

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about the clinical trial.

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Supplemental methods

Definitions of bleeding patterns

- **Subarachnoid bleeding pattern**

Non-contrast computed tomography with hyperdensity in the basal cisterns and/or Sylvian or interhemispheric fissures or an intraparenchymal hyperdensity consistent with a hematoma from an anterior, a pericallosal, a posterior or a middle cerebral artery aneurysm.

Definitions of complications due to SAH

- **Suspected or CT-confirmed recurrent bleeding**

- Suspected recurrent bleeding**

- Definition: Sudden neurological deterioration with change in vital parameters suggestive for recurrent bleeding not confirmed by CT. Sudden increase of fresh blood production from an external ventricular drain.

- CT-confirmed recurrent bleeding**

- Definition: Presence of more SAH on CT than in a previous investigation.

- **Hydrocephalus** (treated with therapeutic lumbar puncture, lumbar or ventricular drainage or definitive shunt)

Definition of hydrocephalus: gradual onset of deterioration of consciousness measured on

the Glasgow Coma Scale with CT evidence of enlarged ventricles and no other explanation for deterioration.

- **Ischemic stroke (delayed cerebral ischemia)**

Definition according to the criteria of Vergouwen et al.¹: The occurrence of focal neurological impairment (such as hemiparesis, aphasia, apraxia, hemianopia, or neglect), or a decrease of at least 2 points on the Glasgow Coma Scale (either on the total score or on one of its individual components [eye, motor on either side, verbal]). This should last for at least 1 hour, is not apparent immediately after aneurysm occlusion, and cannot be attributed to other causes by means of clinical assessment, CT or magnetic resonance imaging scanning of the brain, and appropriate laboratory studies.

Definitions of treatment complications during aneurysm repair

- **Per-procedural rupture during endovascular or surgical treatment**

Definition: extravasation of contrast dye outside of the vascular wall or perforation of the microcatheter, microwire or coil through the aneurysm wall with or without a sudden change in vital parameters suggestive for recurrent bleeding. Rupture of aneurysm during aneurysm surgery.

- **Per-procedural thrombo-embolic event during endovascular treatment**

Definition: reduced passage or stasis of contrast in an artery or slowed venous outflow without the aspect of vascular spasm. Evaluated by the treating intervention neuro radiologist.

Definitions of other adverse events

- **Extracranial thrombosis**

Definition: Lower extremity deep venous thrombosis, upper extremity venous thrombosis, upper extremity arterial thrombosis or pulmonary embolism diagnosed after clinical suspicion.

- **Haemorrhagic complications (intra- and extracranial)**

Definition: on CT proven intracranial haemorrhage (intracerebral, intraventricular, subdural or epidural), increased or newly developed after the primary haemorrhage; any extra cranial haemorrhage for which intervention is necessary; either with neurological deterioration or not.

- **Severe hyponatremia**

At least one measurement of a sodium concentration below 125 mmol/L (mEq/L).

- **Pneumonia**

Definition: Positive sputum culture and/or positive chest x-ray.

- **Meningitis**

Definition: Positive CSF culture.

- **Urinary tract infection**

Definition: Positive urine culture or abnormal urine sample.

- **Seizures, delirium, Terson's syndrome and all other (serious) adverse events**

Definition: At the discretion of the treating physician.

Supplemental results

eTable 1. Additional baseline characteristics of 813 subarachnoid haemorrhage patients by as-treated analyses

| Intention-to-treat analysis | | | |
|---|-----------------------|---------------|--------------|
| | Tranexamic acid group | Control group | Significance |
| | N=409 | N=404 | p-value |
| Medication use^a | | | |
| Platelet inhibitor | 48 (12) | 49 (12) | 0·59 |
| Anticoagulation | 13 (3) | 14 (3) | 0·85 |
| Antihypertensive | 94 (24) | 94 (23) | 0·51 |
| None of the above | 269 (69) | 288 (69) | 0·60 |
| Location of aneurysm^b | | | 0·93 |
| Anterior circulation | 332 (81) | 327 (81) | |
| Posterior circulation | 76 (19) | 77 (19) | |

^a Patients had none or either one or more of the listed medications prior to subarachnoid haemorrhage, resulting that percentages do not add up to a total 100. Medication use: unknown in four patients (0.1%).

