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Antifibrinolytic therapy for aneurysmal subarachnoid haemorrhage (Review)

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[Intervention Review]

Antifibrinolytic therapy for aneurysmal subarachnoid haemorrhage

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ABSTRACT

Background

Rebleeding is an important cause of death and disability in people with aneurysmal subarachnoid haemorrhage. Rebleeding is probably related to dissolution of the blood clot at the site of aneurysm rupture by natural fibrinolytic activity. This review is an update of a previously published Cochrane review.

Objectives

To assess the effects of antifibrinolytic treatment in people with aneurysmal subarachnoid haemorrhage.

Search methods

We searched the Cochrane Stroke Group Trials Register (February 2013), the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 1), MEDLINE (1948 to December 2012), and EMBASE (1947 to December 2012). In an effort to identify further published, unpublished, and ongoing studies we searched reference lists and trial registers, performed forward tracking of relevant references and contacted drug companies.

Selection criteria

Randomised trials comparing oral or intravenous antifibrinolytic drugs (tranexamic acid, epsilon amino-caproic acid, or an equivalent) with control in people with subarachnoid haemorrhage of suspected or proven aneurysmal cause.

Data collection and analysis

Two review authors independently selected trials for inclusion and extracted the data. Three review authors assessed trial quality. For the primary outcome we converted the outcome scales between good and poor outcome for the analysis. We scored death from any cause and rates of rebleeding, cerebral ischaemia, and hydrocephalus per treatment group. We expressed effects as risk ratios (RR) with 95% confidence intervals (CI). We used random-effects models for all analyses.

Main results

We included 10 trials involving 1904 participants. The risk of bias was low in six studies. Four studies were open label and were rated as high risk of performance bias. One of these studies was also rated as high risk for attrition bias. Four trials reported on poor outcome (death,

vegetative state, or severe disability) with a pooled risk ratio (RR) of 1.02 (95% confidence interval (CI) 0.91 to 1.15). All trials reported on death from all causes with a pooled RR of 1.00 (95% CI 0.85 to 1.18). In a trial that combined short-term antifibrinolytic treatment (< 72 hours) with preventative measures for cerebral ischaemia the RR for poor outcome was 0.85 (95% CI 0.64 to 1.14). Antifibrinolytic treatment reduced the risk of re-bleeding reported at the end of follow-up (RR 0.65, 95% CI 0.44 to 0.97; 78 per 1000 participants), but there was heterogeneity (I^2 = 62%) between the trials. The pooled RR for reported cerebral ischaemia was 1.41 (95% CI 1.04 to 1.91, 83 per 1000 participants), again with heterogeneity between the trials (I^2 = 52%). Antifibrinolytic treatment showed no effect on the reported rate of hydrocephalus in five trials (RR 1.11, 95% CI 0.90 to 1.36).

Authors' conclusions

The current evidence does not support the use of antifibrinolytic drugs in the treatment of people with aneurysmal subarachnoid haemorrhage, even in those who have concomitant treatment strategies to prevent cerebral ischaemia. Results on short-term treatment are promising, but not conclusive. Further randomised trials evaluating short-term antifibrinolytic treatment are needed to evaluate its effectiveness.

PLAIN LANGUAGE SUMMARY

Drugs for preventing blood clot dissolution (antifibrinolytic therapy) to reduce the occurrence of rebleeding in aneurysmal subarachnoid haemorrhage

A subarachnoid haemorrhage (SAH) is a bleed into the small space between the brain and skull that contains blood vessels that supply the brain (the subarachnoid space). The cause of a bleeding here is usually a rupture of a weak spot in one of these vessels. A SAH is a relatively uncommon type of stroke, but it often occurs at a young age (half the patients are younger than 50 years). The outcome of SAH is often poor: one-third of people die after the haemorrhage and of those who survive, one-fifth will require help for everyday activities. An important cause of poor recovery after SAH is a second bleed from the weakened vessel (rebleeding). This is thought to be caused by the dissolving of the blood clot at the original bleeding site that results from natural blood clot dissolving (fibrinolytic) activity. Antifibrinolytic therapy that reduces this activity was introduced as a treatment for reducing rebleeding and therefore for improving recovery after SAH. This review included 10 trials, totaling 1904 participants that investigated the effect of these drugs in people with SAH. Antifibrinolytic treatment does indeed reduce the risk of rebleeding, but does not improve survival or the chance of being independent in everyday activities. This may be due to an increase in one of the other common complications of SAH. We conclude that antifibrinolytic treatment should not routinely be given to people with SAH, but new randomised trials are needed to establish if short-term treatment might be beneficial.

BACKGROUND

Description of the condition

In people with aneurysmal subarachnoid haemorrhage (SAH) rebleeding is an important cause of death and disability. Without aneurysm treatment approximately 30% of such people experienced a rebleed within one month of the initial haemorrhage (Locksley 1966). The rebleeding rate has now been reduced to about 15% because in most people the aneurysm is occluded early after admission (Roos 2000b). The risk of rebleeding is highest in the first 24 hours after SAH, with a peak in the first six hours (Guo 2011). The prognosis after rebleeding is poor: approximately 60% of people who rebleed die and another 30% remain dependent for activities of daily living (Naidech 2005).

Description of the intervention

Antifibrinolytic drugs were introduced to reduce the occurrence of rebleeding. These drugs are administered orally or intravenously and block endogenous fibrinolytic activity and could help prevent bleeding.

How the intervention might work

Dissolution of the blood clot at the site of the ruptured aneurysm is thought to be an important factor in the development of rebleeding. This dissolution probably results from endogenous fibrinolytic activity after SAH. Since antifibrinolytic agents reduce fibrinolytic activity, antifibrinolytic therapy may reduce the occurrence of rebleeding and thereby improve clinical outcome after SAH. However, reducing rebleeding might not automatically improve clinical outcome in all instances. Concerns have been raised that antifibrinolytic therapy might increase the occurrence of cerebral ischaemia. Cerebral ischaemia is a complication of SAH that occurs in about 30% to 40% of people between four and 14 days after SAH. In older trials the beneficial effect of antifibrinolytic treatment (reducing rebleeding) was offset by an increase in cerebral ischaemia, resulting in a neutral effect on outcome (Roos 2003).

Why it is important to do this review

In 1967 Gibbs and O'Gorman published the first report on antifibrinolytic treatment in people with SAH (Gibbs 1967). Since then, over 50 studies on antifibrinolytic therapy in aneurysmal SAH have been published. Unfortunately most of these studies are uncontrolled and only a minority of the controlled studies are randomised. Moreover, the results of some of the individual randomised studies contradict each other. Furthermore, as mentioned above, concerns have been raised that antifibrinolytic therapy might increase the occurrence of cerebral ischaemia. In a previous version of this review we found that even in people treated with measures to prevent and reverse cerebral ischaemia (such as administration of nimodipine), clinical outcome was not improved by antifibrinolytic treatment despite a reduction in rebleeding rate. The hypothesis has been posed that, when people with aneurysmal SAH are treated with antifibrinolytic agents, recovery from cerebral ischaemia is impeded by antifibrinolytic treatment. More recently it has been proposed that if antifibrinolytic treatment is discontinued before the period in which cerebral ischaemia typically occurs, the negative effect of antifibrinolytic therapy may be avoided. In this update of a previously published Cochrane review (Roos 2003), we sought to evaluate the effectiveness of short-term antifibrinolytic treatment in people concomitantly treated with measures to prevent or reverse cerebral ischaemia.

OBJECTIVES

To assess the effects of antifibrinolytic treatment in people with aneurysmal SAH.

METHODS

Criteria for considering studies for this review

Types of studies

All truly randomised unconfounded trials were eligible in which, after concealed allocation, antifibrinolytic drugs were compared with control treatment (open studies) or placebo (blind studies) in an intention-to-treat analysis. We excluded all trials in which allocation to treatment or control group was not concealed (e.g. trials in which people were allocated by means of an open random number list, alternation, or based on date of birth, days of the week, or hospital-number), since foreknowledge of treatment allocation might lead to biased treatment allocation (i.e. selective enrolment). We also excluded trials in which an intention-to-treat analysis was not performed and could not be reconstructed on the basis of published data without a loss of 20% or more of all randomised participants.

Types of participants

Trials in which participants were included with clinical symptoms and signs of SAH from a ruptured aneurysm with confirmation of the diagnosis by the presence of subarachnoid blood on computed tomography (CT) scan or on cerebrospinal fluid (CSF) examination were eligible for this review.

Types of interventions

Antifibrinolytic drugs (e.g. tranexamic acid, epsilon amino-caproic acid, or equivalent drugs), oral or intravenous, versus control treatment (open studies) or placebo treatment (blind studies). Since the risk of rebleeding is highest during the first two weeks after the initial bleeding, treatment had to start within two weeks after onset of the SAH. Distinction was made between early and short-term (< 72 hours of onset of symptoms, i.e. before usual timing of onset of cerebral ischaemia) versus long-term (> 72 hours) treatment duration.

Types of outcome measures

Primary outcomes

The primary outcome measure was 'poor outcome' (death, vegetative state, or severe disability, as assessed either with the Glasgow Outcome Scale or the Modified Rankin Scale) at the end of follow-up at least three months after SAH. 'Death from all causes' at a minimum of at least three-weeks follow-up was our second primary outcome, since most studies only reported on case fatality.

Secondary outcomes

Secondary outcome measures were the effect of antifibrinolytic treatment on both the rates of reported and CT scan or autopsy

confirmed (sensitivity analyses) episodes of rebleeding, cerebral ischaemia, and hydrocephalus. In this systematic review, we did not evaluate cerebral vasospasm without clinical signs of cerebral ischaemia.

Search methods for identification of studies

See the 'Specialized register' section in the Cochrane Stroke Group module. We searched for trials in all languages and arranged translations of relevant reports published in languages other than English.

Electronic searches

We searched the Cochrane Stroke Group Trials Register (last searched February 2013), the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 1), MEDLINE (1948 to December 2012) (Appendix 1) and EMBASE (1947 to December 2012) (Appendix 2).

We developed comprehensive search strategies with the help of the Cochrane Stroke Group Trials Search Co-ordinator and adapted the MEDLINE strategy for CENTRAL.

We also searched the following major ongoing trial registers (December 2012): ClinicalTrials.gov (http://www.clinicaltrials.gov/), EU Clinical Trials Register (https://www.clinicaltrialsregister.eu), Stroke Trials Registry (www.strokecenter.org/trials/), Current Controlled Trials (www.controlled-trials.com), and the WHO International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/).

Searching other resources

In an effort to identify further published, unpublished, and ongoing studies:

1. we searched the list of references quoted in all included studies and reviews on antifibrinolytic therapy (Adams 1982; Adams 1987; Biller 1988; Carley 2005; Chawjol 2008; Connolly 2012; Fodstad 1982; Gaberel 2012; Lindsay 1987; Maira 2006; Mayberg 1994; Ramirez 1981; Rinkel 2008; Van Gijn 2001; Van Gijn 2007; Vermeulen 1980; Vermeulen 1996; Weaver 1994; Weir 1987);
2. we used Science Citation Index Cited Reference Search for forward tracking of important articles; and
3. for the first version of this review (1998) we contacted the pharmaceutical company Pharmacia and Upjohn, formerly Kabi, manufacturer and license holder of the antifibrinolytic drug tranexamic acid. We identified no additional (unpublished) studies.

Data collection and analysis

Selection of studies

Two authors (MIB, MRG) independently screened the titles and abstracts of the records obtained from the electronic searches and excluded obviously irrelevant studies. We obtained the full-text articles for the remaining studies and the same two authors independently selected the trials that met the predefined criteria for inclusion in the review. The authors resolved disagreements by discussion and when necessary in consultation with a third review author (YBWEMR).

Data extraction and management

Two authors (MIB, MRG) independently reviewed all eligible studies and extracted details on the number of participants in the treated and the placebo or control group, the randomisation method, blinding method, the definitions for diagnosis and complications, and also ascertained whether an intention-to-treat analyses was done or could be reconstructed from the published data. Whenever consensus could not be reached, the review authors consulted a third review author (YBWEMR).

Assessment of risk of bias in included studies

Three authors (MIB, MRG, YBWEMR) independently assessed the risk of bias of each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion. We assessed the risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We graded each potential source of bias as high, low, or unclear and provided information from each study in the 'Risk of bias' tables.

Measures of treatment effect

We processed data in accordance with the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). For the primary outcome we converted the outcome scales between good and poor outcome for the analysis. We scored death from any cause and rates of rebleeding, cerebral ischaemia, and hydrocephalus per treatment group. We expressed effects as risk ratios (RR) with 95% confidence intervals (CI).

Unit of analysis issues

The unit of analysis were individual participants, since we only included individually conducted randomised trials with a parallel design.

Dealing with missing data

In trials without intention-to-treat analysis, we tried to reconstruct such an analysis based only on the published data. For two trials (Hillman 2002; Tsementzis 1990) we tried to contact the principal investigator to retrieve data on the number of participants in whom rebleeding or cerebral ischaemia were proven on CT scan or at autopsy. We received a reply from one of the authors. We made no effort to obtain additional information for studies published 15 or more years ago.

Assessment of heterogeneity

For each outcome we assessed heterogeneity using the Chi^2 test and I^2 index (Higgins 2011). Because we suspected substantial heterogeneity, we used random-effects models for all analyses.

Assessment of reporting biases

To investigate possible publication bias in this review, we planned to perform funnel plots when possible.

Data synthesis

We used the Review Manager software, RevMan 5.2, for statistical analysis (RevMan 2012), and used Mantel-Haenszel random-effects models for pooled analyses.

Subgroup analysis and investigation of heterogeneity

To assess whether masked studies showed different results compared with unmasked studies we divided all analyses into two groups: trials with control treatment (open studies) and trials with placebo treatment (blind studies). We pre-planned an additional subgroup analysis to evaluate the effectiveness of antifibrinolytic therapy in trials with and without additional measures to prevent or reverse cerebral ischaemia and to evaluate the effectiveness of antifibrinolytic therapy according to treatment duration. We divided the included trials into one of three groups: (1) trials without ischaemia prevention and treatment duration > 72 hours, (2) trials with ischaemia prevention and treatment duration > 72 hours, and (3) trials with ischaemia prevention and treatment duration < 72 hours. We did not include a fourth group (trials without ischaemia prevention and treatment duration < 72 hours) as there were no trials that met these criteria.

Additionally we checked whether data were available on aneurysm treatment (i.e. clipping or coiling) according to antifibrinolytic treatment, to evaluate whether a subgroup analysis on clipping versus coiling was possible.

Sensitivity analysis

Because our secondary outcome measures were more prone to bias, we carried out sensitivity analyses on confirmed (rather than reported) rebleeding, cerebral ischaemia, and hydrocephalus rates.

