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Haemodilution for acute ischaemic stroke (Review)

Chang TS, Jensen MB

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[Intervention Review]

Haemodilution for acute ischaemic stroke

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ABSTRACT

Background

Ischaemic stroke interrupts the flow of blood to part of the brain. Haemodilution is thought to improve the flow of blood to the affected areas of the brain and thus reduce infarct size.

Objectives

To assess the effects of haemodilution in acute ischaemic stroke.

Search methods

We searched the Cochrane Stroke Group Trials Register (February 2014), the Cochrane Central Register of Controlled Trials (Issue 1, 2014), MEDLINE (January 2008 to October 2013) and EMBASE (January 2008 to October 2013). We also searched trials registers, scanned reference lists and contacted authors. For the previous version of the review, the authors contacted manufacturers and investigators in the field.

Selection criteria

Randomised trials of haemodilution treatment in people with acute ischaemic stroke. We included only trials in which treatment was started within 72 hours of stroke onset.

Data collection and analysis

Two review authors assessed trial quality and one review author extracted the data.

Main results

We included 21 trials involving 4174 participants. Nine trials used a combination of venesection and plasma volume expander. Twelve trials used plasma volume expander alone. The plasma volume expander was plasma alone in one trial, dextran 40 in 12 trials, hydroxyethyl starch (HES) in five trials and albumin in three trials. Two trials tested haemodilution in combination with another therapy. Evaluation was blinded in 14 trials. Five trials probably included some participants with intracerebral haemorrhage. Haemodilution did not significantly reduce deaths within the first four weeks (risk ratio (RR) 1.10; 95% confidence interval (CI) 0.90 to 1.34). Similarly, haemodilution did not influence deaths within three to six months (RR 1.05; 95% CI 0.93 to 1.20), or death and dependency or institutionalisation (RR 0.96; 95% CI 0.85 to 1.07). The results were similar in confounded and unconfounded trials, and in trials of isovolaemic and hypervolaemic haemodilution. No statistically significant benefits were documented for any particular type of haemodiluting agents, but the statistical power to detect effects of HES was weak. Six trials reported venous thromboembolic events. There was a tendency towards reduction in deep venous thrombosis or pulmonary embolism or both at three to six months' follow-up (RR 0.68; 95% CI 0.37 to 1.24). There was no statistically significant increased risk of serious cardiac events among haemodiluted participants.

Authors' conclusions

The overall results of this review showed no clear evidence of benefit of haemodilution therapy for acute ischaemic stroke.

These results are compatible with no persuasive beneficial evidence of haemodilution therapy for acute ischaemic stroke. This therapy has not been proven to improve survival or functional outcome.

PLAIN LANGUAGE SUMMARY

Haemodilution for acute ischaemic stroke

Question

We wanted to compare the effectiveness of haemodilution (diluting the blood) treatment, started within 72 hours of stroke onset, versus control or no treatment in people with ischaemic stroke to assess the impact on death or dependence.

Background

Stroke is the second leading cause of death worldwide. Symptoms of stroke include face drooping, arm weakness and difficulty with speech. Most strokes are caused by a blood clot that interrupts blood flow to a part of the brain. If blood flow is not restored quickly, the brain cells will die. Haemodilution improves the flow properties of the blood so that, theoretically, oxygen and nutrient supply to the brain is improved and brain cells threatened to die could survive. This treatment reduces brain infarct (the area of dead cells) size in animals with experimental stroke. Haemodilution can be achieved by blood-letting (removing blood), by giving fluids as an infusion or by a combination of both. The fluids used may be salt solutions but colloid solutions, which consist of large insoluble molecule meant to retain fluid intravascularly, are more effective as haemodilution agents. In many countries, haemodilution has been used in clinical treatment of people with acute stroke since the 1970s. Since then, a large number of clinical studies on haemodilution in acute stroke have been published. The goal of this review was to determine if blood dilution could prevent death in people with stroke due to blood clots.

Study characteristics

We identified 21 trials involving 4174 adult, male and female participants with presumed acute ischaemic stroke. The evidence is current to February 2014. Many trials followed participants for at least three to six months. Interventions included isovolaemic regimens (replacing a portion of blood volume with fluid) and hypervolaemic regimens (increasing the total volume of blood by adding fluid) using different types of solutions.

Key results

This review showed that, when all the studies are taken together, there is no clear evidence of benefit from haemodilution. There is also no clear evidence that any particular mode of haemodilution, with or without blood-letting, using various types of haemodiluting agents, etc, is beneficial. There were no significant serious side effects of this treatment. It is concluded that there is no clear scientific support for the use of haemodilution in the routine treatment of people with acute ischaemic stroke.

Quality of the evidence

The overall quality of the evidence was moderate as individual trials were of varying quality. There was little variation among trials.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Haemodilution, all types, versus control for acute ischaemic stroke

Haemodilution, all types, versus control for acute ischaemic stroke

Patient or population: people with acute ischaemic stroke
Settings:
Intervention: haemodilution, all types, versus control

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Haemodilution, all types, versus control				
Mortality at early follow-up (not later than 28 days)	**Study population**		**RR 1.1** (0.9 to 1.34)	3866 (16 studies)	⊕⊕⊕⊖ **moderate** [1]	-
	90 per 1000	**99 per 1000** (81 to 120)				
	Moderate					
	54 per 1000	**59 per 1000** (49 to 72)				
Mortality at late follow-up (3-6 months)	**Study population**		**RR 1.05** (0.93 to 1.2)	3957 (15 studies)	⊕⊕⊕⊖ **moderate** [2]	-
	185 per 1000	**194 per 1000** (172 to 222)				
	Moderate					
	134 per 1000	**141 per 1000** (125 to 161)				
Dead or dependent/institutionalised at 3-6 months	**Study population**		**RR 0.96** (0.85 to 1.07)	2491 (8 studies)	⊕⊕⊕⊖ **moderate** [3]	-
	526 per 1000	**505 per 1000** (447 to 563)				
	Moderate					

	539 per 1000	**517 per 1000** (458 to 577)				
Venous thromboembolic events at early follow-up (within 28 days)	**Study population**		**RR 0.83** (0.2 to 3.44)	621 (4 studies)	⊕⊕⊕⊖ **moderate** [4]	-
	27 per 1000	**22 per 1000** (5 to 93)				
	Moderate					
	8 per 1000	**7 per 1000** (2 to 28)				
Venous thromboembolic events at late follow-up (3-6 months)	**Study population**		**RR 0.68** (0.37 to 1.24)	865 (6 studies)	⊕⊕⊕⊖ **moderate** [5]	-
	72 per 1000	**49 per 1000** (27 to 89)				
	Moderate					
	37 per 1000	**25 per 1000** (14 to 46)				
Serious cardiac events, cumulative at latest follow-up	**Study population**		**RR 1.16** (0.66 to 2.05)	1358 (7 studies)	⊕⊕⊖⊖ **low** [6,7]	-
	78 per 1000	**90 per 1000** (51 to 160)				
	Moderate					
	78 per 1000	**90 per 1000** (51 to 160)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Four studies lacked or were unclear on blinding of participants and evaluators. Five studies were unclear on randomisation and allocation concealment. However, these risks would be unlikely to increase the effect size.
[2] Five studies lacked or were unclear on blinding of participants and evaluators. Five studies were unclear on randomisation and allocation concealment. However, these risks would be unlikely to increase the effect size.
[3] Two studies lacked or were unclear on blinding of participants and evaluators. Two studies were unclear on randomisation and allocation concealment. However, these risks would be unlikely to increase the effect size.
[4] 15 total events.
[5] 51 total events.
[6] One study was unclear on blinding of participants and evaluators. Two studies were unclear on randomisation and allocation concealment. However, these risks would be unlikely to increase the effect size.
[7] 124 total events.

BACKGROUND

Description of the condition

Stroke is the second leading cause of mortality and third leading cause of disability worldwide (Lozano 2012). Globally, ischaemic stroke constitutes 68% of all strokes (Krishnamurthi 2013). The median age of stroke is 70 years with an age-standardised incidence of 3.4 to 5.2 per 1000 (Feigin 2003). As the one-month case-fatality rate is 13% to 27% (Feigin 2003), and with limited treatment options, many treatments have been studied, including haemodilution.

Description of the intervention

Haemodilution is usually achieved by infusion of a plasma volume expander with or without concomitant venesection. It may be hyper-, iso- or hypovolaemic, depending on the balance between plasma expansion and venesection. The most commonly used plasma expander in clinical stroke trials has been dextran 40, but hydroxyethyl starch (HES, also called pentastarch) and albumin have also been used.

How the intervention might work

There are several clinical observations suggesting that haemorheological factors have a role to play in acute ischaemic stroke.

1. People with polycythaemia vera, having very high haematocrit levels, are prone to various thromboembolic complications, including stroke (Pearson 1978).
2. High haematocrit, even within the 'normal' range, may predict ischaemic stroke (Kannel 1972; Kiyohara 1986), and haematocrit values are significantly higher in people with ischaemic stroke than in matched controls (Harrison 1981; Tohgi 1978). Although this may be a causal relationship, it must be remembered that high haematocrit is related to other cardiovascular risk markers such as hypertension, dyslipidaemia and diabetes (Kiyohara 1986; Lithner 1988).
3. People with stroke have a variety of haematological abnormalities that may increase whole-blood viscosity. This includes decreased red cell deformability, increased red cell aggregation, signs of leukocyte activation, elevated fibrinogen and, as a result, high plasma viscosity (Di Perri 1986; Ott 1986; Wood 1985).

When local blood flow to a region of the brain is suddenly interrupted, collateral blood supply may maintain some delivery of oxygen and nutrients, although at a low level, and structural integrity of the neurons is preserved. Intentional haemodilution has been introduced to improve blood flow to hypoperfused but still viable brain areas supplied by collaterals (penumbra). Haemodilution reduces haematocrit and has dual effects: on the one hand, it improves blood flow, on the other hand, it reduces the oxygen-carrying capacity. The net effect on tissue oxygen supply follows an inverse U-shaped curve. As haematocrit is reduced, oxygen delivery increases to a peak. When haematocrit is reduced further, oxygen delivery starts to fall (Chien 1981). This has been shown in many peripheral tissues in various species, and there is some support for a similar relationship between haematocrit and oxygen delivery in the human brain (Todd 1994).

When an ischaemic stroke occurs, cerebral autoregulatory mechanisms are impaired (Paulson 1971). In people with brain infarction, intentional haemodilution has been associated with increased flow in the infarcted as well as in the contralateral hemisphere (Hartmann 1987; Vorstrup 1989; Wood 1983). This has also been amply shown in animal models of ischaemic stroke, in which beneficial results of haemodilution on infarct size have been demonstrated (Belayev 2001; Liu 2001). Oxygen-carrying haemodilutants, such as per fluorocarbon emulsions or diaspirin cross-linked haemoglobin, have also been used successfully to reduce brain infarct size in animal models (Aronowski 1996; Kline 1991). Other oxygen-carrying agents of potential use in people with ischaemic stroke include polymerised bovine haemoglobin (Standl 2001).

The optimal haematocrit level for oxygen delivery to the ischaemic brain tissue remains to be determined. Several of the clinical trials reviewed here have been based on experimental data suggesting that haematocrit in the 30% to 33% range provides maximal oxygen delivery to normal peripheral tissues (Chien 1981). However, mathematical modelling based on published observations indicate that oxygen supply in the ischaemic brain penumbra decreases at haemoglobin concentrations below 10 g per 100 mL (Dexter 1997). At the other end of the spectrum, there are several indications that haematocrit levels as high as 40% to 45% provide maximal oxygen delivery to brain tissue (Chien 1981; Kusunoki 1981).

Why it is important to do this review

Systematic investigations of haemodilution in the clinical setting started in the 1960s. Initial clinical experiences of haemodilution without randomisation were encouraging, and suggested clinical benefits from various haemodilution regimens (Gottstein 1976; Gottstein 1981; Korosue 1988; Wood 1982). Haemodilution gained wide acceptance and, in many countries, it became the therapy of choice for people with acute ischaemic stroke. Despite the discouraging results of the randomised trials, as shown in the present review, haemodilution is still occasionally recommended to treat people with acute ischaemic stroke (Popov 2000).

Starting in the late 1960s, several randomised controlled trials (RCTs) of haemodilution treatment in people with acute stroke have been performed. The results have been conflicting. The present formal statistical overview includes the results from 21 independent RCTs of haemodilution in acute ischaemic stroke. Compared with the previous version in 2002, the present update includes three additional trials (ALIAS-Part 1 2011; ALIAS-Part 2 2013; Balcarce 1991). Additions include the 'Risk of bias' tool, reformatting of methods, sensitivity analysis and addition of sections throughout the text.