^B One patient with two potentially causative aneurysms in both anterior and posterior circulation.

eTable 2. Baseline characteristics of 812 subarachnoid haemorrhage patients by as-treated analyses

| As-treated analysis | | | |
|---|------------------------------|----------------------|---------------------|
| | Tranexamic acid group | Control group | Significance |
| | N=395 | N=417 | p-value |
| Age (years), mean (SD) | 58·4 (12·7) | 58·4 (12·2) | 0·87 |
| Female | 286 (72) | 291 (70) | 0·41 |
| WFNS^{2,a} | | | 0·57 |
| I | 126 (33) | 148 (36) | |
| II | 77 (20) | 74 (18) | |
| III | 23 (6) | 16 (4) | |
| IV | 84 (22) | 95 (23) | |
| V | 78 (20) | 80 (19) | |
| Fisher Grade Score³ | | | 0·20 |
| II | 21 (5) | 15 (4) | |
| III | 99 (25) | 124 (30) | |
| IV | 275 (70) | 278 (67) | |
| Medication use^a | | | |
| Platelet inhibitor | 48 (12) | 49 (12) | 0·84 |
| Anticoagulation | 13 (3) | 14 (3) | 0·97 |
| Antihypertensive | 94 (24) | 94 (23) | 0·64 |
| None of the above | 269 (69) | 288 (69) | 0·85 |
| Location of aneurysm^b | | | 0·70 |
| Anterior circulation | 318 (81) | 341 (82) | |
| Posterior circulation | 76 (19) | 76 (18) | |
| Treatment modality^c | | | 0·59 |
| Endovascular | 264 (67) | 265 (64) | |
| Clipping | 81 (21) | 94 (23) | |
| None | 49 (12) | 58 (14) | |

^a Patients had none or either one or more of the listed medications prior to subarachnoid haemorrhage, resulting that percentages do not add up to a total 100. Unknown medication use in four patients (0.1%).

^b One patient with two potentially causative aneurysms in both anterior and posterior circulation.

^c One patient with two potentially causative aneurysms, of which one was clipped and one was treated endovascularly

eTable 3. Frequency of tranexamic acid (TXA) discontinuation in patients allocated for tranexamic acid treatment (N=409) by reason

| Reasons for discontinuation of tranexamic acid treatment | N (%) |
|---|--------------|
| Start treatment aneurysm | 252 (62) |
| 24h after first TXA administration | 58 (14) |
| Initially no causative aneurysm found on imaging | 4 (1) |
| Due to an adverse event | 24 (6) |
| TXA not administered | 14 (3) |
| Discontinued for unspecified reasons | 57 (14) |

eTable 4. As-treated analyses for primary outcome (modified Rankin Scale score at six months) and secondary outcomes

| | As-treated analysis* | | | |
|---|--------------------------------------|------------------------------|--------------------|---------------------|
| | Tranexamic acid group (N=395) | Control group (N=417) | OR (95% CI) | aOR (95% CI) |
| Good clinical outcome^a (mRS 0-3) | 227 (58) | 244 (59) | 0·95 (0·72-1·26) | 0·97 (0·72-1·31) |
| Excellent clinical outcome^a (mRS 0-2) | 177 (45) | 209 (51) | 0·80 (0·61-1·06) | 0·80 (0·60-1·07) |
| (Ordinal) shift analysis^a | | | 0·85 (0·66-1·09) | 0·87 (0·68 – 1·12) |
| mRS0 | 13 (3) | 16 (4) | | |
| mRS1 | 25 (6) | 41 (10) | | |
| mRS2 | 139 (36) | 152 (37) | | |
| mRS3 | 50 (13) | 35 (9) | | |
| mRS4 | 22 (6) | 16 (4) | | |
| mRS5 | 31 (8) | 40 (10) | | |
| mRS6 | 111 (28) | 112 (27) | | |
| All-cause mortality at 30 days | 93 (24) | 99 (24) | 0·99 (0·72-1·37) | 0·96 (0·69-1·36) |
| All-cause mortality at six months | 111 (28) | 112 (27) | 1·06 (0·78-1·45) | 1·05 (0·76-1·44) |