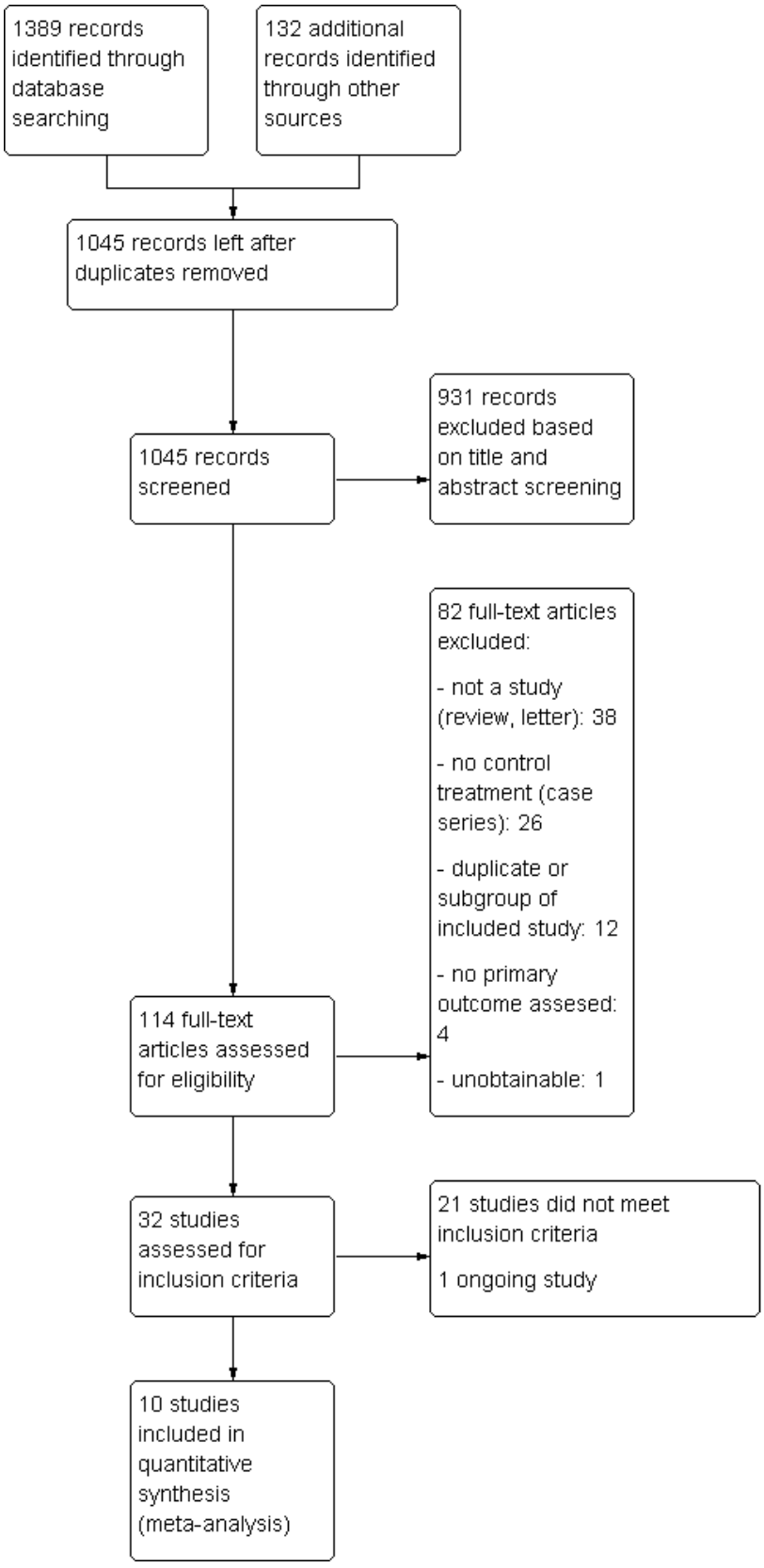
RESULTS

Description of studies

Results of the search

The updated search of the bibliographic databases yielded a total of 1521 records, from which we removed 476 duplicates, leaving a total of 1045 records. After screening titles and abstracts we excluded 931 records, leaving 114 records for which we obtained the full-text articles. Further assessment resulted in 32 potentially relevant trials. Ten trials met the inclusion criteria for the review and we excluded 21 trials. We identified one ongoing trial from the searches of the trial registers. For an overview of the search results see Figure 1.

Figure 1. Study flow diagram.



Included studies

We included 10 studies (Chandra 1978; Fodstad 1981; Girvin 1973; Hillman 2002; Kaste 1979; Maurice 1978; Roos 2000a; Tsementzis 1990; Van Rossum 1977; Vermeulen 1984), which are described in detail in the Characteristics of included studies table. These 10 studies included 1904 participants of whom 959 were randomised to receive antifibrinolytic drugs, 597 received placebo treatment and 348 received control treatment. The Girvin 1973 study used epsilon-amino-caproic acid (39 participants), in all other studies tranexamic acid was used. In two studies participants were concomitantly treated with measures to prevent or reverse cerebral ischaemia (Hillman 2002; Roos 2000a). The duration of antifibrinolytic treatment differed considerably between studies and ranged from less than 72 hours up to six weeks. Short-term treatment was used in only one study (Hillman 2002). In this study, participants were treated up to 72 hours after SAH. All other studies treated participants for at least 10 days (or until occlusion of the aneurysm) after SAH.

Clinical outcome was reported in four studies (Hillman 2002; Roos 2000a; Tsementzis 1990; Vermeulen 1984) and the number of participants with poor outcomes could be reconstructed. Death from all causes and rebleeding rates were reported in all 10 studies. In six studies, episodes of rebleeding were defined primarily by clinical symptoms.

Two trials (Fodstad 1981; Hillman 2002) reported CT scan or autopsy confirmed episodes of rebleeding. The Dutch-British trial (Vermeulen 1984) and the STAR study (Roos 2000a) defined and reported rebleeding in two ways: as 'probable' if the diagnosis was suspected solely on clinical grounds and as 'definite' when proven by CT (after comparison with an earlier CT) or at autopsy.

Cerebral ischaemia was reported in six studies but defined in only three: in two studies (Roos 2000a; Vermeulen 1984) cerebral ischaemia was defined and reported in the same manner as episodes of rebleeding; as 'probable' and as 'definite' (CT-scan or autopsy confirmed) cerebral ischaemia. Again, as for rebleeding, Fodstad 1981 reported on CT-scan or autopsy confirmed cerebral ischaemia. Hillman 2002 reported percentage of transient and permanent delayed ischaemic neurological deficit. No clear definition was given and CT scans were not routinely used for confirmation of cerebral ischaemia. Because other studies did not make a distinction between permanent or transient cerebral ischaemia, we decided to combine these outcomes. In Hillman 2002, visible infarction on CT scan was reported; however, after contact with the author, we decided not to use this as a measure for cerebral ischaemia since this was not correlated to clinical signs of cerebral ischeamia.The other two studies (Girvin 1973; Tsementzis 1990) made no distinction between participants with episodes clinically suggestive of cerebral ischaemia or participants with confirmed cerebral ischaemia, and reported only an all-inclusive number of participants. One study reported on 'delayed cerebral ischaemia' and 'post operative ischaemia' (Roos 2000a). Since all other studies did not make this distinction and reported an overall number of participants with cerebral ischaemia, we grouped these subgroups of ischaemia together for the analysis on cerebral ischaemia.

Five trials reported on hydrocephalus. Hydrocephalus was defined in only one study by means other than clinical grounds and could therefore be included in the sensitivity analysis concerning 'confirmed hydrocephalus' (Roos 2000a). No trials reported on aneurysm treatment modality (i.e. coiling versus clipping) according to antifibrinolytic or control treatment and thus a subgroup analysis based on modality was not possible.

Excluded studies

We excluded 21 studies for various reasons (see Characteristics of excluded studies): some were comparative trials between two or more antifibrinolytic agents, others used unconcealed randomisation methods, and some were not randomised but used historical controls. We excluded Fodstad 1978 as 23% of the participants in the trial were later excluded and an intention-to-treat analysis could not be reconstructed on the basis of the published data.

Risk of bias in included studies

For a summary of the risk of bias please see Figure 2 and Figure 3. Five of the 10 included trials used an intention-to-treat analysis; in one of the remaining trials (Maurice 1978) this analysis could be completely reconstructed using the available follow-up data. In the other trials (Fodstad 1981; Hillman 2002; Tsementzis 1990; Van Rossum 1977) there was no follow-up information available for participants who were excluded after randomisation. In three studies only very few participants (Fodstad 1981: n = 1; Tsementzis 1990: n = 4; Van Rossum 1977: n = 3) were excluded from the final analysis and therefore these studies could still be included in our review. In one study (Hillman 2002) 91 (15%) of the 596 participants were excluded after randomisation. Because this was less than the prespecified proportion of 20% we included this study in our analysis. We rated this study as high risk of bias for incomplete outcome data.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

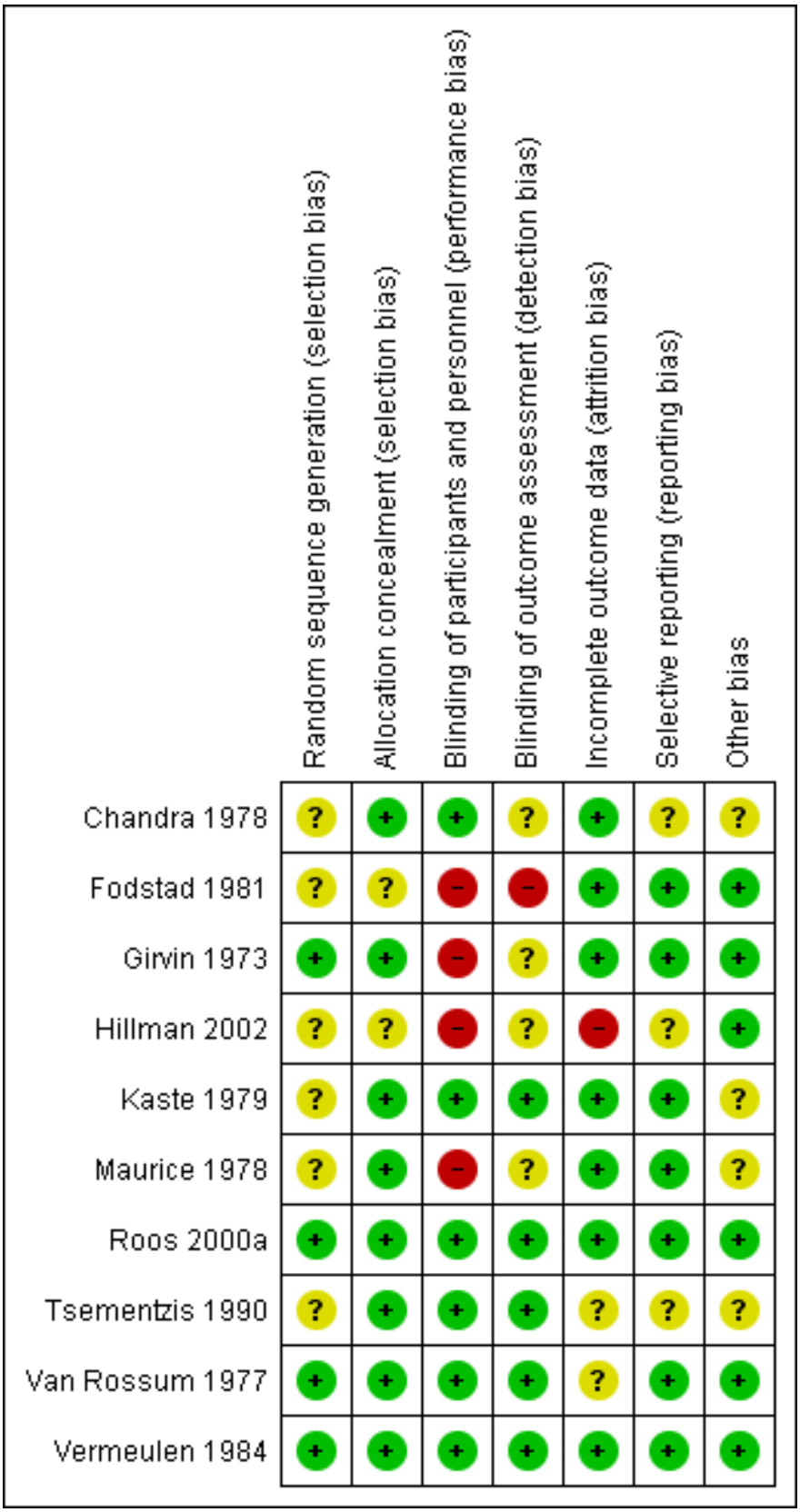
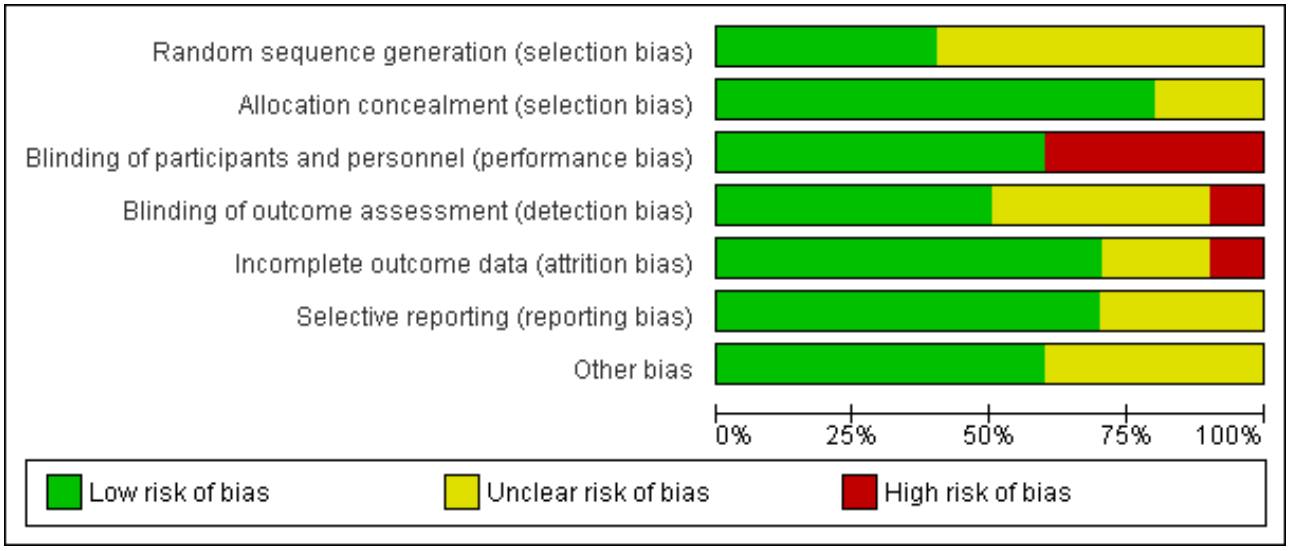


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Six studies used a double-blind method (placebo controlled) and four used a control group with standard treatment without placebo.The control group studies were open label and we rated them as high risk of performance bias (all four studies) and attrition bias (one study).

Girvin 1973 used 'flip-of-a-coin' randomisation as the method of allocation, which is more susceptible to bias compared with, for instance, the sealed envelope method. Nevertheless, we decided to include this study since this is an accepted form of randomisation with allocation concealment according to the Cochrane guidelines. All other studies used a method of concealed allocation that was considered appropriate at time of conducting the trial, although it was not always mentioned whether or not the sealed envelopes that were used were opaque.

Effects of interventions

The pooled RR for our primary outcome measure, 'poor outcome', was 1.02 (95% CI 0.91 to 1.15) (Analysis 1.1). The pooled RR for our second primary outcome measure, 'death from all causes', was 1.00 (95% CI 0.85 to 1.18) (Analysis 1.2).

In the analysis on rebleeding rates (Analysis 1.3), antifibrinolytic therapy significantly reduced the risk of rebleeding (RR 0.65, 95% CI 0.44 to 0.97; 78 per 1000 people). Considerable heterogeneity was detected for this comparison (I^2 = 62%). Similar results were found in the subgroup analysis of the six double-blind and placebo controlled studies (RR 0.64, 95% CI 0.43 to 0.97), the sensitivity analysis including four studies with CT scan or autopsy confirmed rebleeding (RR 0.44, 95% CI 0.26 to 0.75) (Analysis 1.4), as well as in the subgroup analysis of studies with and without ischaemia prevention according to duration of treatment (< 72 hours > 72 hours) (RR 0.65, 95% CI 0.44 to 0.97) (Analysis 1.5).

