* 2013; **35:** 93–112.

4 Germans MR, Coert BA, Vandertop WP, Verbaan D. Time intervals from subarachnoid hemorrhage to rebleed. *J Neurol* 2014; **261:** 1425–31.

5 Baharoglu MI, Germans MR, Rinkel GJ, et al. Antifibrinolytic therapy for aneurysmal subarachnoid haemorrhage. *Cochrane Database Syst Rev* 2013; **8:** CD001245.

6 Hillman J, Fridriksson S, Nilsson O, Yu Z, Saveland H, Jakobsson KE. Immediate administration of tranexamic acid and reduced incidence of early rebleeding after aneurysmal subarachnoid hemorrhage: a prospective randomized study. *J Neurosurg* 2002; **97:** 771–78.

7 Germans MR, Post R, Coert BA, Rinkel GJ, Vandertop WP, Verbaan D. Ultra-early tranexamic acid after subarachnoid hemorrhage (ULTRA): study protocol for a randomized controlled trial. *Trials* 2013; **14:** 143.

8 Post R, Germans MR, Coert BA, Rinkel GJE, Vandertop WP, Verbaan D. Update of the ULtra-early TRranexamic Acid after Subarachnoid Hemorrhage (ULTRA) trial: statistical analysis plan. *Trials* 2020; **21:** 199.

9 Mosesso VN Jr, Brown LH, Greene HL, et al. Conducting research using the emergency exception from informed consent: the Public Access Defibrillation (PAD) trial experience. *Resuscitation* 2004; **61:** 29–36.

10 Mentzelopoulos SD, Mantzanas M, van Belle G, Nichol G. Evolution of European Union legislation on emergency research. *Resuscitation* 2015; **91:** 84–91.

11 Wilson JT, Hareendran A, Grant M, et al. Improving the assessment of outcomes in stroke: use of a structured interview to assign grades on the modified Rankin Scale. *Stroke* 2002; **33:** 2243–46.

12 Wilson JT, Hareendran A, Hendry A, Potter J, Bone I, Muir KW. Reliability of the modified Rankin Scale across multiple raters: benefits of a structured interview. *Stroke* 2005; **36:** 777–81.

13 Janssen PM, Visser NA, Dorhout Mees SM, Klijn CJ, Algra A, Rinkel GJ. Comparison of telephone and face-to-face assessment of the modified Rankin Scale. *Cerebrovasc Dis* 2010; **29:** 137–39.

14 Stienen MN, Visser-Meily JM, Schweizer TA, Hänggi D, Macdonald RL, Vergouwen MDI. Prioritization and timing of outcomes and endpoints after aneurysmal subarachnoid hemorrhage in clinical trials and observational studies: proposal of a multidisciplinary research group. *Neurocrit Care* 2019; **30** (suppl 1): 102–13.

15 van Lieshout JH, Verbaan D, Donders R, et al. Periprocedural aneurysm rerupture in relation to timing of endovascular treatment and outcome. *J Neurol Neurosurg Psychiatry* 2019; **90:** 363–65.

16 Larsen CC, Sørensen B, Nielsen JD, Astrup J. Reduced clot-stability during the first 6 hours after aneurysmal subarachnoid haemorrhage—a prospective case-control study. *Thromb Res* 2012; **129:** e229–32.

17 Vermeulen M, Lindsay KW, Murray GD, et al. Antifibrinolytic treatment in subarachnoid hemorrhage. *N Engl J Med* 1984; **311:** 432–37.

18 Roos Y. Antifibrinolytic treatment in subarachnoid hemorrhage: a randomized placebo-controlled trial. *Neurology* 2000; **54:** 77–82.

19 Zipfel GJ. Ultra-early surgery for aneurysmal subarachnoid hemorrhage. *J Neurosurg* 2015; **122:** 381–82.

20 Tack RW, Vergouwen MD, van der Schaaf I, van der Zwan A, Rinkel GJ, Lindgren AE. Preventable poor outcome from rebleeding by emergency aneurysm occlusion in patients with aneurysmal subarachnoid haemorrhage. *Eur Stroke J* 2019; **4:** 240–46.

21 Narotam PK, Puri V, Roberts JM, Taylon C, Vora Y, Nathoo N. Management of hypertensive emergencies in acute brain disease: evaluation of the treatment effects of intravenous nicardipine on cerebral oxygenation. *J Neurosurg* 2008; **109:** 1065–74.