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=391, control group N=412)

eTable 5. Intention-to-treat analyses for complications during hospital admissions

| | Intention-to-treat analysis | | |
|---|--|-----------------------------------|------------------|
| | Tranexamic acid group (<i>N</i> =409) | Control group (<i>N</i> =404) | OR (95% CI) |
| Any SAE | 346 (85) | 341 (84) | 1·02 (0·69-1·48) |
| Hydrocephalus | 261 (64) | 238 (59) | 1·23 (0·93-1·63) |
| Cerebral infarction related to clipping procedure ^a | 22 (13) | 18 (21) | 1·34 (0·66-2·72) |
| Peri-procedural rupture | | | |
| Coiling | 16 (6) | 12 (5) | 1·28 (0·59-2·76) |
| Clipping | 17 (20) | 22 (25) | 0·75 (0·37-1·54) |
| Hemorrhagic complication ^b | 27 (7) | 33 (4) | 0·80 (0·47-1·35) |
| Severe hyponatremia | 12 (3) | 7 (2) | 1·71 (0·67-4·40) |
| Pneumonia | 55 (13) | 64 (16) | 0·83 (0·56-1·22) |
| Infectious meningitis | 30 (7) | 30 (7) | 0·99 (0·58-1·67) |
| Urinary tract infection | 36 (9) | 42 (10) | 0·83 (0·52-1·33) |
| Seizure | 55 (13) | 38 (9) | 1·50 (0·97-2·32) |
| Delirium | 56 (14) | 54 (13) | 1·03 (0·69-1·54) |
| Terson's syndrome | 18 (4) | 17 (4) | 1·05 (0·53-2·06) |
| SUSARs | 0 | 0 | NA |
| Other | 123 (30) | 118 (29) | 1·04 (0·77-1·41) |

^a data missing in one patient in the control group

^b data missing in one patient in the tranexamic acid group

eTable 6. As-treated analyses for complications during hospital admissions

| | As-treated analysis | | |
|---|-------------------------------------|--------------------------|------------------|
| | Tranexamic acid group (N=395) | Control group (N=417) | OR (95% CI) |
| Any SAE | 332 (84) | 354 (85) | 0.94 (0.64-1.37) |
| All ^a rebleedings before aneurysm treatment | 46 (12) | 65 (16) | 0.71 (0.48-1.07) |
| CT-proven rebleedings | 38 (10) | 57 (14) | 0.67 (0.44-1.04) |
| Hydrocephalus | 251 (64) | 247 (59) | 1.20 (0.90-1.59) |
| Delayed cerebral ischemia ^b | 99 (25) | 108 (26) | 0.95 (0.70-1.31) |
| Thrombo-embolic complications during endovascular treatment [^] | 29 (11) | 33 (13) | 0.87 (0.51-1.48) |
| Cerebral infarction related to clipping procedure ^b | 22 (27) | 18 (19) | 1.55 (0.76-3.16) |
| Peri-procedural rupture | | | |
| Coiling | 15 (6) | 13 (5) | 1.17 (0.54-2.51) |
| Clipping | 16 (20) | 23 (25) | 0.76 (0.37-1.56) |
| Extra-cranial thrombosis | 5 (1) | 7 (2) | 0.75 (0.24-2.39) |
| - Deep venous thrombosis | 0 (0) | 2 (1) | 0.21 (0.01-4.39) |
| - Pulmonary embolism | 4 (1) | 5 (1) | 0.84 (0.23-3.16) |
| Hemorrhagic complication ^c | 26 (7) | 34 (8) | 0.80 (0.47-1.35) |
| Severe hyponatremia | 11 (3) | 8 (2) | 1.47 (0.58-3.68) |
| Pneumonia | 51 (13) | 68 (16) | 0.76 (0.51-1.13) |

| | | | |
|-------------------------|----------|----------|------------------|
| Infectious meningitis | 27 (7) | 32 (8) | 0·88 (0·52-1·50) |
| Urinary tract infection | 36 (9) | 42 (10) | 0·90 (0·56-1·43) |
| Seizure | 52 (13) | 41 (10) | 1·39 (0·90-2·15) |
| Delirium | 54 (14) | 56 (13) | 1·02 (0·68-1·53) |
| Terson's syndrome | 18 (5) | 17 (4) | 1·12 (0·57-2·21) |
| SUSARs | 0 (0) | 0 (0) | NA |
| Other | 115 (48) | 126 (52) | 0·95 (0·70-1·28) |

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

^c data missing in one patient in the tranexamic acid group

References

1. Vergouwen MD, Vermeulen M, van Gijn J, Rinkel GJ, Wijdicks EF, Muizelaar JP, et al. Definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage as an outcome event in clinical trials and observational studies: proposal of a multidisciplinary research group. *Stroke*. 2010;41(10):2391-5.
2. Report of World Federation of Neurological Surgeons Committee on a universal subarachnoid hemorrhage grading scale. *Journal of neurosurgery*. 1988;68:985-6.
3. Fisher CM, Kistler JP, Davis JM. Relation of Cerebral Vasospasm to Subarachnoid Hemorrhage Visualized by Computerized Tomographic Scanning. *Neurosurgery*. 1980;6(1):1-9.