In the six trials that reported cerebral ischaemia rates, antifibrinolytic treatment significantly increased the risk of cerebral ischaemia (RR 1.41, 95% CI 1.04 to 1.91; 83 per 1000 people) (Analysis 1.6). Similar (though non-significant) results were seen in the subgroup analysis of the three placebo controlled trials (RR 1.38, 95% CI 0.87 to 2.19) as well as in the three trials with CT scan or autopsy confirmed cerebral ischaemia (RR 1.34, 95% CI 0.88 to 2.03) (Analysis 1.7). In these analyses there was considerable heterogeneity between the results from the four older studies and the results from the most recent studies (Hillman 2002; Roos 2000a), in which specific treatments to prevent cerebral ischaemia were used (I^2 = 52%).

In five trials hydrocephalus was reported. Antifibrinolytic treatment overall had no effect on the reported rates of hydrocephalus (RR 1.11, 95% CI 0.90 to 1.36) (Analysis 1.8). In the subgroup analysis on placebo versus open studies the RR of antifibrinolytic treatment for hydrocephalus was 1.19 (95% CI 0.95 to 1.48) in the placebo controlled studies, while it was 0.64 (95% CI 0.34 to 1.18) in the open label trials. The sensitivity analysis on one trial with CT scan or autopsy confirmed hydrocephalus showed no effect of therapy on hydrocephalus rate (RR 1.17, 95% CI 0.87 to 1.55) (Analysis 1.9). Ischaemia prevention did not appear to have an effect on hydrocephalus in the subgroup analysis of studies with and without ischaemia prevention according to duration of treatment. The RR of hydrocephalus in people receiving antifibrinolytic treatment during > 72 hours with cerebral ischaemia prevention was 1.17 (95% CI 0.87 to 1.55) and for people receiving antifibrinolytic treatment during > 72 hours without ischaemia prevention the RR was 1.03 (95% CI 0.74 to 1.43) (Analysis 1.10).

In the subgroup analysis of studies with ischaemia prevention according to duration of treatment (< 72 hours versus > 72 hours), the RR for people receiving antifibrinolytic treatment during < 72 hours with cerebral ischaemia prevention was 0.85 (95% CI 0.64 to 1.14) for 'poor outcome' (Analysis 1.11) and 0.83 (95% CI 0.52 to 1.35) for 'death from all causes' (Analysis 1.12). Furthermore, cerebral ischaemia did not significantly increase with antifibrinolytic treatment in trials where participants received concomitant ischaemia preventative treatment (Hillman 2002 and Roos 2000a combined: RR 1.09, 95% CI 0.78 to 1.51) (Analysis 1.13).

DISCUSSION

Summary of main results

Although this systematic review shows that antifibrinolytic treatment reduces the rate of rebleeding by approximately 35%, there is no evidence of benefit from antifibrinolytic treatment on case fatality or poor overall outcome. This analysis further shows that the lack of effect on clinical outcome, despite a reduction in rebleeding, may be caused by an increase in cerebral ischaemia with antifibrinolytic treatment, which was also shown in the sensitivity analysis in trials with data on the number of participants with CT or post-mortem proven cerebral ischaemia (two double-blind, one with open control group). Any possible beneficial effect of the reduction in the rebleeding-rate on clinical outcome was offset by an increase in the rate of cerebral ischaemia. This was also seen in the most recent study (Hillman 2002) in which short-term antifibrinolytic therapy was given with ischaemia preventative measures, although permanent delayed neurological deficit was decreased with antifibrinolytic treatment. This finding could suggest that short-term antifibrinolytic treatment (compared to long-term treatment in the study by Roos 2000a) does not influence recovery from initial ischaemia or development of secondary ischaemia and may, therefore, lead to improved clinical outcome. However, confirmatory evidence is needed.

Overall completeness and applicability of evidence

Trials in which people were included with symptoms and signs of SAH of suspected or proven aneurysmal cause, with confirmation of the diagnosis by the presence of subarachnoid blood on CT or on CSF examination were eligible for inclusion in the review. We chose this pragmatic approach and did not restrict our review to people with angiographically proven aneurysms, because in contrast to angiography, CT scan or CSF examination can be done instantaneously, independent of the clinical condition of the patient. One could argue that currently people with suspected aneurysmal SAH will undergo CT angiography (CT-A) immediately to confirm the presence of an aneurysm. We chose not to limit our analysis to proven aneurysmal SAH, because CT-A was not available at the time most of the trials were conducted. Moreover, CT-A is not always available in referring hospitals without specialised units. Since antifibrinolytic treatment might be most beneficial when started as soon as possible, it is likely that treatment will start in the referring hospital without CT-A confirmation of the presence of an aneurysm. An analysis on oral versus intravenous treatments or a comparison between treatment dosages could not be performed. Only one study used oral antifibrinolytic treatment, whereas other studies used intravenous therapy alone or a combination of intravenous and oral treatment in varying dosages. Furthermore, in the past decade treatment of cerebral aneurysms has changed considerably: whereas most studies were performed in the era where surgical treatment was the only method of occlusion of the aneurysm, currently endovascular coiling is an accepted alternative to surgical occlusion. Because no data on treatment modality were available from the included trials, an analysis according to aneurysm treatment modality was not possible. Such an analysis could, however, prove worthwhile in the future.

Quality of the evidence

In this systematic review we only included true randomised controlled trials and performed a subgroup analysis on masked versus unmasked studies in an attempt to minimise allocation and performance bias. However, many of the included studies were older (1970s and 1980s) and most did not report on many sources of potential bias, such as how the randomisation sequence was generated and if participant outcome was assessed by individuals who were blinded to the intervention given. Therefore, we scored many potential sources of bias as 'unclear risk' as can be seen in Figure 2 and Figure 3. However, most of these studies were small and in total comprised 24% of all included participants. Most included participants originated from three large studies (Hillman 2002; Roos 2000a; Vermeulen 1984). For two of these studies, comprising 50% of all data, we could find no potential sources of bias so we rated them as low risk of bias for each source (Roos 2000a; Vermeulen 1984). For Hillman 2002, however, many potential sources of bias could not be scored and were unclear, such as sequence generation, allocation concealment, and blinded outcome assessment. Moreover, 15% of included participants were later excluded from the analysis and the baseline characteristics and outcome of these participants were not reported. Since this was the only study included in the subgroup analysis for treatment duration of less than 72 hours with ischaemia prevention these results are far from conclusive. We know of only one other case series that evaluated short-term antifibrinolytic treatment (Harrigan 2010). In this study all participants received antifibrinolytic treatment until occlusion of the aneurysm (average 56.5 hours after SAH ictus). Harrigan 2010 reported low rebleeding rates and permanent neurological deficit due to cerebral ischaemia (1.4% and 7.2% respectively). However, no follow-up was done to evaluate the participants' clinical outcomes and no control group was available making it impossible to draw conclusions based on this study.

Potential biases in the review process

We searched all major medical electronic databases and other sources, using sensitive and validated search strategies. However, it is possible that we did not find all relevant publications. Furthermore, we only included studies that were published in medical literature and did not search the grey literature, such as government reports and unpublished information. Although all included trials met the predefined inclusion criteria, the studies differed considerably in participant selection, disease severity at baseline, start of treatment after diagnosis, dosage and type of trial medication, classification of events, and outcome and duration of follow-up. This clinical heterogeneity may in part account for the statistical heterogeneity found in the analyses on rebleeding and cerebral ischaemia.

Agreements and disagreements with other studies or reviews

Our results are comparable to the results from a recent meta-analysis (Gaberel 2012). However, Gaberel 2012 included all studies in which antifibrinolytic treatment was compared with control treatment, including retrospective analyses and studies with historical control groups. Retrospective analyses are known to be much more susceptible to selection and reporting bias, since the decision to treat a patient is made subjectively. Moreover, the other review did not compare placebo controlled versus open studies, which is another potential source of bias, since all outcomes, except for death, are made on subjective clinical grounds and can be easily biased when the outcome assessor is not blinded to the treatment given. In our review we included only randomised

clinical trials and performed several sensitivity analyses, which should yield less biased results. Since most studies did not describe whether outcomes were assessed blinded to treatment, sensitivity analyses are essential. Despite the fact that all authors reported that confirmation of rebleeding was sought, in most instances this was done by examination of the cerebrospinal fluid. Because CSF examination is an unreliable test to confirm rebleeding (Vermeulen 1983) the diagnosis of rebleeding could often not be regarded as proven. The sensitivity analyses we performed on reported versus confirmed (with confirmatory evidence on CT scan or at autopsy) rebleeding, cerebral ischaemia, or hydrocephalus showed similar results to the overall analyses. Lack of confirmatory evidence of these complications thus appears to be of minor importance in our analyses. The analyses we performed on trials with control treatment compared with those given placebo treatment showed similar reducing effects of antifibrinolytic treatment on rebleeding and similar increasing effects on cerebral ischaemia, whereas hydrocephalus trials with control treatment showed a tendency towards a beneficial effect compared with trials with placebo treatment, demonstrating a tendency towards increased hydrocephalus rates.

AUTHORS' CONCLUSIONS

Implications for practice

Antifibrinolytic treatment does not improve clinical outcome in people after SAH, although it does reduce the risk of rebleeding after SAH. Based on the currently available data, treatment with antifibrinolytic drugs cannot be recommended for people with subarachnoid haemorrhage from a presumed or proven aneurysmal origin.

Implications for research

The available data suggest that short-term (less than 72 hours) antifibrinolytic treatment, combined with cerebral ischaemia preventative measures, may reduce rebleeding rates without an increase in the proportion of people with cerebral ischaemia. Thus, short-term treatment with antifibrinolytic therapy may be effective for people with aneurysmal SAH, but confirmatory evidence is lacking and a possible harmful effect can also not be excluded. Based on these findings new randomised trials of short-term antifibrinolytic agents versus control in people with SAH are needed. Recently, a new trial comparing ultra early and short antifibrinolytic treatment (less than 24 hours) with control treatment has been registered and is planned (Verbaan 2012).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Chandra 1978

Methods	Single centre study Random allocation (method of randomisation not described) Double-blind treatment ITT analysis
Participants	Clinical diagnosis of aneurysmal SAH confirmed in CSF and on angiography Male:female: treatment group 11:9; placebo group 10:9 Mean age 51 years (range 20 to 65) Excluded: SAH > 7 days, 'relevant associated illness'
Interventions	Tranexamic acid (6 g per day iv in 6 doses) versus identical-appearing placebo treatment for a treatment duration of 3 weeks No report on surgical interventions
Outcomes	Outcome: deaths from all causes at 3-week follow-up Events: rebleeding: reported, not defined; cerebral ischaemia: not reported; hydrocephalus: not reported
Notes	No report on how many rebleeding were established on CT scan or at necropsy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	In the text, participants were reported to be randomly allocated, but how this was achieved is not reported
Allocation concealment (selection bias)	Low risk	Identical medication; however, unclear how medication was coded
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Neither the investigators nor the patients knew which subjects received which substance"

Chandra 1978 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described in text
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	More male than female participants included, which could point to some form of bias since people with SAH are more often female

Fodstad 1981

Methods	Single-centre study Random allocation (identical sequentially numbered sealed envelope) No blind treatment Not strictly ITT: 1 of the 30 control participants was excluded after randomisation because he had received tranexamic acid before admission
Participants	Clinical diagnosis of aneurysmal SAH verified with CSF, CT scan and angiography Male:female: treatment group 13:17; control group 12:17 Mean age: treatment group 50 years (range 19 to 72); control group 53 years (range 27 to 70) Excluded: SAH > 3 days and known thrombotic disease
Interventions	Tranexamic acid (6 g per day iv in 6 doses during the first week, 4 g in 4 doses iv in week 2 and 6 g orally in 4 doses in week 3 to 6) for a maximum duration of 6 weeks versus control group. Treatment continued until rebleeding, operation, discharge or death
Outcomes	Outcome: deaths from all causes at 6-week follow-up Events: rebleeding: reported, confirmed by CSF examination/spectrophotometry, CT-scan or at necropsy; cerebral ischaemia: reported, not defined; hydrocephalus: reported, not defined
Notes	Of the participants with rebleeding, 5 of 6 in the treatment group and 5 of 7 in the control group died. All had necropsy. In the remaining participants rebleeding was confirmed by CT. 6 of 8 participants with cerebral ischaemia in the treatment group and 2 of 3 in the control group died. All had necropsy, in the remaining participants cerebral ischaemia was established on CT

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described in the text
Allocation concealment (selection bias)	Unclear risk	"Patients were assigned randomly" and "the sealed envelope technique was used" It was not mentioned whether these envelopes were opaque or not
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel were not blinded (open study)

Fodstad 1981 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Part of recurrent haemorrhages were confirmed by lumbar puncture
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant was excluded from final analysis
Selective reporting (reporting bias)	Low risk	Protocol was previously published
Other bias	Low risk	None suspected based on study design and outcome

Girvin 1973

Methods	Single-centre study Random allocation (flip-of-a-coin) No blind treatment ITT
Participants	Clinical diagnosis of aneurysmal SAH probably confirmed on angiography Male:female ratio not described ("in control group were a relatively greater number of female patients") Age distribution not described Excluded: SAH > 7 days
Interventions	Epsilon amino-caproic acid, dosage probably 24 g per day (6 times 4 g) orally versus control group, duration on average in treatment group 7.7 days versus 5.5 in control group Treatment continued until operation or death
Outcomes	Outcome: deaths from all causes (at unknown week) Events: rebleeding: reported, not defined; ischaemia: reported, not defined; hydrocephalus: not reported
Notes	Poor description of study methods, definitions and results

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The cases were randomised on admission, by the flip of a coin"
Allocation concealment (selection bias)	Low risk	See above
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel were not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described in the text

Girvin 1973 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	Primary outcome described as "raison d'etre" of the study
Other bias	Low risk	None suspected based on study design and outcome

Hillman 2002

Methods	Multi-centre study Random allocation (sequence generation not specified) with sealed envelopes (not specified if opaque or not) No blind treatment Not strictly ITT: 91 participants excluded after randomisation because no aneurysm was found
Participants	People suffering from CT-verified SAH within 48 hours prior to hospital admission Male:female ratio: 1.89 in both groups Age distribution similar in both groups Excluded: SAH > 48 hours, age < 15 years, pregnancy, and history of thromboembolic disease. People in whom no aneurysm was demonstrated on angiographic studies were excluded after randomisation
Interventions	Tranexamic acid (1 g iv immediately before transport, 1 g iv after 2 hours, and then 1 g every 6th hour until aneurysm occlusion up to 72 hours after SAH) versus control treatment
Outcomes	Outcome: Glasgow Outcome Scale at 6 months Events: rebleeding confirmed on CT or during operation until 72 hours after admission; clinically established delayed ischaemic neurological deficit at 6 months, not confirmed by imaging
Notes	Poor description of delayed ischaemic neurological deficit and how this was scored No mention of follow-up for rebleeding after 72 hours

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation was not described in the text
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes were used that contained a randomisation document; however, it was not reported how these were ordered and if they were opaque or not
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel were not blinded (open study)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described in the text
Incomplete outcome data (attrition bias)	High risk	15% of included participants not evaluated in final analysis, which might have resulted in an overestimation of the effect estimate

Hillman 2002 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Unclear risk	Previously published protocol was not mentioned, clinical outcome reported although not described in introduction or methods
Other bias	Low risk	None suspected based on study design and outcome