OBJECTIVES

To assess the effects of haemodilution in acute ischaemic stroke.

METHODS

Criteria for considering studies for this review

Types of studies

We sought published and unpublished RCTs that compared haemodilution with control. Treatment in control groups varied between trials. Usually, no specific treatment was used, although

a protocol involving infusions of crystalloids or dextrose was used in the control group in some trials. Blinding of participants or evaluators has not been a selection criterion (see also below).

We have included only those studies that reported clinical endpoints of direct relevance for participants (death, neurological outcome, functional outcome, need for institutional care, vascular or other events, adverse reactions). Thus, we have not included studies reporting on the effects of haemodilution on cerebral blood flow or other intermediary variables but not providing any other clinical data. We also did not include studies that only included neurological examination scale outcomes because these outcomes could not be combined given the variety of neurological scores (see Types of outcome measures). We have not included studies of haemodilution initiated in the late phase after stroke (i.e. later than one week after onset). We have also not included haemodilution to prevent stroke occurring after carotid surgery.

Types of participants

We only included acute trials with start of treatment within the first 72 hours of stroke onset. Although all trials involved only participants with a clinical diagnosis of presumed ischaemic stroke, some participants in five early trials conducted before computed tomography (CT) became available may actually have had a haemorrhagic stroke (Gilroy 1969; Kaste 1976; Matthews 1976; Popa 1989; Spudis 1973). One study performed CT after treatment and included haemorrhagic stroke (IASSG 1988). Some studies have reported results both on an intention-to-treat basis and a per-protocol ('target group') basis (when participants not treated according to the study protocol have been excluded). If so, the data entered into this review are according to the intention-to-treat principle.

Types of interventions

We included trials of hyper- and isovolaemic haemodilution. Thus, some trials combined administration of plasma expanders with venesection, but other trials did not. Plasma expanders were plasma alone, low-molecular-weight dextran (dextran 40), HES and albumin. No study used a hypovolaemic protocol (i.e. blood-letting alone). Two studies were confounded (i.e. haemodilution was used together with another treatment modality) (Frei 1987; Kaste 1976) (see Characteristics of included studies table). We did not include studies that compared two haemodilution modalities (e.g. dextran versus HES) as there was no control.

Types of outcome measures

Information on mortality at early (reported to occur within the first seven days in some studies up to 28 days in others) and at late (reported at three to six months) follow-up was extracted from articles and unpublished reports when available. Since the proportion of participants who become severely dependent on help from other people after stroke may be affected by early death, we used a combined measure (dead or dependent/institutionalised) as a crude measure of functional outcome at three to six months after stroke. Many studies reported on changes in neurological and functional scores. A plethora of scores and measures of distribution were used. Therefore, it has not been possible to report on changes of score sums in a uniform manner. Thromboembolic events (deep venous thrombosis or pulmonary embolism or both) and adverse effects of the haemodilution treatment were reported in a systematic manner only in a few of the trials; these observations are, nevertheless, reported here.

Primary outcomes

1. Death or dependency/institutionalisation at three to six months.

Secondary outcomes

1. Mortality in the early (first 28 days) and late (three to six months) phase of stroke.
2. Venous thromboembolic events in the early (first 28 days) and late (three to six months) phase of stroke.
3. Serious anaphylactoid reactions.
4. Serious cardiac events.

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 translation of relevant papers published in languages other than English.

Electronic searches

We searched the Cochrane Stroke Group Trials Register, which was last searched by the Managing Editor on 18 February 2014. In addition, we searched the following electronic bibliographic databases:

1. the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 1, 2014) (Appendix 1);
2. MEDLINE (Ovid) (January 2008 to October 2013) (Appendix 2);
3. EMBASE (Ovid) (January 2008 to October 2013) (Appendix 3).

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

Using a comprehensive search strategy, the Cochrane Stroke Group Trials Search Co-ordinator has already completed a retrospective search of MEDLINE and EMBASE for all stroke trials to December 2007 and added all relevant trials to the Stroke Group Trials Register. To avoid duplication of effort, we have limited the search of these two databases from January 2008 onwards.

Ongoing trials and research registers

We searched the following trials and research registers (February 2014):

1. ClinicalTrials.gov (www.clinicaltrials.gov/);
2. EU Clinical Trials Register (www.clinicaltrialsregister.eu);
3. Stroke Trials Registry (www.strokecenter.org/trials/);
4. Current Controlled Trials (www.controlled-trials.com);
5. World Health Organization (WHO) International Clinical Trials Registry Platform (www.who.int/ictrp/en/).

Searching other resources

In an effort to identify further published, unpublished and ongoing trials, we carried out the following additional searches:

1. scanned the reference lists of relevant articles;
2. contacted authors and researchers in the field;

3. used Science Citation Index Cited Reference Search for forward tracking of important articles.

For the previous version of the review, the review authors:

1. searched MEDLINE (1966 to June 2002) (Appendix 4);
2. contacted investigators and manufacturers (Pharmacia and Fresenius) known to be active in trials of haemodilution in an effort to identify additional studies.

Data collection and analysis

Selection of studies

Two review authors (TC and MJ for this update) read the titles and abstracts of the records retrieved from the electronic searches and excluded obviously irrelevant papers. We obtained the full-text articles of the remaining studies and the same two review authors independently selected studies for inclusion in the review based on the selection criteria described previously. We resolved any disagreements by discussion.

Data extraction and management

In the first version of this Cochrane review, data were independently extracted from published and unpublished articles by two sets of review authors using forms that included all types of outcome events reported. One review author abstracted information from the three trials added in the 2002 update (Bornstein 1981; MAHST 1998; Rudolf 2002). Two review authors abstracted information from the three additional included trials in this 2014 update (ALIAS-Part 1 2011; ALIAS-Part 2 2013; Balcarce 1991). We entered the data into Review Manager 5 (RevMan 2012).

Assessment of risk of bias in included studies

We assessed the quality of the included studies according to The Cochrane Collaboration's tool for assessing risk of bias (Higgins 2011). One review author (TC) entered the methodological description to the 'Risk of bias' section in the Characteristics of included studies table. When the description of methods was unclear, TC discussed this with MJ to reach a consensus. The overall risk of bias is summarised in Figure 1.

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

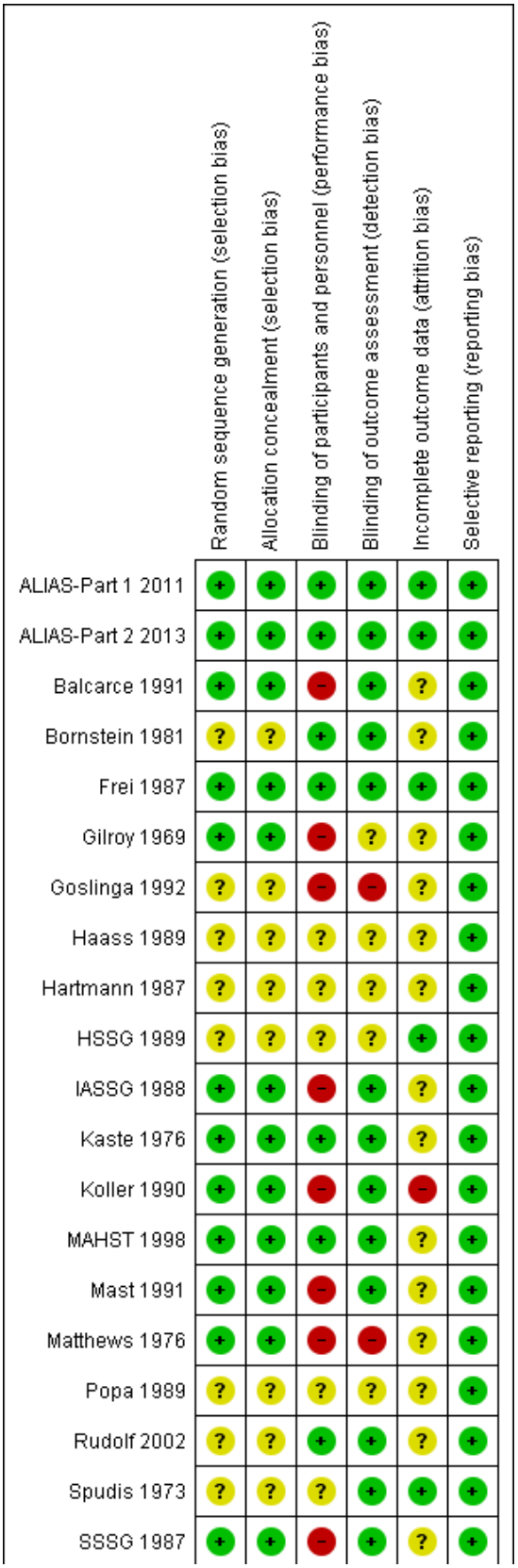
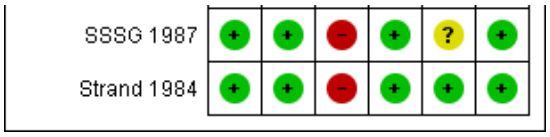


Figure 1. (Continued)



Measures of treatment effect

We used risk ratios (RRs) and 95% confidence intervals (CI) as the effect measure for all dichotomous outcomes.

Unit of analysis issues

All studies randomised participants into a single arm without cross-over. Repeated individual measures were managed by defining short- and long-term follow-up outcomes. Since time points of follow-up varied greatly between trials, we extracted information for early and late follow-up. We defined 'early' as day seven to 28 days after onset; if several follow-ups during this period were reported, we used the one closest to day 21. We defined 'late' as three to six months after stroke; if several time points were reported, we used the one closest to three months.

Dealing with missing data

All studies included the number of events and the total number of individuals for all outcomes. We excluded studies with missing outcome information (e.g. time of death) (Balcarce 1991).

Assessment of heterogeneity

We used the Chi^2 test and I^2 statistic to test for heterogeneity between trials. The Chi^2 test has less power and we considered it significant at a P value of 0.10. An I^2 statistic of 50% represented moderate heterogeneity (Higgins 2011).

Assessment of reporting biases

We used funnel plots to investigate reporting biases when 10 or more studies were included in a meta-analysis outcome. Other reasons, such as heterogeneity and poor methodology, can cause asymmetrical funnel plots.

Data synthesis

We calculated an RR for all outcomes using the Mantel-Haenszel random-effects model based on the DerSimonian and Laird's method to calculate the pooled effect size (DerSimonian 1986). We sought data on participants excluded from the analyses after entry into a trial in the published and unpublished reports to allow intention-to-treat analyses.

Subgroup analysis and investigation of heterogeneity

We performed subgroup analyses on hypervolaemic haemodilution versus control, isovolaemic haemodilution versus control, haemodilution using low-molecular-weight dextran versus control, haemodilution using HES versus control, albumin versus control, unconfounded haemodilution versus control and haemodilution combined with other treatment modalities versus control.

Sensitivity analysis

We performed sensitivity analyses for Analysis 1.1; Analysis 1.2; by removing the largest trial (IASSG 1988), removing the two trials using steroids or glycerol in addition to haemodilution (Frei 1987; Kaste 1976), and removing studies with high risk of performance or detection bias due to lack of blinding.