Kaste 1979

Methods	Single-centre study Random allocation (identical sequentially numbered treatment boxes) Double-blind treatment Code broken after final evaluation ITT
Participants	Clinical diagnosis of aneurysmal SAH verified in the CSF Male:female: active treatment group 16:16; placebo group 14:18 Age distribution similar in both groups Excluded: SAH > 72 hours, myocardial infarction within 6 months, unconsciousness, coagulation disorders or thrombotic disease, renal failure and pregnancy
Interventions	Tranexamic acid (6 g per day iv in 6 doses) versus identical-appearing placebo treatment for a maximum treatment duration of 3 weeks Treatment discontinued at operation
Outcomes	Outcome: deaths from all causes at 3 months. Events: rebleeding: suspected when 2 of sudden deterioration of consciousness, increase of neck rigidity, headache or focal signs - rebleeding verified in CSF or at necropsy; ischaemia: reported, not defined; hydrocephalus: reported, not defined
Notes	No definition on cerebral ischaemia or hydrocephalus: 'vasospasm and ventricular dilatation were seen on angiography'

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation was not described in the text
Allocation concealment (selection bias)	Low risk	Tranexamic acid and placebo were prepared in identical vials and were coded; the code was only broken after final evaluation of the trial
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Tranexamic acid and placebo were prepared in identical vials and were coded; the code was only broken after final evaluation of the trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The code identifying each substance was broken only after the final evaluation of all 64 patients"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data

Kaste 1979 *(Continued)*

Selective reporting (reporting bias)	Low risk	Protocol was previously published
Other bias	Unclear risk	Unconscious people not included causing the results to be less generalisable

Maurice 1978

Methods	Single-centre study Random allocation (identical sequentially numbered sealed envelop) No double-blind treatment Not published as ITT, but ITT analysis could be reconstructed
Participants	Clinical diagnosis of aneurysmal SAH probably verified in the CSF No description of age or sex ratios ('treatment group matched in age and sex control group') Excluded: SAH > 4 days, person > 65 years, unconsciousness
Interventions	Tranexamic acid (6 g per day iv in 6 doses during the first week, 6 g orally in 4 doses in week 2 until week 6) for a maximum duration of 6 weeks versus control group; treatment continued until operation or death
Outcomes	Outcome: deaths from all causes at 3 months Events: rebleeding: reported and defined; 'confirmed in CSF or at necropsy'; ischaemia: reported, not defined; hydrocephalus: reported, not defined
Notes	Rebleeding 'confirmed' by CSF examination are not useable (see text), not reported how many rebleedings were established on CT scan or at necropsy

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequentially numbered, sealed envelopes were used, but no description was made of how these numbers were created
Allocation concealment (selection bias)	Low risk	Sequentially numbered, sealed envelopes were used
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel were not blinded (open study)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described in the text
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data, ITT analysis could be reconstructed
Selective reporting (reporting bias)	Low risk	Protocol was previously published
Other bias	Unclear risk	People "under 65" and "relatively little disturbed by the first bleed" not included in study, causing the results to be less generalisable

Roos 2000a

Methods	Multicentre study Random allocation (identical sequentially numbered treatment boxes), blocked per centre Double-blind treatment: code broken after all events and outcomes had been recorded ITT
Participants	Clinical diagnosis of aneurysmal SAH verified on CT or in the CSF: if negative CT, angiography had to confirm an aneurysm before randomisation Male:female: treatment group 89:140; placebo group 73:160 Mean age: treatment group 56 years; placebo group 55 years Excluded: SAH > 96 hours or operation planned < 48 hours, coagulation disorders or thrombotic disease, renal failure, pregnancy, previous tranexamic acid treatment or people in whom death appeared imminent
Interventions	Tranexamic acid (6 g per day iv in 6 doses in week 1, and 6 g orally per day in 4 doses in week 2 and 3) versus identical-appearing placebo treatment for a maximum treatment duration of 3 weeks All participants received standard anti-ischaemic treatment with nimodipine and hypervolaemia
Outcomes	Outcome: Glasgow Outcome Scale at 3 months Events: rebleeding-definite: confirmed by CT scan or at necropsy; rebleeding-possible: sudden deterioration and death; infarction-definite: confirmed by CT scan or at necropsy; infarction-probable: gradual development of focal neurologic signs with or without deterioration in the level of consciousness; hydrocephalus: gradual deterioration of consciousness with on CT hydrocephalus and no other explanation Postoperative ischaemia: deterioration of consciousness or development of focal neurological signs immediately after recovery from anaesthesia compared to preoperative status, without rebleeding, infarction or hydrocephalus on CT or at autopsy Poor outcome caused by the initial bleeding: impaired consciousness or focal neurological signs from the time of the initial bleeding, without rebleeding, infarction or hydrocephalus on CT or at autopsy
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence was generated by use of random number tables
Allocation concealment (selection bias)	Low risk	Identical, sequentially numbered treatment boxes, blocked per centre were used and boxes were consecutively numbered and administered in the same order to each following participant
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical and sequentially numbered treatment boxes were used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Only after recording of all events and outcomes, the trial code was broken"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data

Roos 2000a *(Continued)*

Selective reporting (reporting bias)	Low risk	Previously published protocol
Other bias	Low risk	None suspected based on study design and outcome

Tsementzis 1990

Methods	Single-centre study Random allocation (identical sequentially numbered medication boxes) Double-blind treatment Not strictly ITT: 4 participants excluded after randomisation who missed a few doses medication
Participants	Clinical diagnosis of aneurysmal SAH verified on CT or in the CSF Male:female: treatment group 20:30; placebo group 26:24 Age distribution similar in both groups Excluded: SAH > 72 hours, antihypertensives or medication known to affect the fibrinolytic or coagulation systems, acute myocardial infarction, coagulation disorders or thrombotic disease, renal failure, pregnancy, previous tranexamic acid-treatment or people in whom death seemed imminent
Interventions	Tranexamic acid (9 g per day, iv in 6 doses in week 1, orally in 4 doses in week 2, 3 and 4) versus identical-appearing placebo treatment for a maximum treatment duration of 4 weeks# Treatment was discontinued if an operation for the aneurysm began or if deep vein thrombosis or pulmonary infarction developed
Outcomes	Outcome: Glasgow Outcome Scale at discharge, 1, 3 and 6 months Events: rebleeding: reported and defined - 'clinical signs confirmed on CT, in the CSF or at necropsy'; ischaemia: reported and defined - 'clinical signs combined with the absence of evidence of rebleeding on CT or CSF'; hydrocephalus: reported, not defined
Notes	No report of how many participants' rebleedings or cerebral ischaemia were established on CT scan or at necropsy No definition on hydrocephalus other then 'ventricular dilatation was seen on angiography'

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation was not described
Allocation concealment (selection bias)	Low risk	Placebo controlled trial with sequentially numbered boxes with trial medication was used
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Boxes with either tranexamic acid or placebo were used that were numbered consecutively by the pharmacist
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported in the text, but because of control with placebo, not thought to have influenced results
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	4 participants were excluded and no mention is made on their outcome

Tsementzis 1990 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Not reported in the text
Other bias	Unclear risk	20 participants with protocol violations were excluded from the analysis after randomisation

Van Rossum 1977

Methods	Multicentre study Random allocation ("drug or placebo randomly administered in a sequence prescribed by and only known to the statistician") Double-blind treatment Not strictly ITT: 3 participants excluded, because of other diagnosis, after randomisation
Participants	Clinical diagnosis of aneurysmal SAH verified in the CSF Male:female ratio or age distribution not described Excluded: SAH > 14 days (in 94% of the participants, treatment started within 1 week)
Interventions	Tranexamic acid (4 g per day iv in 4 doses) versus identically appearing placebo treatment for a maximum treatment duration of 10 days Treatment was discontinued after the aneurysm operation
Outcomes	Outcome: all-cause mortality at 3 months Events: rebleeding: reported and defined - 'clinical signs confirmed in the CSF or at necropsy'; ischaemia: not reported; hydrocephalus: not reported
Notes	Rebleeds 'confirmed' by CSF examination are not useable (see text), not reported how many rebleedings were established on CT scan or at necropsy

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence was generated by an independent statistician
Allocation concealment (selection bias)	Low risk	Sequence was only known to the statistician and "it was impossible for medical staff or patients to distinguish between drug- and placebo-containing ampoules"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"It was impossible for medical staff or patients to distinguish between drug- and placebo-containing ampoules"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported in the text, but because of control with placebo not thought to have influenced results
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3 participants were excluded and not mentioned further
Selective reporting (reporting bias)	Low risk	Protocol was previously published

Van Rossum 1977 *(Continued)*

Other bias	Low risk	None suspected based on study design and outcome

Vermeulen 1984

Methods	Multicentre study Random allocation (identical sequentially numbered treatment boxes), blocked per centre Double-blind treatment Code broken after all events and outcomes had been recorded ITT
Participants	Clinical diagnosis of aneurysmal SAH verified on CT or in the CSF: if negative CT, angiography had to confirm an aneurysm before randomisation Male:female: treatment group 95:146; placebo group 94:144 Mean age in both groups 50 years Excluded: SAH > 72 hours, coagulation disorders or thrombotic disease, renal failure, pregnancy, previous tranexamic acid-treatment or people in whom death appeared imminent
Interventions	Tranexamic acid (6 g per day iv in 6 doses in week 1 and 2, 4 g iv or 6 g orally per day in 4 doses in week 3 and 4) versus identical-appearing placebo treatment for a maximum treatment duration of 4 weeks Treatment was discontinued when an aneurysm-operation began, if the angiography was negative, if venous thrombosis or pulmonary infarction developed or another diagnosis than aneurysm was established
Outcomes	Outcome: Glasgow Outcome Scale at 3 months Events: rebleeding-definite: confirmed by CT scan or at necropsy; rebleeding-possible: sudden deterioration and death; infarction-definite: confirmed by CT scan or at necropsy; infarction-probable: gradual development of focal neurologic signs with or without deterioration in the level of consciousness; hydrocephalus: reported, not defined
Notes	No definition on hydrocephalus other than 'requiring shunting'

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number tables were used
Allocation concealment (selection bias)	Low risk	Consecutively-numbered boxes were used and were administered in that order to included participants
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo was used as control and the trial code was unbroken until the trial was finished
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The trial code was broken in May 1983, after all events and outcomes had been recorded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete data

Vermeulen 1984 *(Continued)*

Selective reporting (reporting bias)	Low risk	Protocol was previously published
Other bias	Low risk	Not suspected based on study design and outcome

CSF: cerebrospinal fluid
CT: computed tomography
ITT: intention-to-treat
iv: intravenous
SAH: subarachnoid haemorrhage

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Adams 1981	Comparative trial between antifibrinolytic agents and blood pressure reduction or fluid restriction
Ameen 1981	Not a randomised trial; historic control group used
Brzecki 1974	All participants received epsikapron, while being randomised between trasylol or placebo; also historical control group
Buchner 1985	Not a randomised trial; historical control group
Chowdhary 1979	Not strictly randomised; allocation to treatment or placebo according to days of the week
Chowdhary 1981	Comparative trial between tranexamic acid and EACA
Chowdhary 1986	No clinical outcome reported, only data on rebleeding and cerebral ischaemia
Fodstad 1978	No ITT analysis possible; too many participants (14 of a of total 60 randomised) excluded from final analysis after randomisation
Gelmers 1980	Not strictly randomised; allocation to treatment or placebo according to days of the week
Gibbs 1971	Not a randomised trial; significant treatment differences, for instance concerning the timing of surgery, between the EACA-treated participants and the control group
Kassell 1984	Not a randomised trial; case-control study
Knuckey 1982	Not a randomised trial; case-control study
Marchel 1992	Not a randomised trial; historic control group used
Nibbelink 1975	Not a randomised trial, no control group
Profeta 1975	Not a randomised trial; historic control group used
Rosenorn 1988	Not a randomised trial; case-control study
Salaschek 1983	Not a randomised trial; historical control group
Sengupta 1976	Not a randomised trial; physicians preferred allocation
Shucart 1980	Not a randomised trial; physicians preferred allocation

Study	Reason for exclusion
Starke 2008	Not a randomised trial; case control study
Wijdicks 1989	Not a randomised trial; case-control study with historical control group

EACA: epsilon amino-caproic acid
ITT: intention-to-treat

Characteristics of ongoing studies *[ordered by study ID]*

Verbaan 2012

Trial name or title	Ultra-early tranexamic acid after subarachnoid haemorrhage. A prospective, randomised, multi-center study
Methods	Multicentre study Random allocation Open treatment with blind endpoint assessment Intention-to-treat
Participants	Clinical diagnosis of aneurysmal SAH verified on CT with inclusion within 24 hours of start of symptoms Excluded: no loss of consciousness after the haemorrhage with WFNS grade 1 or 2 on admission in combination with a perimesencephalic haemorrhage; bleeding pattern on CT compatible with a traumatic SAH; treatment for deep vein thrombosis; history of blood coagulation disorder; pregnancy or breastfeeding; severe renal (serum creatinine > 150 mmol/L) or liver failure (AST > 150 U/l or ALT > 150 U/l or AF > 150 U/l or gamma-GT > 150 U/l); imminent death within 24 hours
Interventions	Standard treatment with additional administration of 1 g tranexamic acid intravenously in 10 minutes, immediately after the diagnosis SAH, succeeded by continuous infusion of 1 g per 8 hours until a maximum of 24 hours
Outcomes	Primary outcome: Modified Rankin Scale score dichotomised as a favourable (0 to 3) or unfavourable (4 to 6) outcome at 6 months after SAH Secondary: case fatality, cause of poor outcome, rebleeding rate, thromboembolic complications, delayed cerebral ischaemia, other complications (hydrocephalus, thromboembolic events, extracranial thrombosis or haemorrhagic complications), care cost
Starting date	January 2013
Contact information	d.verbaan@amc.uva.nl
Notes	

CT: computed tomography
SAH: subarachnoid haemorrhage
WFNS: World Federation of Neurological Societies

DATA AND ANALYSES

Comparison 1. Antifibrinolytic treatment versus control treatment with or without placebo

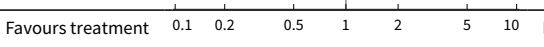
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Poor outcome (death, vegetative or severe disability on Glasgow Outcome Scale at end of follow-up): open versus blind studies	4	1546	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.91, 1.15]
1.1 Trials with control treatment (open studies)	1	505	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.64, 1.14]
1.2 Trials with placebo treatment (blind studies)	3	1041	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.93, 1.21]
2 Death from all causes at end of follow up: open versus blind studies	10	1904	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.85, 1.18]
2.1 Trials with control treatment (open studies)	4	709	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.56, 1.42]
2.2 Trials with placebo treatment (blind studies)	6	1195	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.87, 1.19]
3 Rebleeding reported at end of follow up: open versus blind studies	10	1904	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.44, 0.97]
3.1 Trials with control treatment (open studies)	4	709	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.25, 1.74]
3.2 Trials with placebo treatment (blind studies)	6	1195	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.43, 0.97]
4 Confirmed rebleeding at end of follow-up (sensitivity analysis): open versus blind studies	4	1505	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.26, 0.75]
4.1 Trials with control treatment (open studies)	2	564	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.11, 1.59]
4.2 Trials with placebo treatment (blind studies)	2	941	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.25, 0.86]
5 Rebleeding reported at end of follow-up: trials with and without ischaemia prevention according to treatment duration	10	1904	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.44, 0.97]
5.1 Trials without ischaemia prevention, treatment duration > 72 hours	8	937	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.47, 1.31]
5.2 Trials with ischaemia prevention treatment duration > 72 hours	1	462	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.42, 0.80]
5.3 Trials with ischaemia prevention, treatment duration < 72 hours	1	505	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.09, 0.52]
6 Cerebral ischaemia reported at end of follow-up: open versus blind studies	6	1671	Risk Ratio (M-H, Random, 95% CI)	1.41 [1.04, 1.91]