RESULTS

Description of studies

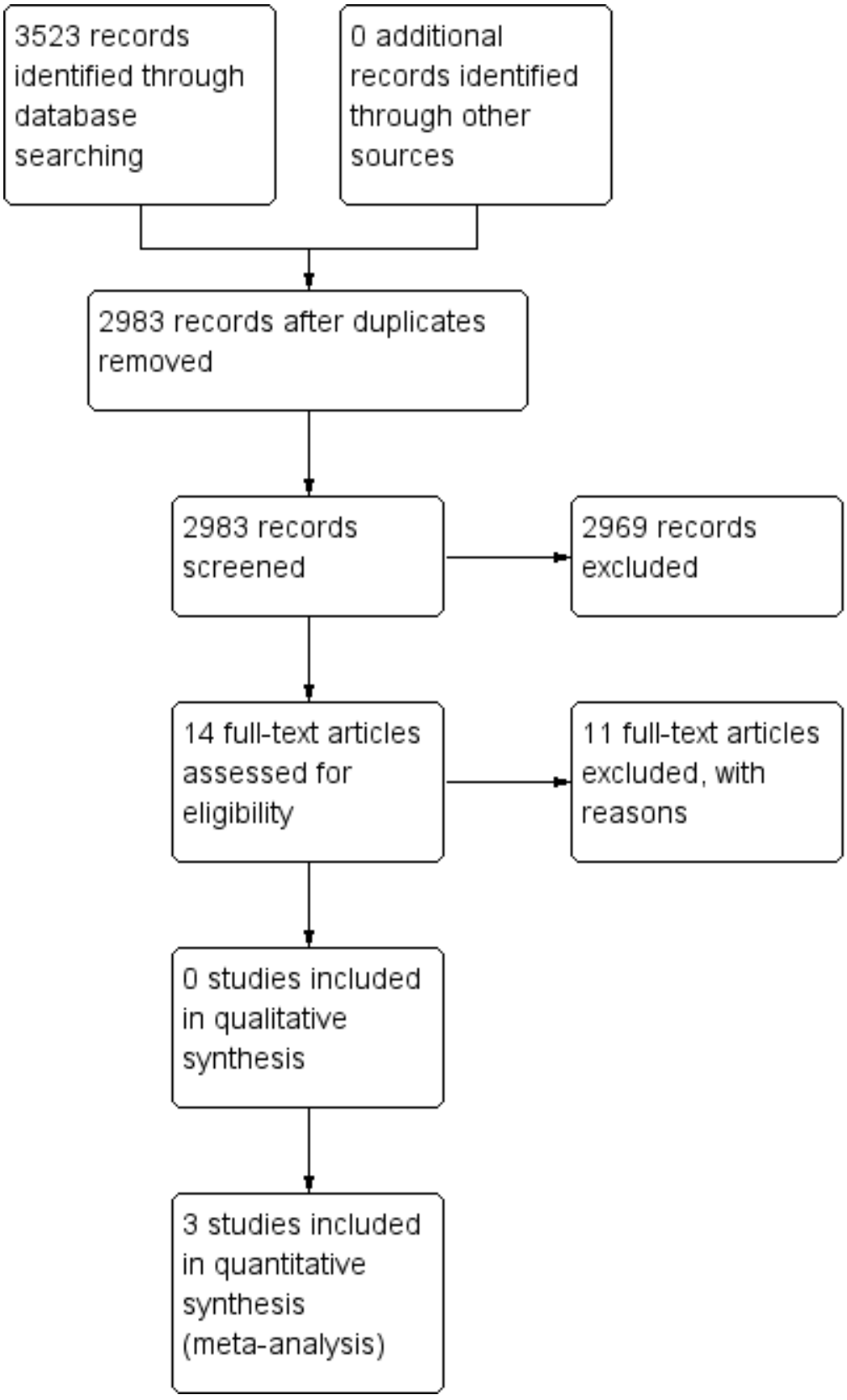
See Characteristics of included studies table.

Results of the search

The search of the Cochrane Stroke Group Trials Register identified 266 citations, the searches of MEDLINE and EMBASE in October 2013 identified 2980 citations, and the search of CENTRAL identified 277 citations. After removing duplicate citations (525) and citations that were already referenced in the 2002 update (15), there were 2983 unique citations. We retrieved 14 full-text articles. For this update, we included three new studies (ALIAS-Part 1 2011; ALIAS-Part 2 2013; Balcarce 1991), and excluded 11 studies (Chen 2006; Grauer 1999; Morgenthaler 2010; Shin 2007; Staedt 1987; Staedt 1989; Staedt 1991; Strand 2002; Tessitore 1990; Woessner 2003; Zhang 1990). There are 21 included studies in this review (see Characteristics of included studies table). We did not identify any ongoing trials.

See the PRISMA flow diagram for details of the study selection process for this current update (Figure 2).

Figure 2. Study flow diagram, showing the results of the searches for this current update.



From the 2002 update, we identified 34 trials with any type of evaluation of haemodilution in people with stroke. Of these, we excluded 15 trials, which were mostly only available as abstracts (Chen 2006; Grauer 1999; Morgenthaler 2010; Schwarz 1998; Shin 2007; Staedt 1987; Staedt 1989; Staedt 1991; Strand 2002; Tessitore 1990; Wang 1990; Wise 1976; Woessner 2003; Zhang 1990; Zhang 1996).

Included studies

We identified 21 independent RCTs of which 18 were published in peer-reviewed medical journals (ALIAS-Part 1 2011; ALIAS-Part 2 2013; Balcarce 1991; Frei 1987; Gilroy 1969; Goslinga 1992; HSSG 1989; IASSG 1988; Kaste 1976; Koller 1990; MAHST 1998; Mast 1991; Matthews 1976; Popa 1989; Rudolf 2002; Spudis 1973; SSSG 1987; Strand 1984). The results of one trial were only partly published but were available to us as a detailed lecture manuscript (Haass 1989), and are included in this review.

The trials used various haemodilution regimens. In the analyses, they were divided into hyper- and isovolaemic. In 12 of the trials, the administration of a plasma volume expander was not combined with venesection and was, therefore, defined as hypervolaemic (ALIAS-Part 1 2011; ALIAS-Part 2 2013; Bornstein 1981; Frei 1987; Gilroy 1969; Haass 1989; Hartmann 1987; Kaste 1976; MAHST 1998; Matthews 1976; Rudolf 2002; Spudis 1973). In one study, venesection was performed only if there were signs of volume overload; this trial was also considered as hypervolaemic (HSSG 1989). In the remaining eight studies, the administration of a plasma volume expander was combined with venesection in most of the participants (Balcarce 1991; Goslinga 1992; IASSG 1988; Koller 1990; Mast 1991; Popa 1989; SSSG 1987; Strand 1984). This is operationally called 'isovolaemic haemodilution' in this overview, although in most instances the treatment protocols suggest that the haemodilution was, in fact, slightly or moderately hypervolaemic.

The trials were also subdivided depending on the type of plasma volume expander used. Plasma alone was used in one study (Balcarce 1991), dextran in 12 (Bornstein 1981; Frei 1987; Gilroy 1969; IASSG 1988; Kaste 1976; Koller 1990; Mast 1991; Matthews 1976; Popa 1989; Spudis 1973; SSSG 1987; Strand 1984), HES in five (Haass 1989; Hartmann 1987; HSSG 1989; MAHST 1998; Rudolf 2002), and albumin in three (ALIAS-Part 1 2011; ALIAS-Part 2 2013; Goslinga 1992) (see Characteristics of included studies table).

In two of the trials, haemodilution was combined with other therapies in the intervention group (confounded trials) (Frei 1987; Kaste 1976). In one trial, dexamethasone was used (Kaste 1976), and in the other trial, glycerol was used together with haemodilution (Frei 1987). We performed separate analyses with these two trials since we excluded them to isolate the effects of unconfounded haemodilution.

IASSG 1988 included participants where treatment was started before a CT was performed; 164 of 1215 participants had a haemorrhagic stroke.

Excluded studies

The reasons for excluding studies are given in the Characteristics of excluded studies table.

The most frequent reasons were 1. no details on the intervention were provided (only general descriptions such as 'isovolemic haemodilution' or 'hypervolaemic haemodilution'), 2. neither mortality, functional (activities of daily living (ADL)) outcome nor institutionalisation at follow-up were reported, 3. providing only neurological outcome and 4. comparing two haemodilution treatments.

We did not obtain access to data from one study in which HES and venesection were tested in approximately 55 participants. This trial was interrupted early for logistic reasons and no information has been available to us, despite written requests and personal contacts with the principle investigator and the manufacturer (Hartmann unpubl.). There are no published trials awaiting assessment.

Risk of bias in included studies

See the Characteristics of included studies table for full 'Risk of bias' assessment for each study.

Sequence generation (selection bias)

Three multicentre trials used centralised randomisation (ALIAS-Part 1 2011; ALIAS-Part 2 2013; IASSG 1988), eight used closed envelopes to randomise participants (Balcarce 1991; Frei 1987; Gilroy 1969; MAHST 1998; Mast 1991; Matthews 1976; SSSG 1987; Strand 1984), and two used identical looking vials (Kaste 1976; Koller 1990). We considered these 13 RCTs as low risk. Details of the randomisation procedure were missing for eight of the trials (Bornstein 1981; Goslinga 1992; Haass 1989; Hartmann 1987; HSSG 1989; Popa 1989; Rudolf 2002; Spudis 1973).

Allocation

Allocation concealment was low risk for the 13 studies describing their randomisation procedure (ALIAS-Part 1 2011; ALIAS-Part 2 2013; Balcarce 1991; Frei 1987; Gilroy 1969; IASSG 1988; Kaste 1976; Koller 1990; MAHST 1998; Mast 1991; Matthews 1976; SSSG 1987; Strand 1984).

Blinding

Seven studies were double-blinded and low risk (ALIAS-Part 1 2011; ALIAS-Part 2 2013; Bornstein 1981; Frei 1987; Kaste 1976; MAHST 1998; Rudolf 2002). Six additional studies described blinding of evaluators but not blinding of participants (Balcarce 1991; HSSG 1989; Koller 1990; Mast 1991; SSSG 1987; Strand 1984). We considered these studies at high risk of performance bias and low risk for detection bias. Two studies were high risk for bias as they did not blind participants or evaluators (Goslinga 1992; Matthews 1976). Blinding of participants was not possible in studies involving venesection. Information on blinding of participants, medical staff and evaluators was missing in four studies (Haass 1989; Hartmann 1987; HSSG 1989; Popa 1989). One study had high performance bias risk and unclear detection bias risk (Gilroy 1969), while another study had unclear performance bias risk and low detection bias risk (Spudis 1973).

In reports from 14 of the trials, it was clearly stated that blinded evaluators had been used (ALIAS-Part 1 2011; ALIAS-Part 2 2013; Balcarce 1991; Bornstein 1981; Frei 1987; IASSG 1988; Kaste 1976; Koller 1990; MAHST 1998; Mast 1991; Rudolf 2002; Spudis 1973; SSSG 1987; Strand 1984), whereas information on blinding was

missing in the remaining seven (Gilroy 1969; Goslinga 1992; Haass 1989; Hartmann 1987; HSSG 1989; Matthews 1976; Popa 1989).

Only four trials were truly placebo-controlled (Bornstein 1981; Frei 1987; Hartmann 1987; Kaste 1976). Participants and managing physicians were not blinded in the trials that involved venesection (Balcarce 1991; Goslinga 1992; HSSG 1989; IASSG 1988; Koller 1990; Mast 1991; Popa 1989; SSSG 1987; Strand 1984).

Incomplete outcome data

Six studies specifically described withdrawals after randomisation and were considered low risk (ALIAS-Part 1 2011; ALIAS-Part 2 2013; Frei 1987; HSSG 1989; Spudis 1973; Strand 1984). The remaining trials did not provide data to address attrition bias.

Selective reporting

Based on the methods and reported results, all included studies were low risk of bias for selective reporting. Funnel plots from analyses with more than 10 studies were symmetrical. Although there was moderate heterogeneity in some analyses (Analysis 1.4; Analysis 1.7; Analysis 3.3), the funnel plots were symmetrical. The funnel plot of Analysis 1.1 is shown in Figure 3 and that of Analysis 3.3 is shown Figure 4. The funnel plots analysed are symmetric despite the fact that some studies are of poor methodology based on the risk of bias tool.

Figure 3. Funnel plot of comparison: 1 Haemodilution, all types, versus control, outcome: 1.1 Mortality at early follow-up (not later than 28 days).