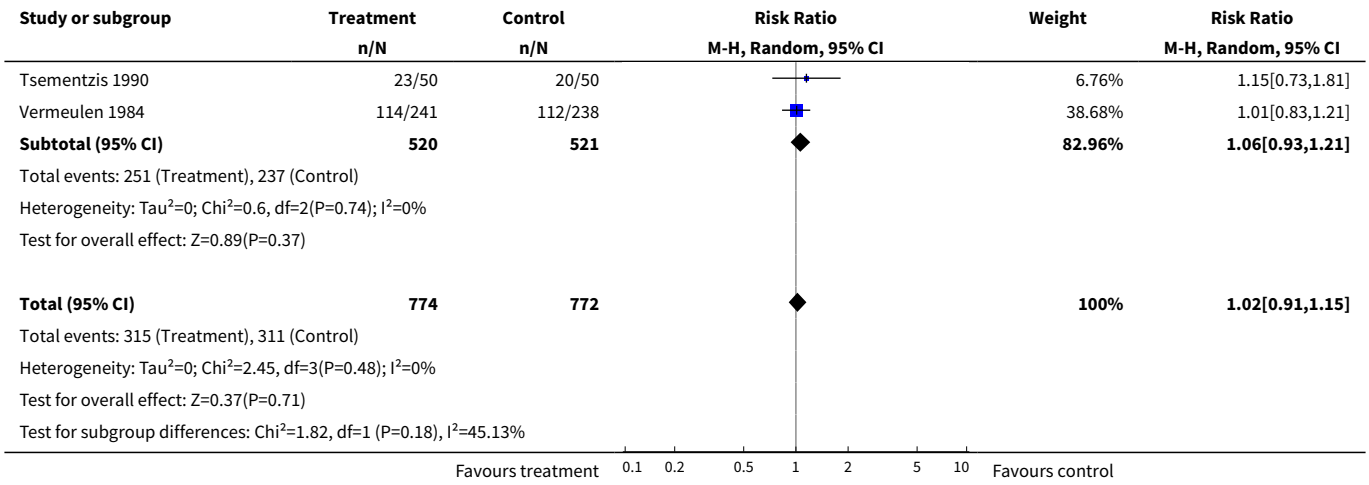
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Trials with control treatment (open studies)	3	630	Risk Ratio (M-H, Random, 95% CI)	1.46 [0.99, 2.14]
6.2 Trials with placebo treatment (blind studies)	3	1041	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.87, 2.19]
7 Confirmed cerebral ischaemia at end of follow-up (sensitivity analysis): open versus blind studies	3	1000	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.88, 2.03]
7.1 Trials with control treatment (open studies)	1	59	Risk Ratio (M-H, Random, 95% CI)	2.58 [0.76, 8.77]
7.2 Trials with placebo treatment (blind studies)	2	941	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.82, 1.89]
8 Hydrocephalus reported at end of follow-up: open versus blind studies	5	1179	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.90, 1.36]
8.1 Trials with control treatment (open studies)	2	138	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.34, 1.18]
8.2 Trials with placebo treatment (blind studies)	3	1041	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.95, 1.48]
9 Confirmed hydrocephalus at end of follow up (sensitivity analysis): open versus blind studies	1	462	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.87, 1.55]
9.1 Trials with control treatment (open studies)	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.2 Trials with placebo treatment (blind studies)	1	462	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.87, 1.55]
10 Hydrocephalus reported at end of follow-up: trials with and without ischaemia prevention according to treatment duration	5	1179	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.90, 1.36]
10.1 Trials without ischaemia prevention, treatment duration > 72 hours	4	717	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.74, 1.43]
10.2 Trials with ischaemia prevention, treatment duration > 72 hours	1	462	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.87, 1.55]
10.3 Trials with ischaemia prevention, treatment duration < 72 hours	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11 Poor outcome (death, vegetative or severe disability on Glasgow Outcome Scale at end of follow-up): trials with and without ischaemia prevention according to treatment duration	4	1546	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.91, 1.15]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Trials without cerebral ischaemia prevention, treatment duration > 72 hours	2	579	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.86, 1.22]
11.2 Trials with ischaemia prevention, treatment duration > 72 hours	1	462	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.91, 1.34]
11.3 Trials with cerebral ischaemia prevention, treatment duration < 72 hours	1	505	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.64, 1.14]
12 Death from all causes at end of follow-up: trials with and without ischaemia prevention according to treatment duration	10	1904	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.85, 1.18]
12.1 Trials without ischaemia prevention, treatment duration > 72 hours	8	937	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.78, 1.35]
12.2 Trials with ischaemia prevention with treatment duration > 72 hours	1	462	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.79, 1.34]
12.3 Trials with ischaemia prevention with treatment duration < 72 hours	1	505	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.52, 1.35]
13 Cerebral ischaemia reported at end of follow-up: trials with and without ischaemia prevention according to treatment duration	6	1671	Risk Ratio (M-H, Random, 95% CI)	1.41 [1.04, 1.91]
13.1 Trials without ischaemia prevention, treatment duration > 72 hours	4	704	Risk Ratio (M-H, Random, 95% CI)	1.77 [1.30, 2.40]
13.2 Trials with ischaemia prevention, treatment duration > 72 hours	1	462	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.75, 1.23]
13.3 Trials with ischaemia prevention, treatment duration < 72 hours	1	505	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.89, 2.04]

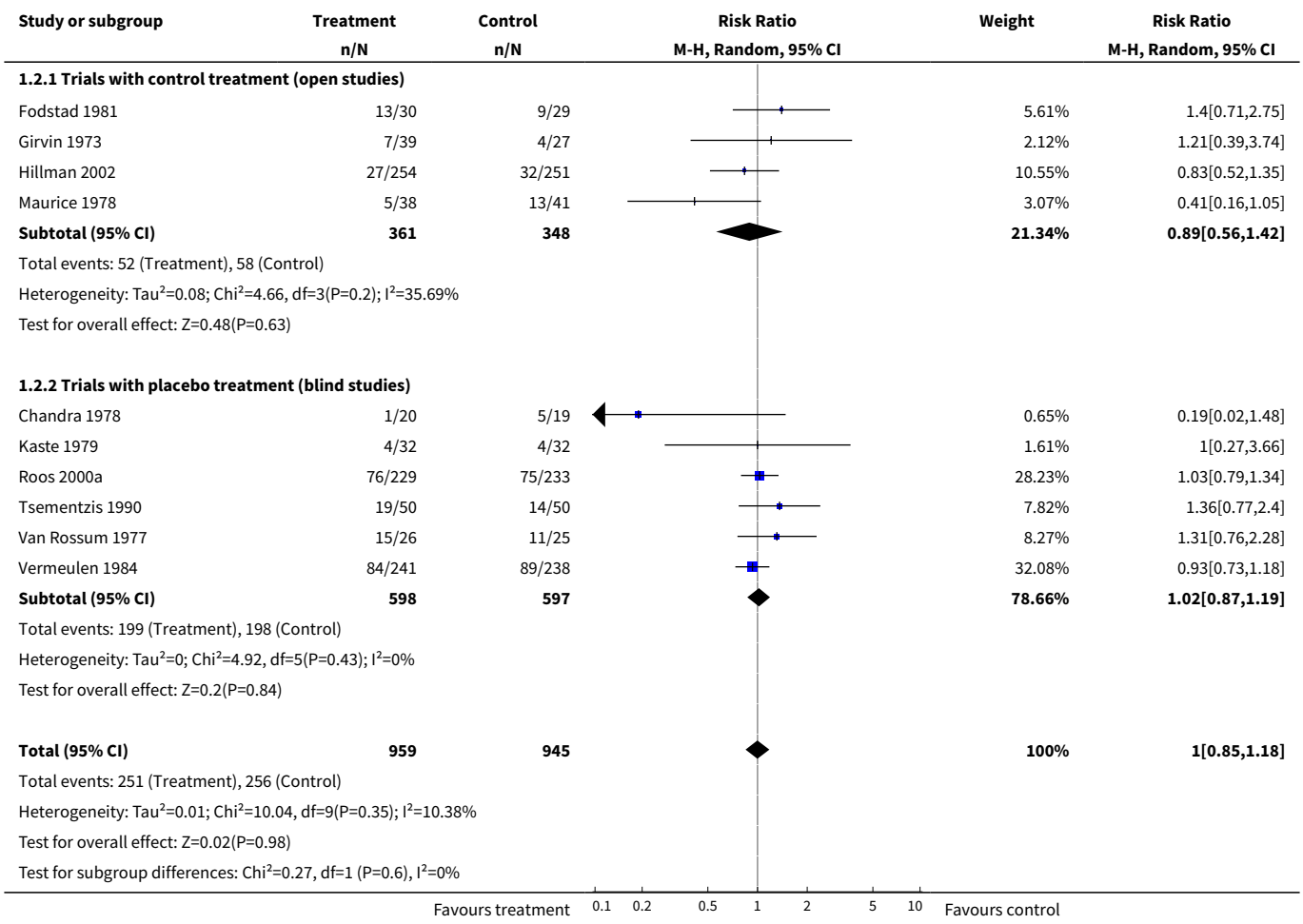
Analysis 1.1. Comparison 1 Antifibrinolytic treatment versus control treatment with or without placebo, Outcome 1 Poor outcome (death, vegetative or severe disability on Glasgow Outcome Scale at end of follow-up): open versus blind studies.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Trials with control treatment (open studies)					
Hillman 2002	64/254	74/251		17.04%	0.85[0.64,1.14]
Subtotal (95% CI)	**254**	**251**		**17.04%**	**0.85[0.64,1.14]**
Total events: 64 (Treatment), 74 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.08(P=0.28)					
1.1.2 Trials with placebo treatment (blind studies)					
Roos 2000a	114/229	105/233		37.52%	1.1[0.91,1.34]



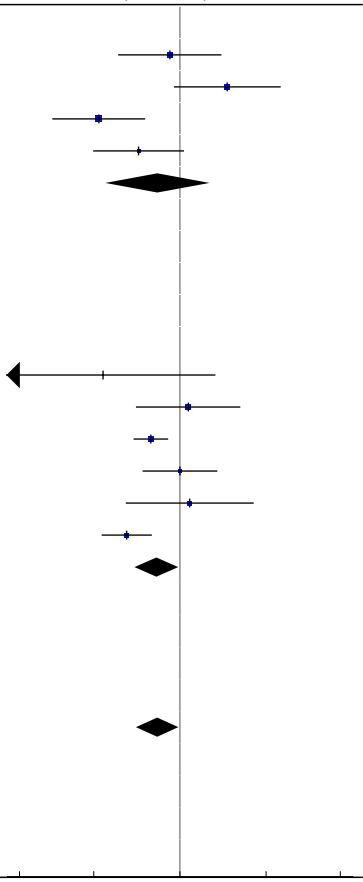


Analysis 1.2. Comparison 1 Antifibrinolytic treatment versus control treatment with or without placebo, Outcome 2 Death from all causes at end of follow up: open versus blind studies.



Analysis 1.3. Comparison 1 Antifibrinolytic treatment versus control treatment with or without placebo, Outcome 3 Rebleeding reported at end of follow up: open versus blind studies.

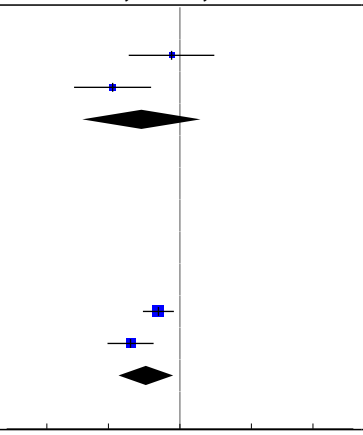
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Trials with control treatment (open studies)					
Fodstad 1981	6/30	7/29		8.92%	0.83[0.32,2.17]
Girvin 1973	14/39	4/27		8.6%	2.42[0.89,6.57]
Hillman 2002	6/254	27/251		9.92%	0.22[0.09,0.52]
Maurice 1978	6/38	14/41		10.12%	0.46[0.2,1.08]
Subtotal (95% CI)	**361**	**348**		**37.57%**	**0.66[0.25,1.74]**
Total events: 32 (Treatment), 52 (Control)					
Heterogeneity: Tau^2=0.77; Chi^2=13.58, df=3(P=0); I^2=77.92%					
Test for overall effect: Z=0.85(P=0.4)					
1.3.2 Trials with placebo treatment (blind studies)					
Chandra 1978	1/20	4/19		3%	0.24[0.03,1.94]
Kaste 1979	7/32	6/32		8.82%	1.17[0.44,3.09]
Roos 2000a	44/229	77/233		16.8%	0.58[0.42,0.8]
Tsementzis 1990	12/50	12/50		11.92%	1[0.5,2.01]
Van Rossum 1977	5/26	4/25		6.95%	1.2[0.36,3.97]
Vermeulen 1984	21/241	56/238		14.95%	0.37[0.23,0.59]
Subtotal (95% CI)	**598**	**597**		**62.43%**	**0.64[0.43,0.97]**
Total events: 90 (Treatment), 159 (Control)					
Heterogeneity: Tau^2=0.11; Chi^2=10.03, df=5(P=0.07); I^2=50.13%					
Test for overall effect: Z=2.11(P=0.03)					
Total (95% CI)	**959**	**945**		**100%**	**0.65[0.44,0.97]**
Total events: 122 (Treatment), 211 (Control)					
Heterogeneity: Tau^2=0.22; Chi^2=23.6, df=9(P=0); I^2=61.87%					
Test for overall effect: Z=2.1(P=0.04)					
Test for subgroup differences: Chi^2=0, df=1 (P=0.97), I^2=0%					



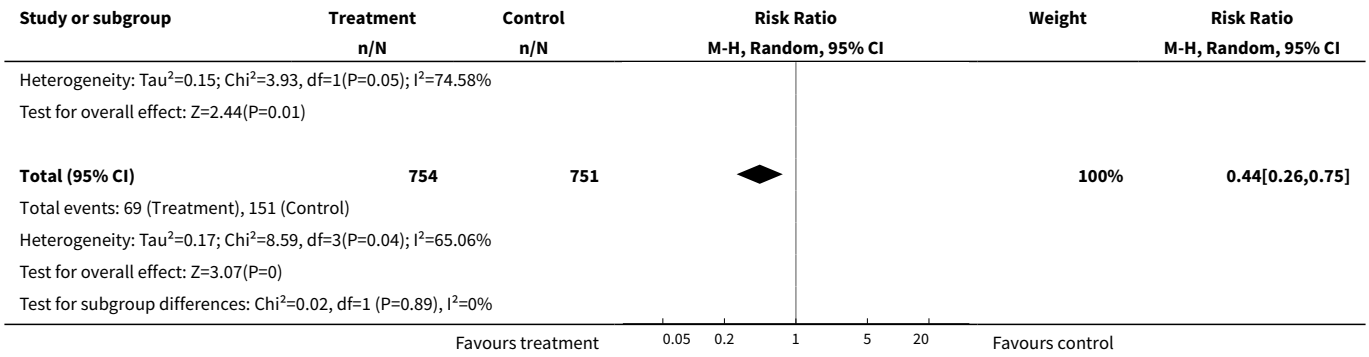
Favours treatment — Favours control

Analysis 1.4. Comparison 1 Antifibrinolytic treatment versus control treatment with or without placebo, Outcome 4 Confirmed rebleeding at end of follow-up (sensitivity analysis): open versus blind studies.

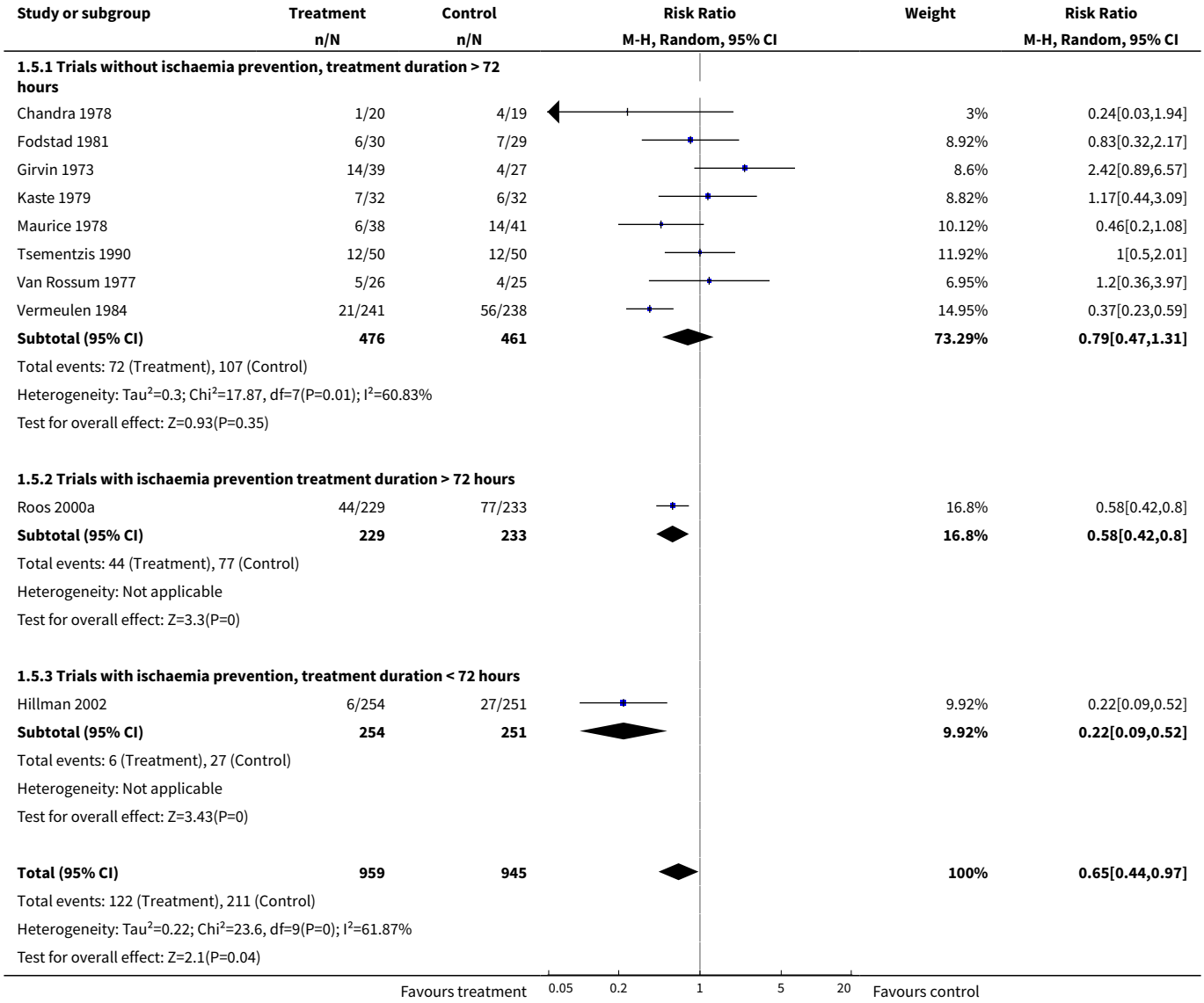
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Trials with control treatment (open studies)					
Fodstad 1981	6/30	7/29		17.03%	0.83[0.32,2.17]
Hillman 2002	6/254	27/251		19.16%	0.22[0.09,0.52]
Subtotal (95% CI)	**284**	**280**		**36.2%**	**0.42[0.11,1.59]**
Total events: 12 (Treatment), 34 (Control)					
Heterogeneity: Tau^2=0.7; Chi^2=4.21, df=1(P=0.04); I^2=76.25%					
Test for overall effect: Z=1.28(P=0.2)					
1.4.2 Trials with placebo treatment (blind studies)					
Roos 2000a	40/229	66/233		34.67%	0.62[0.44,0.87]
Vermeulen 1984	17/241	51/238		29.13%	0.33[0.2,0.55]
Subtotal (95% CI)	**470**	**471**		**63.8%**	**0.46[0.25,0.86]**
Total events: 57 (Treatment), 117 (Control)					



Favours treatment — Favours control



Analysis 1.5. Comparison 1 Antifibrinolytic treatment versus control treatment with or without placebo, Outcome 5 Rebleeding reported at end of follow-up: trials with and without ischaemia prevention according to treatment duration.



Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for subgroup differences: Chi²=6.2, df=1 (P=0.05), I²=67.73%					

Favours treatment 0.05 0.2 1 5 20 Favours control

Analysis 1.6. Comparison 1 Antifibrinolytic treatment versus control treatment with or without placebo, Outcome 6 Cerebral ischaemia reported at end of follow-up: open versus blind studies.

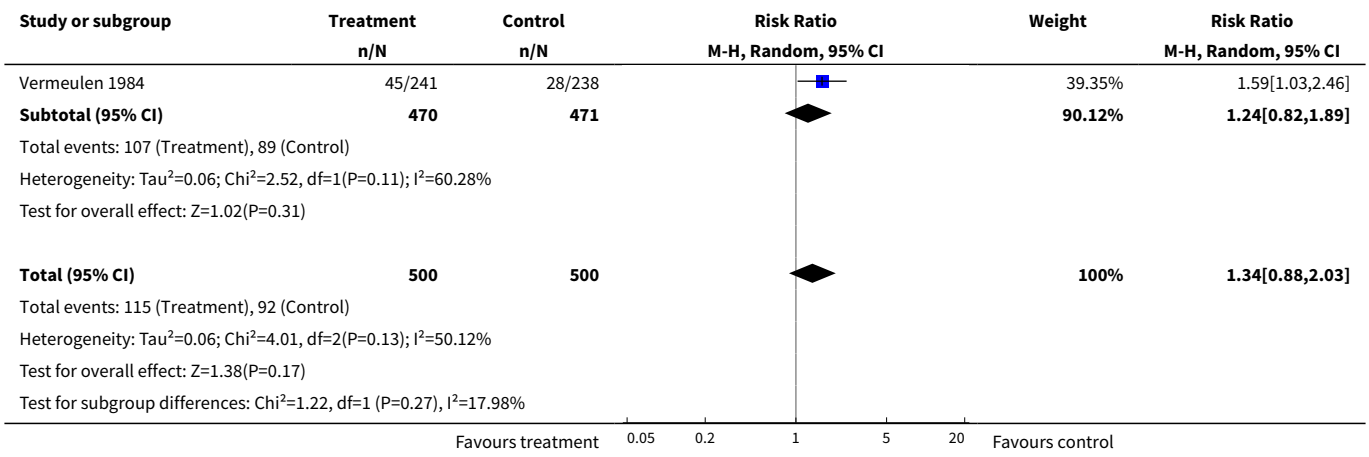
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 Trials with control treatment (open studies)					
Fodstad 1981	8/30	3/29		5.39%	2.58[0.76,8.77]
Girvin 1973	3/39	1/27		1.84%	2.08[0.23,18.92]
Hillman 2002	45/254	33/251		22.53%	1.35[0.89,2.04]
Subtotal (95% CI)	**323**	**307**		**29.76%**	**1.46[0.99,2.14]**
Total events: 56 (Treatment), 37 (Control)					
Heterogeneity: Tau²=0; Chi²=1.07, df=2(P=0.59); I²=0%					
Test for overall effect: Z=1.91(P=0.06)					
1.6.2 Trials with placebo treatment (blind studies)					
Roos 2000a	79/229	84/233		30.61%	0.96[0.75,1.23]
Tsementzis 1990	22/50	11/50		15.27%	2[1.09,3.68]
Vermeulen 1984	59/241	36/238		24.37%	1.62[1.11,2.35]
Subtotal (95% CI)	**520**	**521**		**70.24%**	**1.38[0.87,2.19]**
Total events: 160 (Treatment), 131 (Control)					
Heterogeneity: Tau²=0.12; Chi²=8.48, df=2(P=0.01); I²=76.41%					
Test for overall effect: Z=1.38(P=0.17)					
Total (95% CI)	**843**	**828**		**100%**	**1.41[1.04,1.91]**
Total events: 216 (Treatment), 168 (Control)					
Heterogeneity: Tau²=0.06; Chi²=10.42, df=5(P=0.06); I²=52%					
Test for overall effect: Z=2.18(P=0.03)					
Test for subgroup differences: Chi²=0.03, df=1 (P=0.87), I²=0%					

Favours treatment 0.1 0.2 0.5 1 2 5 10 Favours control

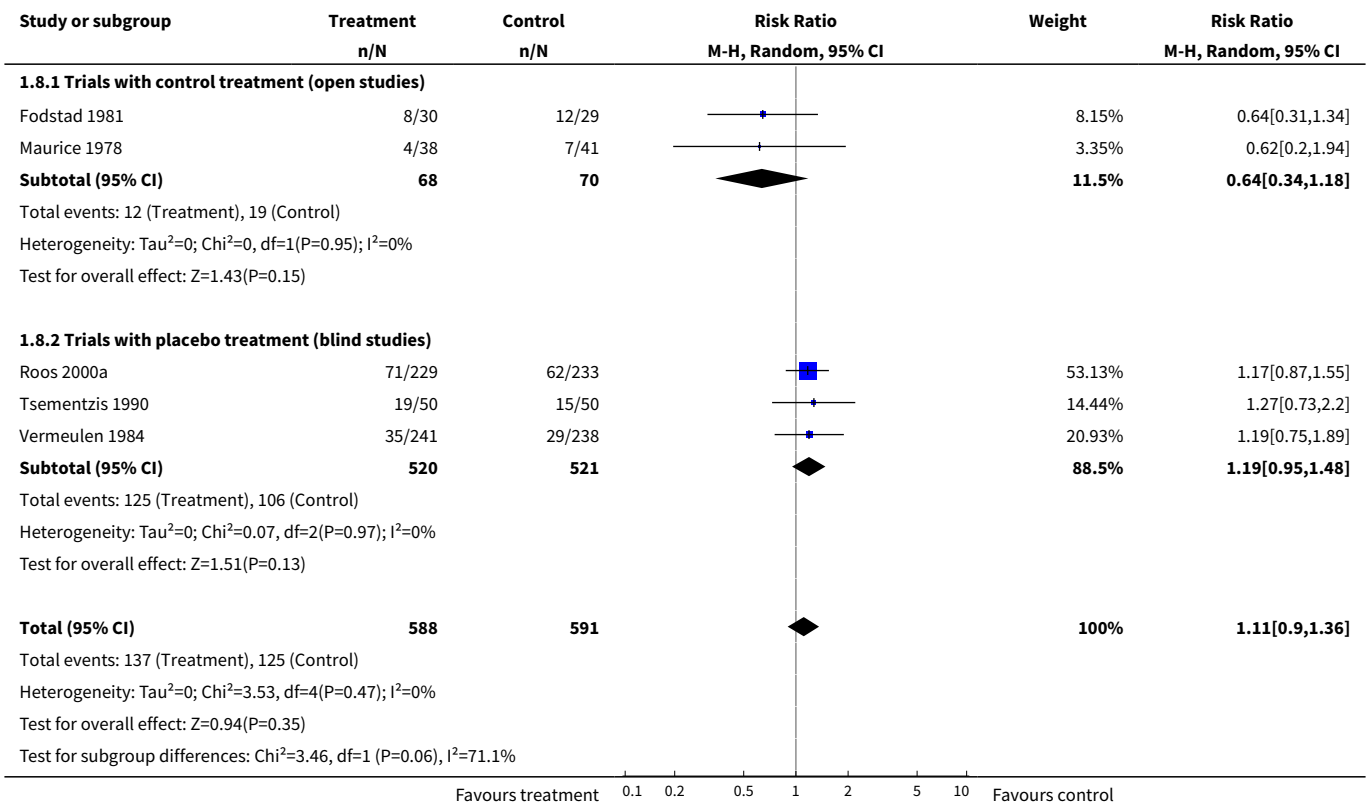
Analysis 1.7. Comparison 1 Antifibrinolytic treatment versus control treatment with or without placebo, Outcome 7 Confirmed cerebral ischaemia at end of follow-up (sensitivity analysis): open versus blind studies.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.7.1 Trials with control treatment (open studies)					
Fodstad 1981	8/30	3/29		9.88%	2.58[0.76,8.77]
Subtotal (95% CI)	**30**	**29**		**9.88%**	**2.58[0.76,8.77]**
Total events: 8 (Treatment), 3 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.52(P=0.13)					
1.7.2 Trials with placebo treatment (blind studies)					
Roos 2000a	62/229	61/233		50.78%	1.03[0.76,1.4]

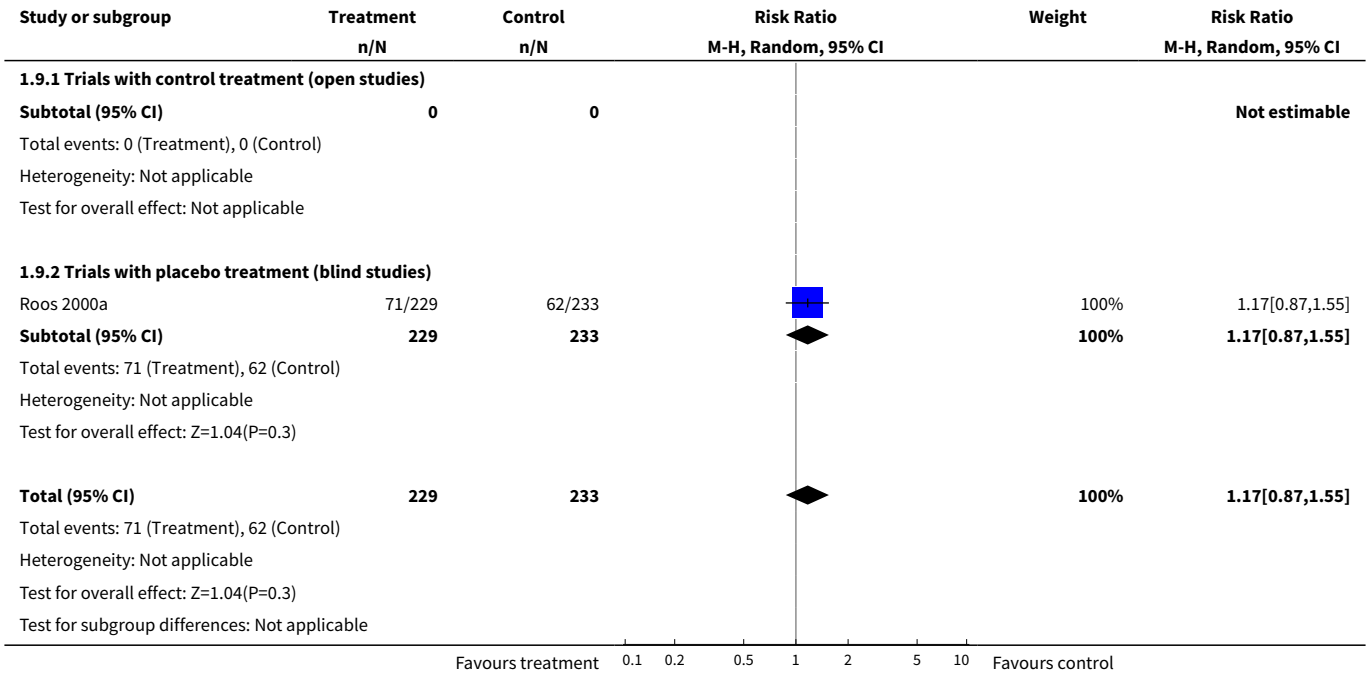
Favours treatment 0.05 0.2 1 5 20 Favours control