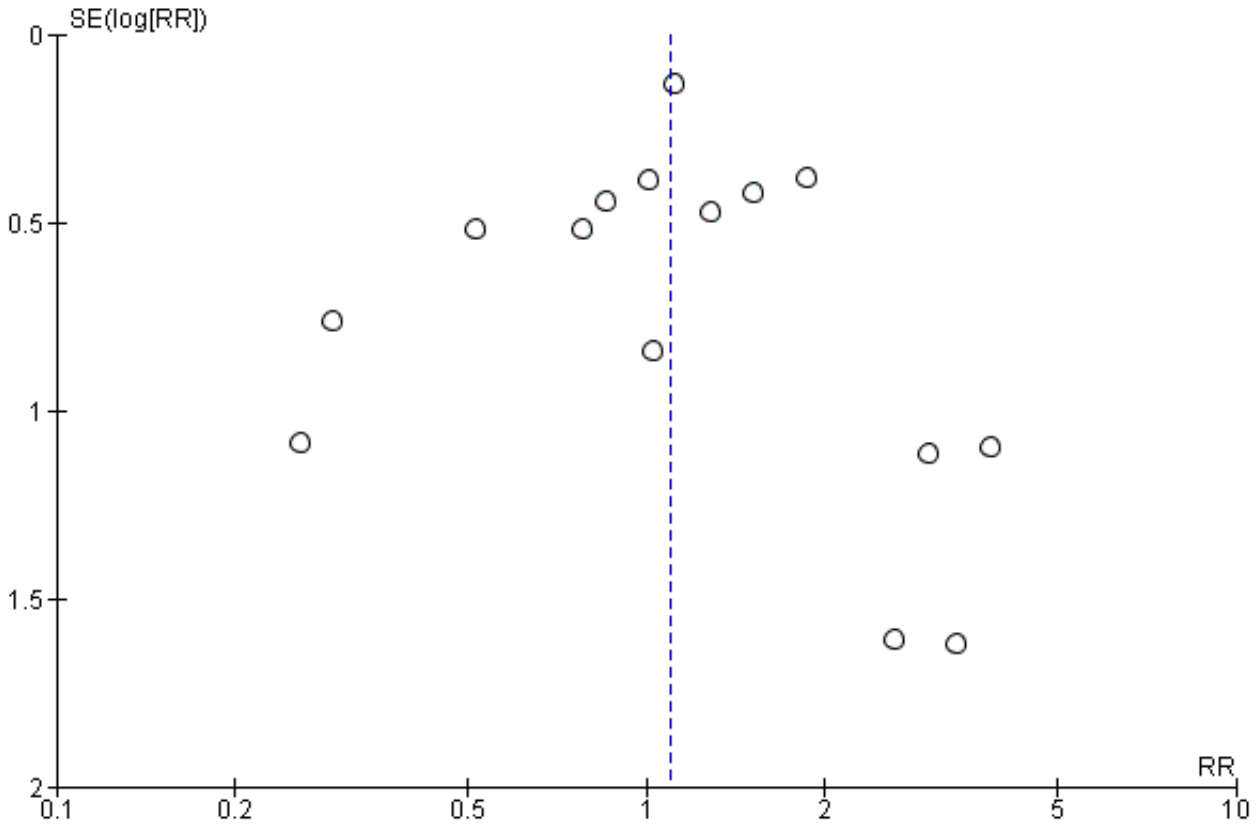
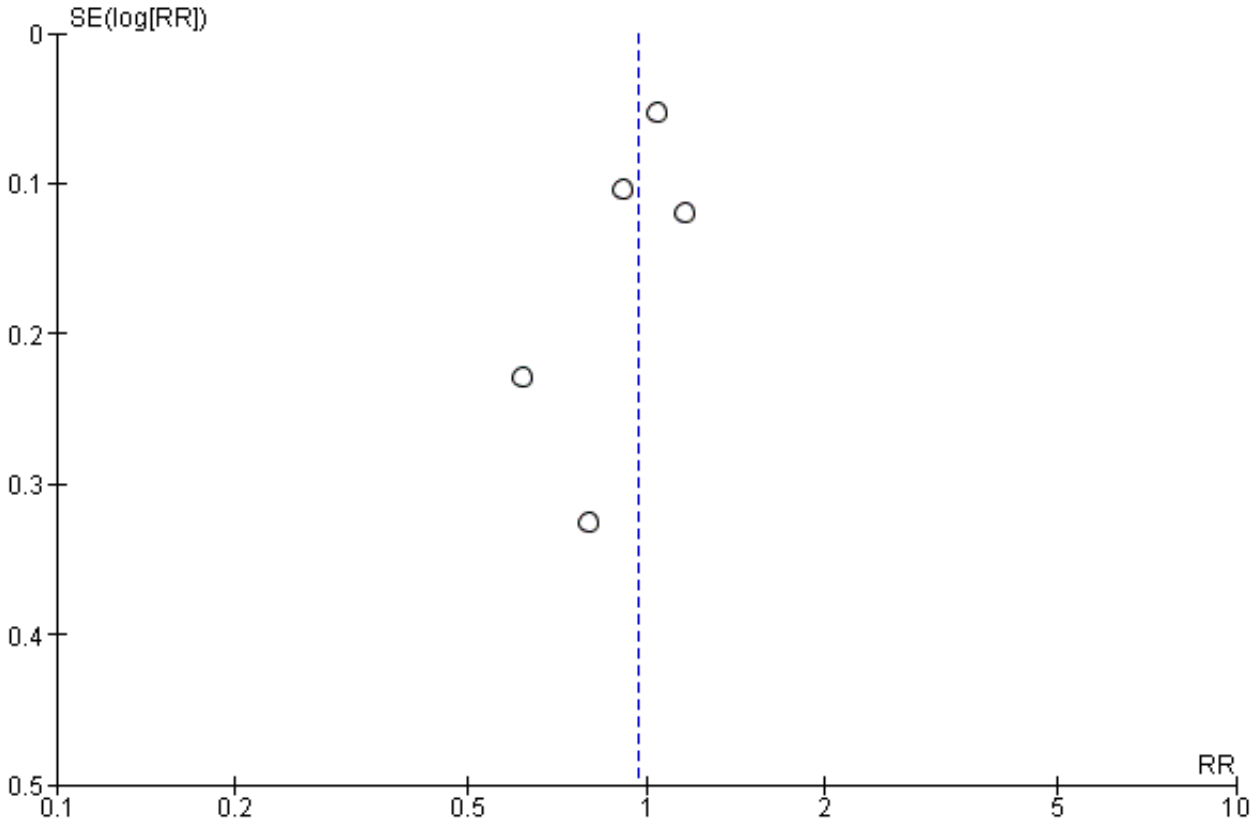


Figure 4. Funnel plot of comparison: 3 Isovolaemic haemodilution (including venesection) versus control, outcome: 3.3 Dead or dependent/institutionalised (3-6 months).



Other potential sources of bias

The diagnosis of ischaemic stroke was based on CT examinations in 15 trials (ALIAS-Part 1 2011; ALIAS-Part 2 2013; Balcarce 1991; Frei 1987; Goslinga 1992; Haass 1989; Hartmann 1987; HSSG 1989; IASSG 1988; Koller 1990; MAHST 1998; Mast 1991; Rudolf 2002; SSSG 1987; Strand 1984), on bedside diagnosis and findings at autopsy in five trials (see remarks in Characteristics of included studies table), whereas information on diagnostic procedures was missing in one report. Thirteen per cent of IASSG 1988 participants had haemorrhagic stroke as the CT was performed before 48 hours and treatment was initiated within 12 hours.

MAHST 1998 was interrupted early when an interim analysis showed a very low likelihood of reaching statistically significant beneficial effects. ALIAS-Part 1 2011 was interrupted during interim analysis because 90-day death rates in participants older than 83 years were 2.3 times higher with albumin compared with saline. Due to this result, the following study excluded participants over 83 years old (ALIAS-Part 2 2013).

Effects of interventions

See: **Summary of findings for the main comparison** Haemodilution, all types, versus control for acute ischaemic stroke

We included 21 studies with 3866 participants. Most studies were small with fewer than 110 participants in 15 of the studies (Balcarce 1991; Bornstein 1981; Frei 1987; Gilroy 1969; Haass 1989; Hartmann 1987; HSSG 1989; Kaste 1976; Koller 1990; Mast 1991; Matthews 1976; Popa 1989; Rudolf 2002; Spudis 1973; Strand 1984). The largest study, the Italian multicentre trial (IASSG 1988), accounted for 33% of all participants and the three largest studies (ALIAS-Part 1 2011; ALIAS-Part 2 2013; IASSG 1988), accounted for 65% of all participants.

As shown in Analysis 1.4 (P value = 0.09, I^2 = 58%); Analysis 1.7 (P value = 0.02, I^2 = 59%); and Analysis 3.3 (P value = 0.09, I^2 = 50%) there was moderate heterogeneity. No other analyses showed significant heterogeneity.

The four studies published in the years 1969 to 1976 focused on dextran and its action in decreasing platelet and erythrocyte aggregation (Gilroy 1969; Kaste 1976; Matthews 1976; Spudis 1973). Therefore, changes in haemoglobin, haematocrit and whole-blood viscosity were not reported. No venesection was used, so they constitute hypervolaemic haemodilution regimens. Many of the later trials used a combination of venesection and administration of a plasma volume expander (isovolaemic haemodilution) (Balcarce 1991; Goslinga 1992; IASSG 1988; Koller 1990; MAHST 1998; Popa 1989; SSSG 1987; Strand 1984).

The plasma expander used was plasma alone in one trial (Balcarce 1991), dextran 40 in 12 trials (Bornstein 1981; Frei 1987; Gilroy 1969; IASSG 1988; Kaste 1976; Koller 1990; Mast 1991; Matthews 1976; Popa 1989; Spudis 1973; SSSG 1987; Strand 1984), HES in five trials (Haass 1989; Hartmann 1987; HSSG 1989; MAHST

1998; Rudolf 2002), and albumin in three trials (ALIAS-Part 1 2011; ALIAS-Part 2 2013; Goslinga 1992). In some of the studies, a standardised, moderately hypervolaemic regimen was used. Other protocols included more aggressive hypervolaemic treatment. Target haematocrit ranged from less than 38% to less than 33%. In three studies, haemodynamic monitoring was used to achieve individually tailored haemodilution and hypervolaemia without increasing the central venous pressure or the pulmonary wedge pressure to intolerable levels (Goslinga 1992; HSSG 1989; Rudolf 2002).

Despite large differences in treatment protocols and target haematocrit levels, the reduction in reported haematocrit was remarkably similar in all trials but for one that reported on haematocrit ranging from 2% to 7% in absolute terms and from 5% to 16% in relative terms (for details, see Asplund 1991 and MAHST 1998).

Haemodilution, all types, versus control

Mortality at early follow-up (not later than 28 days)

Early mortality was reported in 16 of the 21 studies (ALIAS-Part 1 2011; ALIAS-Part 2 2013; Bornstein 1981; Frei 1987; Gilroy 1969; Hartmann 1987; HSSG 1989; IASSG 1988; Kaste 1976; MAHST 1998; Mast 1991; Matthews 1976; Rudolf 2002; Spudis 1973; SSSG 1987; Strand 1984). In none of them was there any statistically significant effect of haemodilution on survival at early follow-up.

When the 16 trials were taken together, the RR for death was 1.10 (i.e. somewhat more deaths in the treatment group), with a narrow 95% CI (0.90 to 1.34) (Analysis 1.1), indicating no beneficial effects of haemodilution on early survival. The large Italian multicentre study contributed over half all deaths (IASSG 1988). Therefore, we calculated the RR for survival excluding the Italian study. The RR remained essentially unchanged at 1.08. The mortality rate within each group was lower in the two large albumin trials (ALIAS-Part 1 2011; ALIAS-Part 2 2013) compared with the Italian multicentre study (IASSG 1988). This may have been due to the large albumin trials reporting neurological death within seven days and the Italian study reporting death at discharge.

The two confounded trials involving steroids (Frei 1987) and glycerol (Kaste 1976) were small with 83 included participants (i.e. 2% of the total participant population in the haemodilution trials). Excluding these two trials from the analysis changed the outcome of the formal overview analyses only marginally (RR for early death went from 1.10 to 1.08). Steroids and glycerol are the subject of separate Cochrane reviews (Righetti 2004; Sandercock 2011). Excluding the trials with high risk of performance or detection bias (Gilroy 1969; IASSG 1988; Mast 1991; Matthews 1976; SSSG 1987; Strand 1984), the RR increased to 1.19 (95% CI 0.78 to 1.8).

Case fatality at late follow-up (three to six months)

Case fatality was reported at three months in 13 trials (ALIAS-Part 1 2011; ALIAS-Part 2 2013; Balcarce 1991; Frei 1987; Goslinga 1992; Haass 1989; HSSG 1989; Koller 1990; MAHST 1998; Popa 1989; Rudolf 2002; SSSG 1987; Strand 1984), and at six months in two trials (IASSG 1988; Matthews 1976), whereas no late follow-up was done in the remaining six trials (Bornstein 1981; Gilroy 1969; Haass 1989; Kaste 1976; Mast 1991; Spudis 1973). In total, there were 752 deaths with equal distribution among haemodiluted and control participants (RR 1.05; 95% CI 0.93 to 1.20) (Analysis 1.2). In none of the individual trials was any statistically significant positive or negative effect on survival at late follow-up noted.

Excluding the only confounded trial that reported mortality at late follow-up had very little impact on the overall results, the RR still being 1.05 (Frei 1987). Excluding the Italian study (IASSG 1988), and trials with high risk of performance or detection bias (Balcarce 1991; Goslinga 1992; IASSG 1988; Koller 1990; Matthews 1976; SSSG 1987; Strand 1984), the RR increased to 1.10 (95% CI 0.92 to 1.34) and 1.20 (95% CI 0.94 to 1.53), respectively.