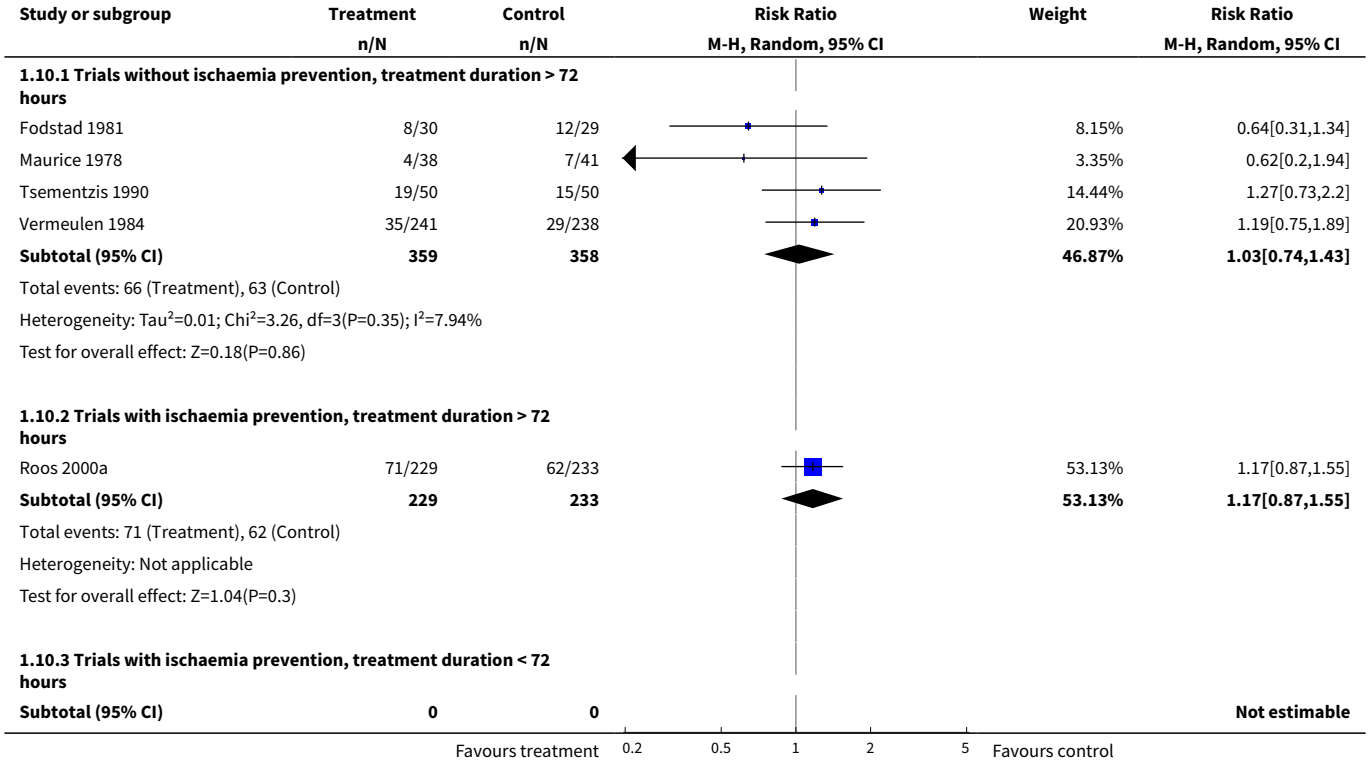
Analysis 1.8. Comparison 1 Antifibrinolytic treatment versus control treatment with or without placebo, Outcome 8 Hydrocephalus reported at end of follow-up: open versus blind studies.

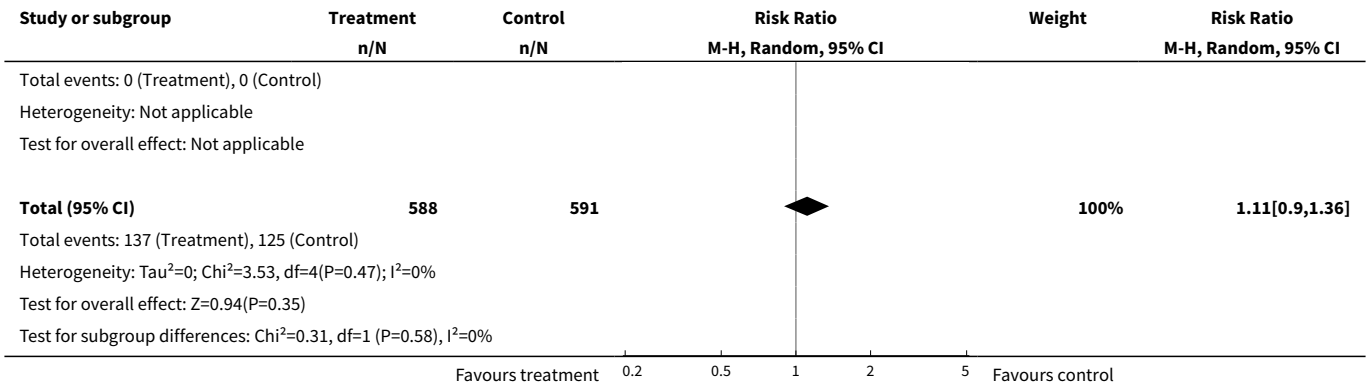


Analysis 1.9. Comparison 1 Antifibrinolytic treatment versus control treatment with or without placebo, Outcome 9 Confirmed hydrocephalus at end of follow up (sensitivity analysis): open versus blind studies.

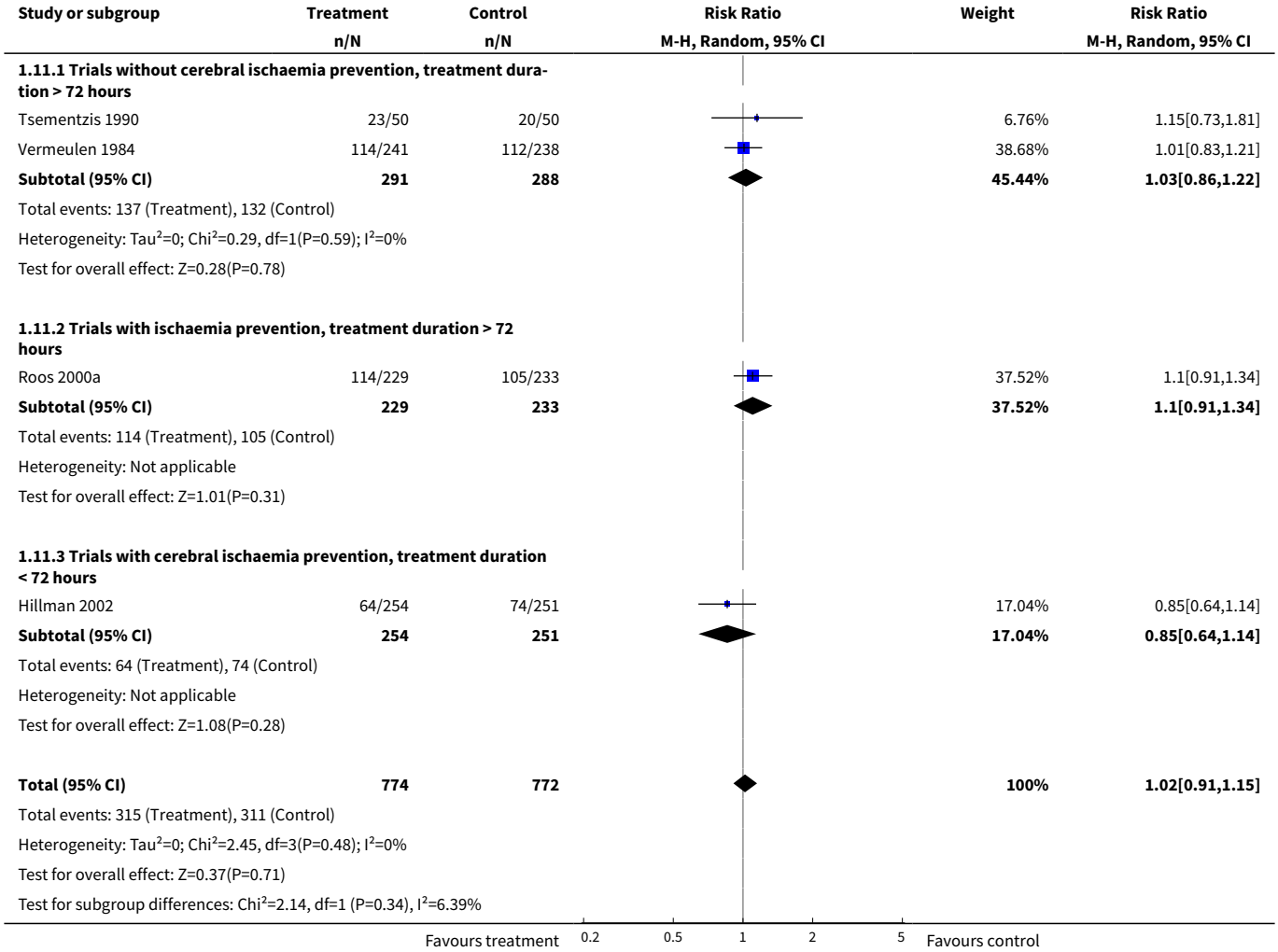


Analysis 1.10. Comparison 1 Antifibrinolytic treatment versus control treatment with or without placebo, Outcome 10 Hydrocephalus reported at end of follow-up: trials with and without ischaemia prevention according to treatment duration.

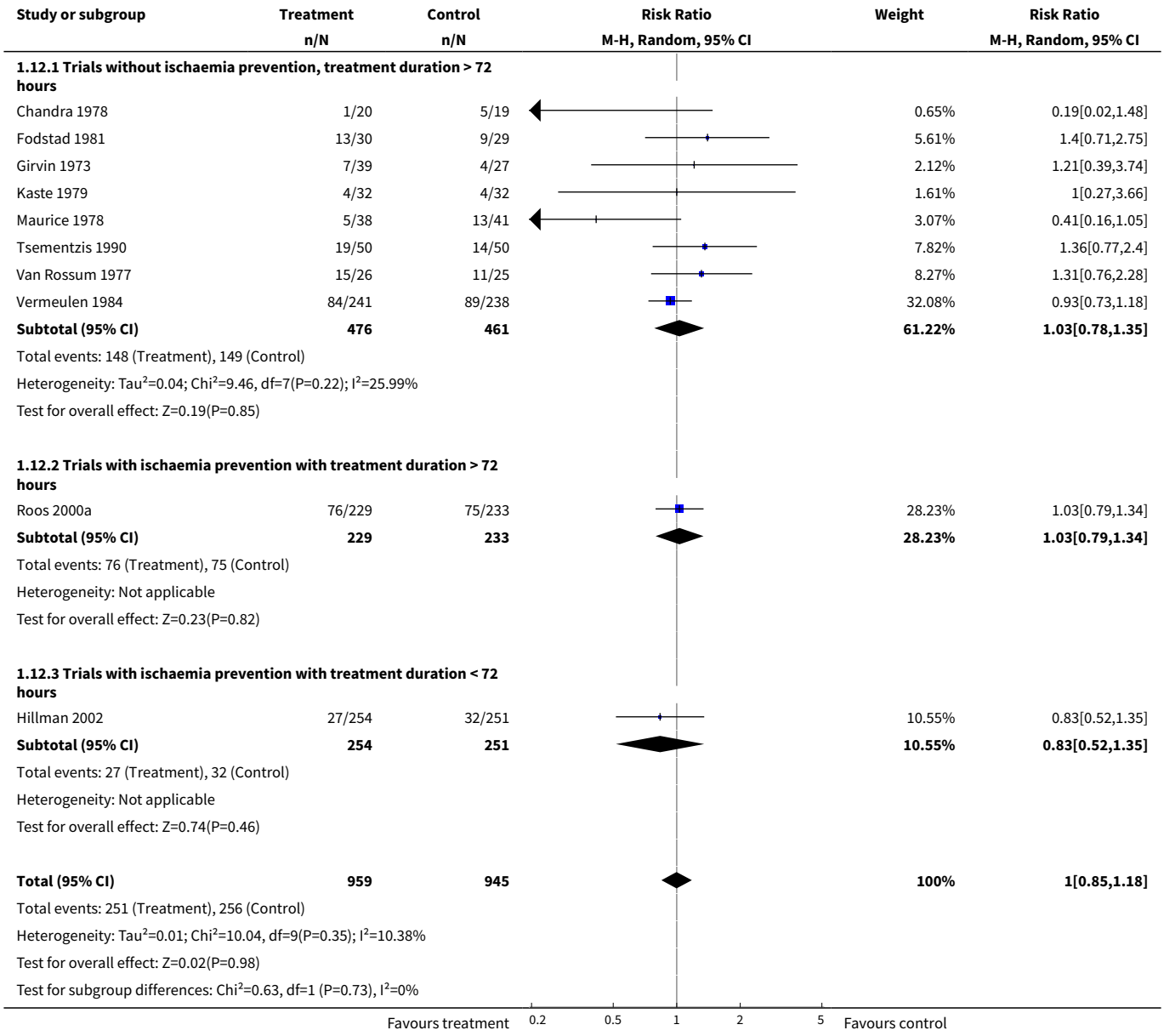




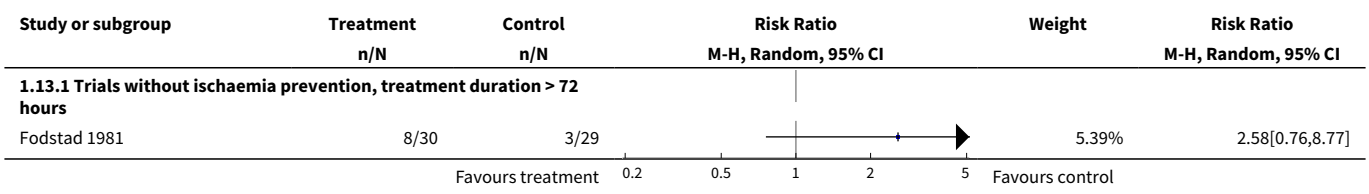
Analysis 1.11. Comparison 1 Antifibrinolytic treatment versus control treatment with or without placebo, Outcome 11 Poor outcome (death, vegetative or severe disability on Glasgow Outcome Scale at end of follow-up): trials with and without ischaemia prevention according to treatment duration.