Dead or dependent/institutionalised (three to six months)

The definition of 'dependency' at follow-up was not uniform between the trials. In this overview, dependency on other people for primary ADL or need for institutional care has been used to indicate poor functional outcome. We used the combined outcome measure of 'dead or dependent/institutionalised' to eliminate the possibility that with more participants dying, the proportion of severely affected people with stroke at follow-up would be reduced (and vice versa).

The analyses were confined to unconfounded haemodilution trials, since none of the confounded trials reported dependency at late follow-up.

Sufficient data from eight of the trials were available for estimating the outcome variable 'dead or dependent/institutionalised' (Goslinga 1992; IASSG 1988; Koller 1990; MAHST 1998; Matthews 1976; Rudolf 2002; SSSG 1987; Strand 1984). In one trial, there was a statistically significant effect in favour of haemodilution therapy (Strand 1984), whereas no significant effects were noted in the other trials. In the summary statistics, no beneficial effects of haemodilution emerged (RR 0.96; 95% CI 0.85 to 1.07) (Analysis 1.3). The same conclusion was reached if the analysis was restricted to all trials except IASSG 1988.

ADL performance was followed in detail in five studies (Haass 1989; HSSG 1989; MAHST 1998; Rudolf 2002; SSSG 1987), four of which reported a somewhat better outcome in haemodiluted participants (Haass 1989; HSSG 1989; MAHST 1998; Rudolf 2002), and the fifth (the largest of the trials) reported a better outcome in control participants (SSSG 1987); only in Haass 1989 did the difference in favour of haemodilution treatment reach statistical significance.

Venous thromboembolic events

Four of the studies reported explicitly comparisons of all events of venous thromboembolism in haemodiluted and control participants beyond the first few days (Kaste 1976; MAHST 1998; SSSG 1987; Strand 1984), whereas three studies only reported fatal events (Matthews 1976; Popa 1989; Koller 1990). In one carefully monitored safety study, venous thromboembolism was not mentioned among the adverse events, and it is assumed that no such events occurred during the trial (Rudolf 2002). None of the studies used systematic laboratory screening for thromboembolism in all participants, but the diagnosis was based on clinical presentation, substantiated by laboratory investigations in suspected cases and findings at autopsy. A statistically significant reduction of venous thrombosis, pulmonary embolism or both was reported in one of the studies, and there was a tendency towards reduction in the overview analysis (RR 0.68; 95% CI 0.37 to 1.24) (Analysis 1.5). Notably, this possible beneficial effect was not

observed during the acute phase (follow-up within one month) but only at three to six months' follow-up.

Adverse reactions

None of the studies published before 1984 reported adverse circulatory events. Anaphylactic/anaphylactoid reactions to dextran or HES were reported in six instances among 1136 participants receiving plasma volume expanders (RR versus controls 3.89; 95% CI 0.83 to 18.30) (Analysis 1.6). None of the events were fatal. Such reactions were reported only in trials of dextran (IASSG 1988; Spudis 1973; SSSG 1987; Strand 1984), in which they occurred in 0.6% of the treated participants.

Direct comparisons of the number of serious cardiac events, mainly myocardial infarction and acute congestive heart failure, were reported in seven studies (ALIAS-Part 1 2011; Koller 1990; MAHST 1998; Popa 1989; Rudolf 2002; SSSG 1987; Strand 1984). The total number of reported events was 168 among 1358 participants (12.3%) with an RR of 1.16 (95% CI 0.66 to 2.05) (Analysis 1.7). The Scandinavian multicentre trial reported a significant increase in the number of cardiac events during the treatment period (first five days; odds ratio (OR) 2.64; 95% CI 1.03 to 6.80), but at follow-up 90 days after stroke the difference in cardiac events between the two groups was no longer significant (OR 1.44; 95% CI 0.76 to 2.73). Myocardial infarction had an OR of 5.15 (95% CI 1.95 to 13.59) in ALIAS-Part 1 2011. In ALIAS-Part 2 2013, congestive heart failure was combined with pulmonary oedema and could not be added to this outcome. An excess risk of serious cardiac events was not observed in any of the other trials. The overview analysis of the cumulated number of cardiac events at latest follow-up (usually three to six months after stroke) indicated no detrimental effects of haemodilution on the risk for serious cardiac events (OR 0.99; 95% CI 0.66 to 1.50).

Subgroups analyses: a word of caution

In the following, the results have been subdivided by mode of haemodilution, type of haemodiluting agent, delay to start of treatment and characteristics of participants treated. It must be emphasised that results of subgroup analyses should be interpreted with caution (even if the individual trials have been testing predetermined hypotheses), in particular when there is no overall effect of the intervention.

Hypervolaemic haemodilution (without venesection) versus control

In 12 trials, the administration of a plasma volume expander was not combined with venesection, or venesection was performed only when signs of volume overload occurred (ALIAS-Part 1 2011; ALIAS-Part 2 2013; Bornstein 1981; Frei 1987; Gilroy 1969; Hartmann 1987; HSSG 1989; Kaste 1976; MAHST 1998; Matthews 1976; Rudolf 2002; Spudis 1973). In four of these trials of hypervolaemic regimens, the number of included participants exceeded 100. In total, 2055 participants were randomised. In the overall analyses, we observed no significant effects on early (RR 0.98; 95% CI 0.68 to 1.40) (Analysis 2.1), or late (RR 1.19; 95% CI 0.94 to 1.51) (Analysis 2.2) mortality or on functional outcome at late follow-up (RR 0.92; 95% CI 0.74 to 1.14, only three trials (MAHST 1998; Matthews 1976; Rudolf 2002) reporting on this outcome measure) (Analysis 2.3).

Isovolaemic haemodilution (including venesection) versus control

The haemodilution regimens in eight studies were operationally defined as 'isovolaemic', since the administration of a plasma volume expander was combined with venesection (Balcarce 1991; Goslinga 1992; IASSG 1988; Koller 1990; MAHST 1998; Popa 1989; SSSG 1987; Strand 1984). However, in most instances the treatment protocols suggest that the haemodilution was, in fact, slightly or moderately hypervolaemic. The largest trial used 'isovolaemic' haemodilution (IASSG 1988). There were no significant effects on mortality at early (RR 1.15; 95% CI 0.91 to 1.46) follow-up (Analysis 3.1), late (RR 1.00; 95% CI 0.86 to 1.17) follow-up (Analysis 3.2), and the proportion dead or dependent/institutionalised at late follow-up was not affected (RR 0.97; 95% CI 0.83 to 1.13) (Analysis 3.3).

Different types of plasma expanders used in the haemodilution trials

Four different types of plasma volume expanders, namely plasma alone, low-molecular-weight dextran, HES and albumin, have been used in the haemodilution trials. Only one trial used plasma alone in combination with venesection.

Low-molecular-weight dextran versus control

Most of the haemodilution trials used dextran 40. In particular, it was used in two (IASSG 1988; SSSG 1987) of the four largest trials (ALIAS-Part 1 2011; ALIAS-Part 2 2013; IASSG 1988; SSSG 1987). We observed no significant effects on any of the outcome variables (RR 1.03; 95% CI 0.88 to 1.20 for three- to six-month mortality; Analysis 4.2; RR 1.01; 95% CI 0.84 to 1.20 for death or being dependent/institutionalised at three to six months; Analysis 4.3).

Hydroxyethyl starch versus control

HES, also called pentastarch, was used as the haemodiluting agent in five trials (Haass 1989; Hartmann 1987; HSSG 1989; MAHST 1998; Rudolf 2002), the largest of which included 200 participants (MAHST 1998). Case fatality was not affected at early (RR 1.04; 95% CI 0.47 to 2.33) (Analysis 5.1) or late (RR 1.12; 95% CI 0.57 to 2.19) (Analysis 5.2) follow-up. Only two studies reported functional outcome. There was a tendency towards better outcome in participants receiving HES than in control participants but the difference did not reach statistical significance (RR 0.87; 95% CI 0.71 to 1.07) (Analysis 5.3).

Albumin versus control

Three studies used albumin as a part of the haemodilution regimen (ALIAS-Part 1 2011; ALIAS-Part 2 2013; Goslinga 1992). There were no significant effects on mortality at early follow-up (RR 1.21; 95% CI 0.69 to 2.12; Analysis 6.1) based on the two ALIAS studies (ALIAS-Part 1 2011; ALIAS-Part 2 2013), or late follow-up (RR 1.12; 95% CI 0.78 to 1.61; Analysis 6.2) based on all three studies (ALIAS-Part 1 2011; ALIAS-Part 2 2013; Goslinga 1992).

Dextran versus hydroxyethyl starch as the haemodiluting agent

In direct comparisons, HES and dextran 40 seem to have similar effects on cerebral blood flow (Hartmann 1987) and plasma viscosity (Haass 1986; Staedt 1986). Two small randomised trials compared clinical outcome in participants with acute ischaemic stroke treated with dextran 40 (Krepp 1984) and HES (Schneider 1985). No overall effect on death or neurological outcome was noted (reviewed in Asplund 1991, data not shown here).

Effects of haemodilution in relation to delay from onset of symptoms to start of treatment

Some of the randomised trials entered participants up to 48 hours or even 72 hours after onset of symptoms. Four trials included only participants within the first six hours of onset of stroke symptoms (ALIAS-Part 1 2011; ALIAS-Part 2 2013; MAHST 1998; Rudolf 2002), and in five trials, subset analyses of participants included within six hours (IASSG 1988) or 12 hours (Haass 1989; HSSG 1989; Popa 1989; SSSG 1987) of onset of stroke were performed. Two studies showed non-significant trends in favour of early versus late start of treatment (reviewed in Asplund 1991, data not shown here) (Haass 1989; HSSG 1989). The other three trials did not note such trends. In the large Italian multicentre study, which showed no benefit from haemodilution, all participants were treated within the first 12 hours (IASSG 1988). In this trial, haemodilution had no beneficial effects in participants treated within six hours. Similarly, no statistically significant effects were observed in the Austrian or German multicentre trials that both had a six-hour upper time limit for inclusion of participants (Austrian trial: MAHST 1998; German trial: Rudolf 2002). However, these two small trials both showed a tendency towards improved functional outcome in HES-treated participants (see subgroup analysis of HES).

Selection of people for haemodilution

In ischaemic stroke, the pathophysiological mechanisms may differ markedly from person to person. Is it then futile to try a standardised protocol to treat people with acute stroke unless a more precise mechanism is known in each individual person? Could the lack of beneficial effects of haemodilution be explained by detrimental effects in some people, counterbalancing beneficial effects in others?

An extensive subgroup analysis in SSSG 1987 showed similar clinical outcome when participants were subdivided into groups based on easily available clinical criteria, such as sex, age, a cardiac source of embolism, hypertension, heart failure, diabetes and severity of neurological deficits. A similar subgroup analysis was performed in ALIAS-Part 2 2013, showing no difference based on thrombolysis treatment, demographic characteristics, baseline National Institutes of Health Stroke Scale, stroke onset or baseline imaging.

No beneficial effect of haemodilution was observed in the subgroup with highest haematocrit levels at entry in the Scandinavian (SSSG 1987), the Italian (IASSG 1988), the Romanian (Popa 1989), or the Dutch (Goslinga 1992), trials.

In the HSSG 1989 trial, a significantly better early neurological recovery was noted in participants who were able to increase their cardiac output during haemodilution when compared with participants who failed to do so, whereas outcomes at three months were similar. In SSSG 1987, the outcome was no different in participants with and without a history of cardiac failure (a marker for reduced capacity to increase the cardiac output as a response to haemodilution). Participants with a marked reduction in blood pressure following haemodilution had a similar outcome as participants who maintained their blood pressure.

Only one study addressed the question of the site of the brain lesion (SSSG 1987). Participants with infarcts in deep structures (internal capsule, basal ganglia, thalamus or brain stem) had a significantly higher mortality rate if they had received been haemodilution, whereas mortality rates were the same in treated and control participants if cortical structures were involved.

As described previously, ALIAS-Part 1 2011 was stopped early due increased 90-day death rates for albumin versus control in participants older than 83 years. It was hypothesised that the albumin predisposed participants to myocardial stress, which acted in combination with other factors to increase mortality five to 30 days after treatment. Due to this result, the protocol was revised and ALIAS-Part 2 2013 excluded people older than 83 years old.

DISCUSSION

Summary of main results

When we analysed all the trials together, there were no beneficial effects of haemodilution on mortality at early or late follow-up or on functional outcome. The largest three studies accounted for two-thirds of all participants (ALIAS-Part 1 2011; ALIAS-Part 2 2013; IASSG 1988), and the Italian study accounted for over half of all deaths (IASSG 1988). Sensitivity analysis when removing IASSG 1988 did not alter results. It is reasonable to conclude that haemodilution, as used in the trials conducted so far, has no major beneficial effects on survival or on functional outcome in acute ischaemic stroke.

There was a slight, statistically insignificant, tendency towards more early deaths among haemodiluted participants. The excess mortality observed in participants with deep brain infarctions in one study could be due to chance, but another tentative explanation is that deep brain structures are supplied by end-arteries and that an adequate collateral blood supply is needed for haemodilution not to be harmful (or beneficial) (SSSG 1987). The significant increase in mortality for participants older than 83 years warranted the interim stopping of ALIAS-Part 1 2011. However, it must be emphasised that results of subgroup analyses in individual trials should be interpreted with caution even if they are testing predetermined hypotheses, especially when there is no overall effect of the intervention.

These trials used many different modes of haemodilution. The overview analyses showed no positive effects whether the administration of plasma volume expanders was combined with venesection or not (i.e. was iso- or hypervolaemic). However, the statistical power to detect differences in the hypervolaemic group was relatively weak.

Low-molecular-weight dextran was used as the haemodiluting agent in many of the randomised trials. It has been reported that repeated dextran 40 infusions result in an accumulation of large dextran molecules and an increase in plasma viscosity (Kroemer 1987; Tsuda 1987). It has therefore been claimed that HES or albumin are better choices as plasma volume expanders. However, other studies have shown similar decreases in plasma viscosity with dextran and HES (Haass 1986; Staedt 1986). In people with ischaemic stroke, HES counteracts the increased intracranial pressure (Schwarz 1998). The half-life of albumin in the circulation is much longer than that of dextran 40 or HES, and the risk for short-term variations in whole-blood viscosity is possibly lower.

The total number of participants in the HES trials was small (Haass 1989; Hartmann 1987; HSSG 1989; Mast 1991; Rudolf 2002). In the overview analyses, there was no trend towards improved survival

among people treated with HES. However, there was a tendency towards better functional outcome in HES-treated people, but this was not statistically significant. If this is a true beneficial effect, there may be an interaction with early onset of treatment, since the two HES trials (MAHST 1998; Rudolf 2002) reporting on functional outcome were two of the four haemodilution trials (ALIAS-Part 1 2011; ALIAS-Part 2 2013; MAHST 1998; Rudolf 2002) in which all participants were included within the first six hours after stroke onset.

In animal models of stroke, treatment with human albumin markedly increases cortical perfusion, reduces brain swelling and infarct volume, and improves neurological outcome (Belayev 2001; Liu 2001). Albumin was used as the haemodiluting agent in three clinical trials (ALIAS-Part 1 2011; ALIAS-Part 2 2013; Goslinga 1992). There was no statistically significant harm or benefit to albumin although there was a tendency towards harm given the increase in cardiovascular-related deaths and death in participants older than 83 years (ALIAS-Part 1 2011).

Whereas no beneficial effects on mortality or functional dependency were documented in the formal overview analyses, there was a tendency towards significant reduction of the risk for venous thromboembolic events in participants who had received haemodilution. This is in line with the prophylactic effects of dextran against deep venous thrombosis and pulmonary embolism after major surgery. However, the results of the overview analysis must be interpreted with caution. The CIs were wide. The diagnosis of a deep vein thrombosis was based on clinical presentation and findings at autopsy. It seems that, in most instances, the clinicians making the diagnosis were not blinded as to which group the participant had been assigned. It is remarkable that the effect was most evident at late follow-up (three to six months), making it unlikely that dextran, HES or albumin had any specific effect on the risk of venous thromboembolism. It may be speculated that low haematocrit in people who have undergone venesection reduces the risk of deep venous thrombosis and pulmonary embolism to some extent even after the acute phase of stroke.

There has been concern that many haemodilution regimens may involve a risk of volume overload in people with stroke with incipient or manifest heart failure. Cardiovascular events (ALIAS-Part 1 2011) and cardiopulmonary events (ALIAS-Part 2 2013) were more common in albumin-treated participants in the ALIAS trials. Haemodynamic monitoring with a Swan-Ganz catheter during the haemodilution procedure has been introduced to reduce the risk of left ventricular failure during hypervolaemic haemodilution (Goslinga 1992; HSSG 1989). The overview analysis of trials reporting cardiovascular events in a systematic manner, did not document any major increase in adverse circulatory events in participants who had received haemodilution (Goslinga 1992; HSSG 1989). The number of anaphylactic or anaphylactoid reactions was small and was reported in less than 1% of all participants receiving plasma volume expanders. Pretreatment with hapten-dextran was used in three of the studies (IASSG 1988; Koller 1990; SSSG 1987), and this may have reduced the risk of anaphylaxis to dextran.

Overall completeness and applicability of evidence

Our objective was to evaluate the efficacy of haemodilution therapy in people with acute ischaemic stroke. We have identified relevant randomised trials investigating a variety of haemodilution strategies including plasma, dextran, HES and albumin with or without venesection for acute ischaemic stroke. The results are applicable to people meeting trial inclusion and exclusion criteria. As the inclusion criteria included people with presumed ischaemic stroke, 164 participants from IASSG 1988 had haemorrhagic stroke identified after treatment and five additional studies were performed before CT was available to rule out haemorrhagic stroke (Gilroy 1969; Kaste 1976; Matthews 1976; Popa 1989; Spudis 1973).

We have searched comprehensively the Cochrane Stroke Group Trials Register up to February 2014. This register contains all stroke trials from MEDLINE and EMBASE to December 2007. We searched MEDLINE and EMBASE from 2008 to October 2013, and CENTRAL up to Issue 1, 2014. It could have been possible to re-search all of MEDLINE and EMBASE from 2002, but relevant stroke trials were included in the Cochrane Stroke Group Trials Register before December 2007 and the current search results had already returned 2983 citations.

The 21 studies included in this analysis are sufficient to address the objective. There are improvements that could be made.

There are likely to be more methods used for haemodilution, such as venesection plus plasma replacement, which were only studied in one randomised trial (Balcarce 1991). Additional subgroups based on treatments other than haemodilution, such as thrombolysis (ALIAS-Part 2 2013), could have been included in more studies. ALIAS studies reported neurological death within seven days, which was included in the early mortality data (ALIAS-Part 1 2011; ALIAS-Part 2 2013). Death from any cause was reported at 30 days, but was not included in the 28-day cut-off for early mortality. Additional outcomes, especially serious adverse events, could have been included in more studies.

We acknowledge there are excluded studies that meet eligibility criteria (based on types of studies, participants and interventions), but do not have relevant or appropriate outcomes. These outcomes included haematological values, laboratory values, imaging and neurological score. Haematological and laboratory values, considered as intermediary outcomes, may not correlate well with the clinical outcomes of interest. Only one excluded study reported imaging outcomes (Shin 2007). Clinical neurological scores were relevant outcomes but could not be combined in a meta-analysis given the wide variety of scores used. Ideally, neurological score changes would be combined for analysis to measure more fine-grained differences in outcomes. Unfortunately, this was not feasible given the variety of scoring methods and time points of evaluation. Although there may have been benefit or harm for neurological outcome after haemodilution therapy, this meta-analysis does show that haemodilution therapy has no benefit for the clinical outcome of mortality.

Current practice of haemodilution in acute ischaemic stroke is likely to vary within and across countries. While older studies occasionally recommend haemodilution (Popov 2000), the American Heart Association does not recommend haemodilution based on the 2002 version of this review (Jauch 2013). Other guidelines, do not comment on haemodilution (ESO 2008; NICE 2008).

Quality of the evidence

There were 21 included studies consistently showing an inability to reject the null hypothesis of haemodilution treatment in acute

ischaemic stroke having no harm or benefit. Using the GRADE system, the quality of evidence was moderate for outcomes including all haemodilution therapies, except for cardiac events, which was considered low (Summary of findings for the main comparison). There was little heterogeneity with only three analyses showing moderate heterogeneity (Analysis 1.4; Analysis 1.7; Analysis 3.3). All funnel plots were symmetrical.

Using the 'Risk of bias' tool, there were eight studies with more than three unclear categories as the information was not reported (Bornstein 1981; Goslinga 1992; Haass 1989; Hartmann 1987; HSSG 1989; Popa 1989; Rudolf 2002; Spudis 1973). Nine other studies had a high risk of performance or detection bias because the participants or evaluators or both were not blinded (Balcarce 1991; Gilroy 1969; Goslinga 1992; IASSG 1988; Koller 1990; Mast 1991; Matthews 1976; SSSG 1987; Strand 1984). These studies were unable to blind the interventions. Other study interventions were able to blind the intervention and control arm. Only six studies specifically reported on the number of participants who were withdrawn after randomisation making them at low risk of incomplete outcome bias (ALIAS-Part 1 2011; ALIAS-Part 2 2013; Frei 1987; HSSG 1989; Spudis 1973; Strand 1984). Eight studies did not describe the randomisation procedure (Bornstein 1981; Goslinga 1992; Haass 1989; Hartmann 1987; HSSG 1989; Popa 1989; Rudolf 2002; Spudis 1973). All studies had low risk of reporting bias.

Potential biases in the review process

We attempted to reduce bias by performing a comprehensive literature search without language restrictions. The review authors of previous versions contacted authors for published and unpublished data. We did not contact the authors of the two studies included in this version as these studies were well documented (ALIAS-Part 1 2011; ALIAS-Part 2 2013). Other citations that we did and did not receive full text on could have had unpublished data relevant to this review. Unfortunately, we were unable to contact them all. The subgroup analysis should also be interpreted with caution, as this is a post-hoc analysis.

Agreements and disagreements with other studies or reviews

This review and previous versions are the most recent systematic review of haemodilution in acute ischaemic stroke. In an early systematic review of haemodilution trials in acute stroke (Asplund 1991), it was shown that, despite large differences in treatment protocols and target haematocrit levels, the reduction in haematocrit was remarkably similar, ranging from 4% to 7% in absolute terms and from 9% to 16% in relative terms in all but one study (Koller 1990), in which the reduction in haematocrit was more pronounced. In the only trial reporting on the change of haematocrit, haemodilution by HES and without venesection reduced haematocrit by 2% in absolute and by 5% in relative terms (MAHST 1998).

Non-systematic reviews of acute ischaemic stroke therapies including neuroprotection (Ginsberg 2008) and albumin (Prajapati 2011) have been published. Ginsberg 2008 discusses haemodilution trials referenced in this review. Both reviews discuss the promise of albumin therapy, but these reviews were completed while the ALIAS studies were underway.

AUTHORS' CONCLUSIONS

Implications for practice

As shown in the International Stroke Trial, intentional haemodilution has until recently been widely used in some countries to treat people with acute ischaemic stroke (International Stroke Trial Collaborative Group, personal communication). The present systematic review shows that this clinical practice has no clear scientific support. No benefit of haemodilution on mortality or on functional outcome in survivors has been documented, and the overall results of this review showed no clear evidence of benefit of this therapy. This conclusion concerns both hyper- and isovolaemic haemodilution regimens and all types of haemodiluting agents used (dextran, hydroxyethyl starch and albumin). Haemodilution for acute ischaemic stroke should not be used outside of clinical trials with the possible exception of people with severe polycythaemia.