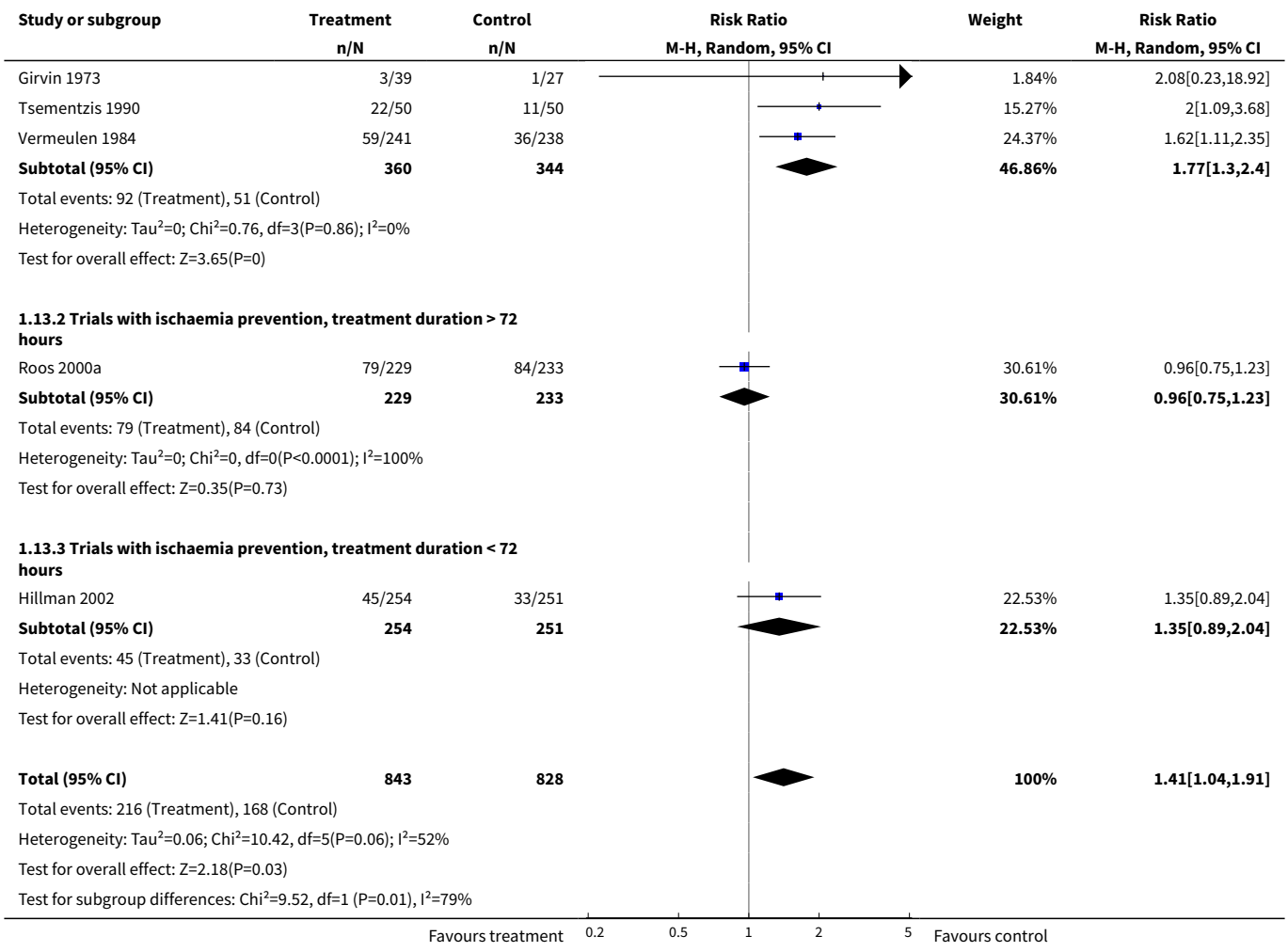


Analysis 1.12. Comparison 1 Antifibrinolytic treatment versus control treatment with or without placebo, Outcome 12 Death from all causes at end of follow-up: trials with and without ischaemia prevention according to treatment duration.



Analysis 1.13. Comparison 1 Antifibrinolytic treatment versus control treatment with or without placebo, Outcome 13 Cerebral ischaemia reported at end of follow-up: trials with and without ischaemia prevention according to treatment duration.





APPENDICES

Appendix 1. MEDLINE search strategy

1. Subarachnoid Hemorrhage/
2. intracranial hemorrhages/ or cerebral hemorrhage/
3. Intracranial Aneurysm/
4. Rupture, Spontaneous/
5. 3 and 4
6. Aneurysm, Ruptured/
7. exp brain/ or exp meninges/
8. 6 and 7
9. ((subarachnoid or arachnoid) adj6 (haemorrhage$ or hemorrhage$ or bleed$ or blood$)).tw.
10. Vasospasm, Intracranial/
11. ((cerebral or intracranial or cerebrovascular) adj6 (vasospasm or spasm)).tw.
12. sah.tw.
13. 1 or 2 or 5 or 8 or 9 or 10 or 11 or 12
14. exp Antifibrinolytic Agents/
15. (anti-fibrinolytic$ or antifibrinolytic$ or antifibrinolysin$ or anti-fibrinolysin$ or antiplasmin$ or anti-plasmin$ or (plasmin adj3 inhibitor$)).tw.
16. (fibrinolysis adj3 (prevent$ or inhib$ or antag$)).tw.
17. tranexamic acid/

18. (4 amino methylcyclohexane carboxylate or 4 aminomethylcyclohexanecarbonic acid or 4 aminomethylcyclohexanecarboxylic acid or amca or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanocarboxylic acid or aminomethylcyclohexanoic acid or amstat or anexan or antivoff or anvitoff orcaprilon or cis 4 aminomethylcyclohexanecarboxylic acid or cis aminomethyl cyclohexanecarboxylic acid or cl 65336 or cl65336 or cyclocapron or cyclokapron or cyklocapron or cyklokapron or exacyl or fibrinon or frenolyse or hemostan or hexacapron or hexakapron or kabi 2161 or kalnex or micranex or para aminomethylcyclohexane carboxylic acid or rikaparin or ronex or spotof or theranex or tramic or tranex or tranexam or tranexamic acid or tranexanic acid or tranexic or trans 1 aminomethylcyclohexane 4 carboxylic acid or trans 4 aminomethylcyclohexane 1 carboxylic acid or trans 4 aminomethylcyclohexane carboxylic acid or trans 4 aminomethylcyclohexanecarboxylic acid or trans achma or trans amcha or trans aminomethyl cyclohexane carboxylic acid or trans aminomethylcyclohexane carboxylic acid or trans aminomethylcyclohexanecarboxylic acid or transamin or transaminomethylcyclohexane carboxylic acid or transexamic acid or traxamic or trenaxin or ugurol).tw,nm.
19. exp Aminocaproic Acids/
20. (acikaprin or afibrin or amicar or amino caproic acid or aminocaproic acid or aminohexanoic acid or capracid or capramol or caproamin or caprocid or caprogel or caprolest or caprolisin or caprolisine or caprolysin orcapromol or cl 10304 or cl10304 or cy 116 or cy116 or e aminocaproic acid or EACA or ecapron or ekaprol or epsamon or epsicaprom or epsicapron or epsikapron or epsilcapramin or epsilon amino caproate or epsilon amino caproic aci or depsilon aminocaproate or epsilon aminocaproic acid or epsilonaminocaproic acid or epsilonaminocapronsav or etha aminocaproic acid or ethaaminocaproic acid or gamma aminocaproic acidor gamma aminohexanoic acidor hemocaprol or hepin or hexalense or ipsilon or jd 177 or jd177 or neocaprol or nsc 26154 or nsc26154 or resplamin or tachostyptan).tw,nm.
21. Aprotinin/
22. (9921 rp or antagosan or antilysin or antilysine or apronitin or apronitine or apronitrine or aprotimbin or aprotinin bovine or aprotinine or aprotonin or bayer a 128 or bayer a128 or bovine pancreatic secretory trypsin inhibitor or contrical or contrycal or contrykal or frey inhibitor or gordox or haemoprot or iniprol or kallikrein trypsin inhibitor or kazal type trypsin inhibitor or kontrikal or kontrycal or Kunitz inhibitor or Kunitz trypsin inhibitor or midran or pancreas antitrypsin or pancreas secretory trypsin inhibitor or pancreas trypsin inhibitor or pancreatic antitrypsin or pancreatic secretory trypsin inhibitor or pancreatic trypsin inhibitor or protinin orriker 52g or rivilina or rp 9921 or rp9921 or tracylol or trascolan or trasilol or traskolan or trasylol or trazylol or tumor associated trypsin inhibitor or zymofren).tw,nm.
23.(4 aminomethylbenzoic acid or 4 amino methylbenzoic acid or alpha amino para toluic acid or amino methylbenzoic acid or aminomethyl benzoic acid or aminomethylbenzoic acid or PAMBA or para aminomethylbenzoic acid or para amino methylbenzoic acid or styptopur or styptosolut).tw,nm
24. Fibrinolysis/ai, de [Antagonists & Inhibitors, Drug Effects]
25. or/14-24
26. 13 and 25
27. exp animals/ not humans.sh.
28. 26 not 27

Appendix 2. EMBASE search strategy

1. Subarachnoid Hemorrhage/
2. brain hemorrhage/ or brain artery aneurysm rupture/
3. Brain Vasospasm/
4. exp Intracranial Aneurysm/
5. exp rupture/
6. 4 and 5
7. Aneurysm Rupture/
8. exp brain/ or exp meninx/
9. 7 and 8
10. ((subarachnoid or arachnoid) adj6 (haemorrhage$ or hemorrhage$ or bleed$ or blood$)).tw.
11. ((cerebral or intracranial or cerebrovascular) adj6 (vasospasm or spasm)).tw.
12. sah.tw.
13. 1 or 2 or 3 or 6 or 9 or 10 or 11 or 12
14. exp antifibrinolytic agent/
15. (anti-fibrinolytic$ or antifibrinolytic$ or antifibrinolysin$ or anti-fibrinolysin$ or antiplasmin$ or anti-plasmin$ or (plasmin adj3 inhibitor$)).tw.
16. (fibrinolysis adj3 (prevent$ or inhib$ or antag$)).tw.
17. tranexamic acid/
18. (4 amino methylcyclohexane carboxylate or 4 aminomethylcyclohexanecarbonic acid or 4 aminomethylcyclohexanecarboxylic acid or amca or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanocarboxylic acid or aminomethylcyclohexanoic acid or amstat or anexan or antivoff or anvitoff orcaprilon or cis 4 aminomethylcyclohexanecarboxylic acid or cis aminomethyl cyclohexanecarboxylic acid or cl 65336 or cl65336 or cyclocapron or cyclokapron or cyklocapron or cyklokapron or exacyl or fibrinon or frenolyse or

hemostan or hexacapron or hexakapron or kabi 2161 or kalnex or micranex or para aminomethylcyclohexane carboxylic acid or rikaparin or ronex or spotof or theranex or tramic or tranex or tranexam or tranexamic acid or tranexanic acid or tranexic or trans 1 aminomethylcyclohexane 4 carboxylic acid or trans 4 aminomethylcyclohexane 1 carboxylic acid or trans 4 aminomethylcyclohexane carboxylic acid or trans 4 aminomethylcyclohexanecarboxylic acid or trans achma or trans amcha or trans aminomethyl cyclohexane carboxylic acid or trans aminomethylcyclohexane carboxylic acid or trans aminomethylcyclohexanecarboxylic acid or transamin or transaminomethylcyclohexane carboxylic acid or transexamic acid or traxamic or trenaxin or ugurol).tw.
19. aminocaproic acid/
20. (acikaprin or afibrin or amicar or amino caproic acid or aminocaproic acid or aminohexanoic acid or capracid or capramol or caproamin or caprocid or caprogel or caprolest or caprolisin or caprolisine or caprolysin orcapromol or cl 10304 or cl10304 or cy 116 or cy116 or e aminocaproic acid or EACA or ecapron or ekaprol or epsamon or epsicaprom or epsicapron or epsikapron or epsilcapramin or epsilon amino caproate or epsilon amino caproic aci or depsilon aminocaproate or epsilon aminocaproic acid or epsilonaminocaproic acid or epsilonaminocapronsav or etha aminocaproic acid or ethaaminocaproic acid or gamma aminocaproic acidor gamma aminohexanoic acidor hemocaprol or hepin or hexalense or ipsilon or jd 177 or jd177 or neocaprol or nsc 26154 or nsc26154 or resplamin or tachostyptan).tw.
21. aprotinin/
22. (9921 rp or antagosan or antilysin or antilysine or apronitin or apronitine or apronitrine or aprotimbin or aprotinin bovine or aprotinine or aprotonin or bayer a 128 or bayer a128 or bovine pancreatic secretory trypsin inhibitor or contrical or contrycal or contrykal or frey inhibitor or gordox or haemoprot or iniprol or kallikrein trypsin inhibitor or kazal type trypsin inhibitor or kontrikal or kontrycal or Kunitz inhibitor or Kunitz trypsin inhibitor or midran or pancreas antitrypsin or pancreas secretory trypsin inhibitor or pancreas trypsin inhibitor or pancreatic antitrypsin or pancreatic secretory trypsin inhibitor or pancreatic trypsin inhibitor or protinin orriker 52g or rivilina or rp 9921 or rp9921 or tracylol or trascolan or trasilol or traskolan or trasylol or trazylol or tumor associated trypsin inhibitor or zymofren).tw.
23. 4 aminomethylbenzoic acid/
24. (4 aminomethylbenzoic acid or 4 amino methylbenzoic acid or alpha amino para toluic acid or amino methylbenzoic acid or aminomethyl benzoic acid or aminomethylbenzoic acid or PAMBA or para aminomethylbenzoic acid or para amino methylbenzoic acid or styptopur or styptosolut).tw.
25. fibrinolysis/pc [Prevention]
26. or/14-25
27. 13 and 26
28. limit 27 to human

WHAT'S NEW

Date	Event	Description
5 September 2013	Amended	Minor layout changes

HISTORY

Protocol first published: Issue 3, 1998
Review first published: Issue 3, 1998

Date	Event	Description
4 February 2013	New citation required and conclusions have changed	A new subgroup analysis was added and the conclusions changed.
4 February 2013	New search has been performed	Updated searches completed and a new study added. We included one new study (Hillman 2002) with 505 participants. This study is different in treatment timing and duration of therapy and contributes 26.5% of all participants. The review now includes 10 trials and 1904 participants in total.
21 July 2008	Amended	Converted to new review format.
7 February 2003	New search has been performed	The results of the recently published STAR-study, the second largest placebo-controlled randomised trial of antifibrinolytic treatment in subarachnoid haemorrhage, has been added to the

Date	Event	Description
		review. This study contributes 33% of all included patients in this review and 39% of the patients included in the comparison of antifibrinolytic treatment versus placebo. Furthermore, a Plain language summary of the review has been added.

CONTRIBUTIONS OF AUTHORS

Irem Baharoglu: co-ordinated the updated review; collected data; undertook all aspects of the searches; was responsible for data management and entering data into RevMan; analysis of the data; and writing the updated review.

Menno Germans: participated in data collection; reviewed all data and participated in writing this update.

Yvo Roos: co-ordinated and wrote previous versions of this review and oversaw the data collection and writing of the present update.

Gabriel Rinkel: participated in writing the current and previous versions of the review as well as securing funding.

Ale Algra: participated in writing the current and previous versions of the review and has also performed previous work which was the foundation of the current review.

Marinus Vermeulen: secured funding and participated in writing previous versions of the review and has also performed previous work which was the foundation of the current review.

Van Gijn: participated in writing previous versions of the review; and has also performed previous work which was the foundation of the current review.

All the authors participated in conceiving and designing the review; developing the search strategy; interpreting the data; providing methodological, clinical policy and consumer perspectives; and providing general advice on the review.

DECLARATIONS OF INTEREST

Some authors (YBWEMR, GJER, MV) participated in one of the two largest trials included in this review (Roos 2000a; Vermeulen 1984), which were co-ordinated by two of the current review authors. MRG has written a protocol for a new trial (Verbaan 2012). None of the review authors have any financial or other commercial conflict of interest to disclose.

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Internal sources

- No sources of support supplied

External sources

- Nederlandse Hartstichting (Netherlands Heart Foundation), Netherlands.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Aminocaproic Acid [administration & dosage] [*therapeutic use]; Antifibrinolytic Agents [administration & dosage] [*therapeutic use]; Brain Ischemia [chemically induced]; Confidence Intervals; Injections, Intravenous; Intracranial Aneurysm [complications]; Randomized Controlled Trials as Topic; Secondary Prevention; Subarachnoid Hemorrhage [*drug therapy] [prevention & control]; Tranexamic Acid [administration & dosage] [*therapeutic use]; Treatment Outcome

MeSH check words

Humans