Implications for research

In most participants included in the trials reviewed here, haemodilution treatment has been initiated later than six hours after onset of stroke symptoms and there has been a considerable additional delay before a significant reduction of haematocrit levels have been achieved. However, the available data from participants treated by isovolaemic and hypervolaemic haemodilution within six hours do not provide support for another large-scale clinical trial of this treatment. There is growing support from animal experimental models of ischaemic stroke that haemodilution initiated within the first few hours may limit brain infarct size and improve neurological outcome. While there was promise for albumin therapy, the large ALIAS trials enrolled participants within five hours of stroke onset and did not show benefit, suggesting that future clinical trials using albumin would have less clinical equipoise. The development of new oxygen-carrying haemodilutants and neuroprotectant agents is interesting. New clinical trials are warranted only if the balance between beneficial effects and adverse reactions of new modes of haemodilution have been solidly documented in experimental stroke models.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

ALIAS-Part 1 2011

Methods	RCT Centralised step-forward, web-based 1 : 1 randomisation process All study personnel and participants were blinded
Participants	People aged ≥ 18 years with acute ischaemic stroke within 5 hours of stroke onset and within 60 minutes of intravenous tPA Diagnosis of ischaemic stroke by CT or MRI scan
Interventions	25% albumin therapy (2 g/kg intravenously administered over 120 minutes) versus isovolaemic 0.9% normal saline
Outcomes	Death Neurological score Functional score
Notes	Study suspended in 2007 after interim analysis of differences in overall death between groups Neurological death reported at 7 days Death from any cause reported at 30 and 90 days

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Centralized step-forward, web-based 1:1 randomisation process was used"
Allocation concealment (selection bias)	Low risk	Quote: "Centralized step-forward, web-based"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "All study personnel and patients were blinded"

ALIAS-Part 1 2011 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All study personnel and patients were blinded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Albumin: 8 participants did not receive allocated intervention, 9 participants lost to follow-up Control: 2 participants did not receive allocated intervention, 2 participants lost to follow-up ITT analysis
Selective reporting (reporting bias)	Low risk	All outcomes reported

ALIAS-Part 2 2013

Methods	RCT Centralised step-forward, web-based 1 : 1 randomisation All study personnel and participants were blinded
Participants	People aged 18-83 years with acute ischaemic stroke within 5 hours of stroke onset and within 60 minutes of intravenous tPA Diagnosis of ischaemic stroke by CT or MRI scan
Interventions	25% albumin therapy (2 g/kg intravenously administered over 120 minutes) versus isovolaemic 0.9% normal saline
Outcomes	Death Neurological score Functional score
Notes	Neurological death reported at 7 days Death from any cause reported at 30 and 90 days

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Centralized step-forward, web-based 1:1 randomisation process with a biased coin minimisation approach that accounted for the status of treatment group balance within and across sites"
Allocation concealment (selection bias)	Low risk	Quote: "Centralized step-forward, web-based 1:1 randomization process"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All study personnel and patients were masked to the identity of the study drug. Each sealed kit contained two bottles (initially of 500 mL and 250 mL, then, for manufacturing reasons, both of 500 mL) of the same substance (either albumin or saline) encased in cardboard blinding boxes similar to those used in the Saline versus Albumin Fluid Evaluation (SAFE) Trial, in addition to filters and opaque sheathing to conceal the intravenous tubing. ... A bedside

ALIAS-Part 2 2013 *(Continued)*

		nurse or other personnel not associated with the trial administered the study drug (8 mL/kg estimated bodyweight) by constant intravenous infusion over 2 h (plus or minus 15 min)"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All study personnel and patients were masked to the identity of the study drug"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Albumin: 3 participants withdrew, 11 participants lost to follow-up Control: 3 participants withdrew, 13 participants lost to follow-up, 10 other participants with 90-day assessment missing ITT analysis
Selective reporting (reporting bias)	Low risk	All outcomes reported

Balcarce 1991

Methods	RCT, single-blind Randomisation by envelopes
Participants	People with acute ischaemic stroke within 48 hours and haematocrit 39-55%, no age limit Diagnosis of ischaemic stroke by CT scan
Interventions	Venesection with plasma replacement based on the following criteria: • if haematocrit 42-55%, 500 mL blood removed, 1 unit plasma infusion • if haematocrit 39-41%, 250 mL blood removed, 1/2 unit plasma infusion Haemodilution was performed daily during the first 5 days or until haematocrit decreased to 38%
Outcomes	Death
Notes	Published in Spanish

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Using enveloped containing the group of each patient"
Allocation concealment (selection bias)	Low risk	Quote: "Using enveloped containing the group of each patient"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Single-blinded", "The evaluation was conducted by employees trained by neurologist who were blinded to which group each patient belonged to"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The evaluation was conducted by employees trained by neurologist who were blinded to which group each patient belonged to"

Balcarce 1991 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details not given
Selective reporting (reporting bias)	Low risk	All outcomes reported

Bornstein 1981

Methods	RCT, double-blind Details of randomisation procedure not given
Participants	People with acute ischaemic stroke within 24 hours of onset
Interventions	Hypervolaemic: dextran 40 versus placebo (not specified)
Outcomes	Death Neurological score
Notes	Published in Hebrew

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Details not given
Allocation concealment (selection bias)	Unclear risk	Details not given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details not given
Selective reporting (reporting bias)	Low risk	All outcomes reported

Frei 1987

Methods	RCT Randomisation by using closed envelopes Evaluators and participants blinded

Frei 1987 *(Continued)*

Participants	People with acute ischaemic stroke within 30 hours of onset Diagnosis of ischaemic stroke by CT scan
Interventions	Hypervolaemic: dextran 40 plus glycerol versus placebo infusion
Outcomes	Death Neurological score Venous thromboembolic events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by using closed envelopes
Allocation concealment (selection bias)	Low risk	Adequate
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	61 participants entered. 10 deaths, 2 participants discontinued in intervention
Selective reporting (reporting bias)	Low risk	All outcome reported

Gilroy 1969

Methods	RCT Randomisation by using closed envelopes Information on blinding of evaluators or participants, or both, not given
Participants	People with acute presumed ischaemic stroke within 72 hours of onset, haemorrhage excluded by CSF analysis
Interventions	Hypervolaemic: dextran 40 for 72 hours versus a dextrose-saline infusion
Outcomes	Death Clinical improvement/deterioration (global assessment) Change in neurological score
Notes	

Risk of bias

Gilroy 1969 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "An envelope was taken in numerical series from 100 envelopes assorted in a random manner"
Allocation concealment (selection bias)	Low risk	Quote: "An envelope was taken in numerical series from 100 envelopes assorted in a random manner"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The instruction 'treat' or 'control' which was contained in the envelope dictated the method of treatment"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information not provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information not provided
Selective reporting (reporting bias)	Low risk	All outcomes reported

Goslinga 1992

Methods	RCT Stratified randomisation, other details about the randomisation procedure not known Evaluators or participants, or both, not blinded
Participants	People with acute ischaemic stroke within 48 hours of onset Diagnosis of ischaemic stroke by CT scan
Interventions	Isovolaemic: 20% albumin plus crystalloids plus venesection for 5 days versus crystalloids alone
Outcomes	Death Functional outcome
Notes	300 participants randomised, data at follow-up not reported in 1 participant receiving haemodilution and 2 participants receiving control

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not provided
Allocation concealment (selection bias)	Unclear risk	Information not provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "One of the problems with the methodology of haemodilution trials is that a blind control group is not possible, either for the patient or for the medical staff"

Goslinga 1992 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "One of the problem with the methodology of haemodilution trials is that a blind control group is not possible, either for the patient or for the medical staff"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Exclusion information was provided. Post-randomisation withdrawal was not provided
Selective reporting (reporting bias)	Low risk	All outcomes reported

Haass 1989

Methods	RCT Details of randomisation procedure not known Possible blinding of evaluators or participants, or both, not known
Participants	People with acute ischaemic stroke within 24 hours of onset Diagnosis of ischaemic stroke by CT scan
Interventions	Hypervolaemic: HES for 10 days versus crystalloid infusions
Outcomes	Death Neurological score Functional score
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not provided
Allocation concealment (selection bias)	Unclear risk	Information not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information not provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information not provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information not provided
Selective reporting (reporting bias)	Low risk	All outcomes reported

Hartmann 1987

Methods	RCT Randomisation procedure not known Blinding of evaluators or participants, or both, not known
Participants	People with acute ischaemic stroke in the carotid artery territory within 24 hours of onset Diagnosis of ischaemic stroke by CT scan in all participants
Interventions	Hypervolaemic: HES 200 for 7 days versus no specific treatment
Outcomes	Cerebral blood flow Death Complications
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not provided
Allocation concealment (selection bias)	Unclear risk	Information not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information not provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information not provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information not provided
Selective reporting (reporting bias)	Low risk	All outcomes reported

HSSG 1989

Methods	RCT Randomisation procedure not known Multicentre (13 centres) Evaluators blinded but not participants or managing physicians
Participants	People with acute ischaemic stroke within 24 hours of onset Diagnosis of ischaemic stroke by CT scan
Interventions	Individualised hypervolaemic or isovolaemic: HES for 72-96 hours plus venesection in selected participants during the first 24 hours versus no specific treatment
Outcomes	Death

HSSG 1989 *(Continued)*

	Neurological score
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not provided
Allocation concealment (selection bias)	Unclear risk	Information not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information not provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information not provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Hypervolaemic: 15 participants did not complete the study: 9 died and 6 due to allergy, low haematocrit, lost to follow-up, confined to distant nursing home, study terminated early Control: 6 participants did not complete the study: 3 died, other 3 due to malingering, lost to follow-up, study terminated early
Selective reporting (reporting bias)	Low risk	All outcomes reported

IASSG 1988

Methods	RCT Multicentre (31 centres) Telephone randomisation by lists kept at the co-ordinating centre Evaluation of functional outcome by blinded telephone interview
Participants	People with acute ischaemic and haemorrhagic stroke within 12 hours of onset Diagnosis of stroke subtype by CT scan in 97% of cases
Interventions	Isovolaemic: dextran 40 plus venesection during the first 24 hours versus no specific therapy
Outcomes	Death Functional independency/dependency at discharge and at 6-month follow-up
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by lists

IASSG 1988 *(Continued)*

Allocation concealment (selection bias)	Low risk	Telephone randomisation by lists kept at the co-ordinating centre
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Since it was not possible to use a sham procedure the patient in the control group received only the most appropriate general treatment, the same as that provided for the patients in the haemodilution group"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Evaluation of functional outcome by blinded telephone interview
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information not provided
Selective reporting (reporting bias)	Low risk	All outcomes reported

Kaste 1976

Methods	RCT Randomisation by choosing from identical-looking vials Evaluators and participants blinded
Participants	People with acute presumed ischaemic stroke within 24 hours of onset Diagnosis of ischaemic stroke by CSF analysis and brain isotope scanning in all participants
Interventions	Hypervolaemic: dextran 40 for 72 hours plus dexamethasone for 14 days versus placebo
Outcomes	Death Neurological score
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "We were unaware of the identity of the phials [sic] being used"
Allocation concealment (selection bias)	Low risk	Quote: "We were unaware of the identity of the phials [sic] being used"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The code being broken only after final evaluation of the patients' conditions"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The code being broken only after final evaluation of the patients' conditions"
Incomplete outcome data (attrition bias)	Unclear risk	Information not provided

Kaste 1976 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	All outcomes reported

Koller 1990

Methods	RCT Randomisation by using closed envelopes Evaluators but not participants blinded
Participants	People with acute ischaemic stroke in the middle cerebral artery territory within 24 hours of onset Diagnosis of ischaemic stroke by CT scan
Interventions	Isovolaemic: dextran 40 plus venesection for 72 hours versus saline infusion
Outcomes	Death Neurological score
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation by using closed envelopes
Allocation concealment (selection bias)	Low risk	Randomisation by using closed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Evaluators blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Haemodilution: 1 participant refused last follow-up examination Control: 3 participants withdrawn due to misdiagnosis and doctor in charge changed treatment
Selective reporting (reporting bias)	Low risk	All outcomes reported

MAHST 1998

Methods	RCT Randomisation by selecting from identical-looking bottles Evaluators, participants and attending physicians blinded

MAHST 1998 *(Continued)*

Participants	People with acute ischaemic stroke within 6 hours of onset Diagnosis of ischaemic stroke by CT
Interventions	Hypervolaemic: HES plus crystalloid solution for 5 days versus crystalloids alone
Outcomes	Death Neurological scores Functional score
Notes	The trial was intended to include 400 participants. It was interrupted after an interim analysis performed when 200 participants had been included. There were 3 reasons: the originally planned sample size would have been too small to demonstrate any effects of haemodilution, recruitment to the study was slow and there were financial constraints

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization scheme was generated by permutation of random numbers (Sofware Randomsys, University of Linz) in 150 blocks with length of four patients each by an external biometrics consultant"
Allocation concealment (selection bias)	Low risk	Quote: "By an external biometrics consultant"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT and per-protocol analysis performed. 42 participants were not considered for the per-protocol analysis due to cerebral haematoma, brain stem and cerebellar infarcts, protocol violation, low haematocrit, elevated creatine and cardiac complication. Which group had these characteristics was not reported
Selective reporting (reporting bias)	Low risk	All outcomes reported

Mast 1991

Methods	RCT Randomisation by using closed envelopes Evaluators but not participants blinded
Participants	People with acute ischaemic stroke within 24 hours of onset Diagnosis of ischaemic stroke by CT scan
Interventions	Isovolaemic: dextran 40 plus venesection versus no specific treatment
Outcomes	Death Neurological score at 2 weeks

Mast 1991 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by using closed envelopes
Allocation concealment (selection bias)	Low risk	Randomisation by using closed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Evaluators blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information not provided
Selective reporting (reporting bias)	Low risk	All outcomes reported

Matthews 1976

Methods	RCT Randomisation by using closed envelopes Evaluators not blinded
Participants	People with presumed ischaemic stroke within 48 hours of onset Haemorrhage excluded by CSF analysis
Interventions	Hypervolaemic: dextran 40 for 72 hours versus dextrose infusion
Outcomes	Death Neurological score Functional score Need for institutional care
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly allocated to either dextran group or the control group by opening the next one of a series of envelopes"
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomly allocated to either dextran group or the control group by opening the next one of a series of envelopes"

Matthews 1976 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Information on patient blinding not provided Quote: "After entry to the trial they remained under the care of the firm that had admitted them who did of course know whether dextran or 5 per cent dextrose solution was administered"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "After entry to the trial they remained under the care of the firm that had admitted them who did of course know whether dextran or 5 per cent dextrose solution was administered"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information not provided
Selective reporting (reporting bias)	Low risk	All outcomes reported

Popa 1989

Methods	RCT Randomisation procedure unknown No information on blinding of evaluators, participants, or both
Participants	People with presumed ischaemic stroke, haemorrhage excluded by CSF analysis
Interventions	Isovolaemic: dextran 40 for 5 days plus venesection for 2 days versus no specific treatment
Outcomes	Death Neurological score Functional score
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not provided
Allocation concealment (selection bias)	Unclear risk	Information not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information not provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information not provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information not provided

Popa 1989 *(Continued)*

Selective reporting (reporting bias)	Low risk	All outcomes reported

Rudolf 2002

Methods	Randomised placebo-controlled trial Multicentre (16 centres) Randomisation procedure not described
Participants	People with ischaemic stroke (CT scan) within 6 hours of onset
Interventions	Hypervolaemic: HES 10% for 7 days versus saline infusions
Outcomes	Death Neurological scores Functional scores
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not provided
Allocation concealment (selection bias)	Unclear risk	Information not provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Of the 107 patients randomised, 106 patients received at least one dose of study drug" No additional information provided on number of participants that completed the study
Selective reporting (reporting bias)	Low risk	All outcomes reported

Spudis 1973

Methods	RCT Randomisation procedure not known Evaluators but not participants blinded
Participants	People with presumed ischaemic stroke within 24 hours of onset

Spudis 1973 *(Continued)*

	Haemorrhage excluded by CSF analysis in all participants
Interventions	Hypervolaemic: dextran 40 for 72 hours versus no specific treatment
Outcomes	Death Change in neurological signs
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not provided
Allocation concealment (selection bias)	Unclear risk	Information not provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Information not provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "After one week the patient was independently graded by a second author, and after three weeks, by the author.... The second and third examiners never had an opportunity to see the patients while dextran was running and had little reason to try to guess which patients were controls"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dextran: 1 participant eliminated due to flushing and apnoea Controls: no participants withdrawn
Selective reporting (reporting bias)	Low risk	All outcomes reported

SSSG 1987

Methods	RCT Multicentre (15 centres) Stratified randomisation by using closed envelopes Evaluators blinded, participants and attending physicians not blinded
Participants	People with acute ischaemic stroke within 48 hours of onset Diagnosis of ischaemic stroke by CT scan in 63% and by CSF analysis in the remaining participants
Interventions	Isovolaemic: dextran 40 for 48 hours plus venesection for the first 24-48 hours versus no specific treatment
Outcomes	Death Neurological score Functional score Need for institutional care Other clinical events

SSSG 1987 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratification by centre, age, prognostic neurological score by "preset multiple of 4 by drawing envelopes containing a slip assigning a particular patient to one of the two groups"
Allocation concealment (selection bias)	Low risk	Quote: "Drawing envelopes containing a slip assigning a particular patient to one of the two groups"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and attending physicians not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Evaluators blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided
Selective reporting (reporting bias)	Low risk	All outcomes reported

Strand 1984

Methods	RCT Randomisation by using closed envelopes Evaluators blinded, participants and attending physicians not blinded
Participants	People with acute ischaemic stroke within 48 hours of onset Diagnosis of ischaemic stroke by CT scan and CSF analysis in all participants
Interventions	Isovolaemic: dextran 40 for 7 days plus venesection during the first 24-48 hours versus no specific treatment
Outcomes	Death Neurological score Functional score Need for institutional care Other circulatory events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by using closed envelopes

Strand 1984 *(Continued)*

Allocation concealment (selection bias)	Low risk	Closed envelope
Blinding of participants and personnel (performance bias) All outcomes	High risk	People and attending physicians not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Evaluators blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 participants with small intracerebral haemorrhage (2 in intervention and control), 4 participants not fulfilling inclusion criteria, and 1 deaf and blind participant were inadvertently randomised. ITT analysis on the remaining participants Haemodilution was interrupted in 2 participants with anaphylactoid reaction
Selective reporting (reporting bias)	Low risk	All outcomes reported

CSF: cerebrospinal fluid; CT: computed tomography; HES: hydroxyethyl starch; ITT: intention-to-treat; MRI: magnetic resonance imaging; RCT: randomised controlled trial; tPA: tissue plasminogen activator.

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

Study	Reason for exclusion
Chen 2006	Randomised trial comparing venesection and haemodilution plus herbal medicine of 1 form versus herbal medicine of another form. Death was reported
Ding 1992	Quasi-randomised trial of 2 different haemodilution regimens: normovolaemic (venesection plus dextran) versus hypervolaemic (dextran only)
Grauer 1999	Randomised double-blind study comparing low- and medium-dose HES with haematological and neurological score outcome
Hamamoto 1992	Randomised trial of unspecified 'hypervolaemic haemodilution', no information or detail of therapy. Cerebral blood flow and neurological score reported but not mortality, dependency or institutional care. Abstract only
Hartmann unpubl.	The trial was terminated early for logistical reasons. No data have been available to the review authors (despite personal contacts and reminders to the principal investigator and the manufacturer during the years 1993-1995)
Hayes 2000	Study on the effects of transcranial Doppler directed dextran 40 therapy to prevent postoperative stroke in people undergoing carotid endarterectomy. Historical controls
Koppi 1996	Cerebrolysin (so-called "neuron metabolism specific treatment") compared with haemodilution in a non-randomised trial
Krack 1989	Study on the haemodynamic effects of HES in people with stroke. Participants were their own controls (before versus after haemodilution) and no clinical outcome data were given (except the haemodynamic variables)

Study	Reason for exclusion
Luo 1991	Non-randomised trial (controls were matched with treated participants) with initial venesection plus low-molecular-weight dextran, then dextran daily for 15 days. Neurological score and laboratory variables were reported but not mortality or dependency or institutional care
Morgenthaler 2010	RCT comparing 2 doses of HES with haemodynamics and rheology as outcomes. Adverse event questionnaire included pruritus
Porro 1985	Randomised trial of isovolaemic haemodilution (7 participants; procedure not described) versus conventional treatment (8 participants) Emphasis on haemorheological outcome variables. Clinical effects described as "the neurological symptoms were not apparently influenced" without more detailed specifications
Schwarz 1998	Study of the effects of HES and mannitol on intracranial pressure and cerebral perfusion pressure, not possible to abstract clinical endpoints
Shin 2007	Randomised trial comparing albumin versus saline. Outcomes included neurological score and imaging
Staedt 1987	Clinical trial comparing HES versus dextran with neurological outcome
Staedt 1989	Prospective cross-over study comparing HES, dextran and isotonic solution with haematological and eye oxygenation outcome
Staedt 1991	Randomised trial comparing hypervolaemic haemodilution with haematocrit goal of 41-43% versus 37-39%. 1 death was reported but it is unknown in which group the death occurred. In addition, it does not report the number of people in each group. Abstract only
Stoll 1998	Study of the acute effects of HES on haemodynamic variables and neurological score. No randomised control group
Strand 2002	RCT comparing venesection plus dextran versus control with neurological score as outcome
Tessitore 1990	Randomised trial comparing haemodilution and placebo with haematocrit and gross motor function outcomes
Torun 1995	RCT of isovolaemic haemodilution (venesection plus HES; 95 participants) versus control (84 participants). No numbers given on survival or functional outcome
Walzl 1994	Randomised trial of extracorporal fibrinogen and platelet precipitation, reporting only on intermediary (laboratory) outcome variables; no clinical information
Wang 1988	Non-randomised study of the combination of blood-letting and either dextran 40 or hydroxyethyl amylum. Control group matched by age, sex and severity of stroke
Wang 1990	Randomised trial of 2 different haemodilution regimens: plasma expander 706 (unknown content) plus crystalloid solution plus venesection versus low-molecular-weight dextran plus Chuan Xiong Qing (Chinese herb)
Wise 1976	Randomised trial of 3 different interventions, of which 1 included a combination of a steroid (dexamethasone) and dextran. No figures on outcome given. Abstract only
Woessner 2003	Randomised double-blind trial comparing HES versus crystalloid solution. Outcomes only included haemodynamic parameters

Study	Reason for exclusion
Zhang 1990	Randomised trial of intervention isovolaemic blood dilution with plasma substitute plus vitamin B and C versus control low-molecular-weight dextran and ligustrazine, a Chinese herbal medicine, plus vitamin B and C
Zhang 1996	Controlled trial, but not clear if it was a randomised study. Mixture of people with acute stroke and in late phase after stroke (> 30 days). Wide variations between participants in the duration of follow-up

HES: hydroxyethyl starch; RCT: randomised controlled trial.

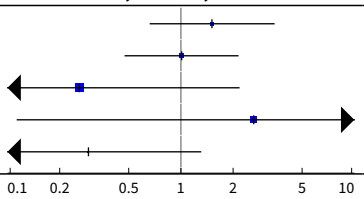
DATA AND ANALYSES

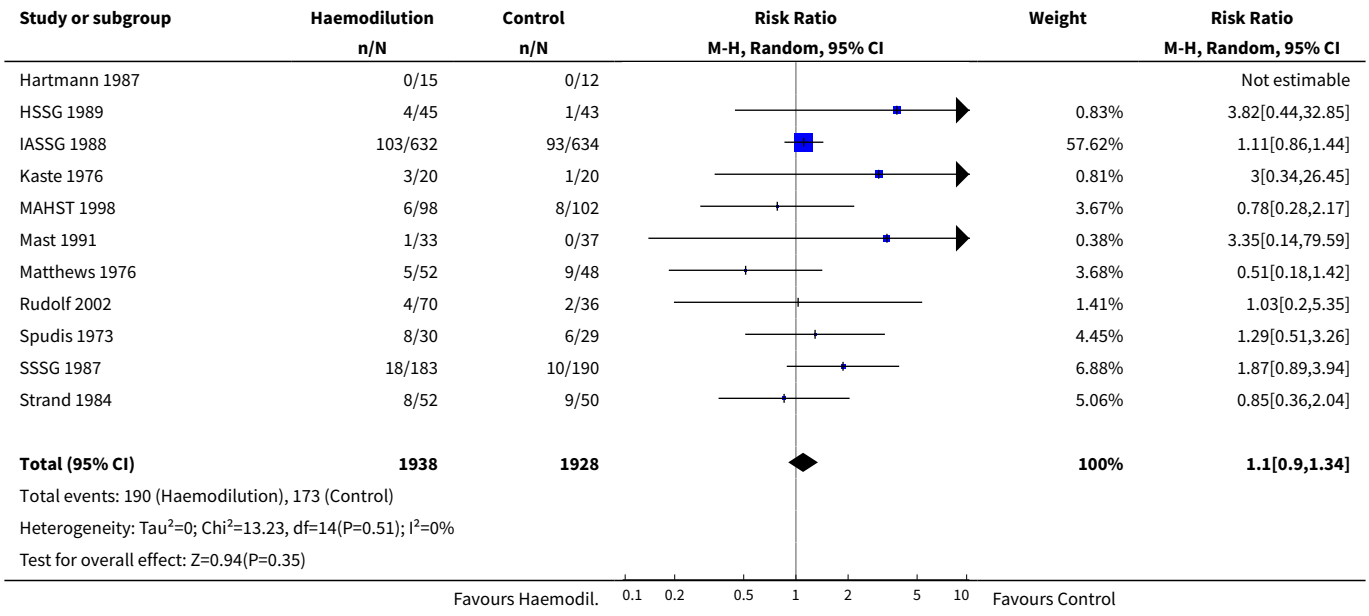
Comparison 1. Haemodilution, all types, versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality at early follow-up (not later than 28 days)	16	3866	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.90, 1.34]
2 Mortality at late follow-up (3-6 months)	15	3957	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.93, 1.20]
3 Dead or dependent/institutionalised (3-6 months)	8	2491	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.85, 1.07]
4 Venous thromboembolic events at early follow-up (within 28 days)	4	621	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.20, 3.44]
5 Venous thromboembolic events at late follow-up (3-6 months)	6	865	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.37, 1.24]
6 Anaphylactic (or anaphylactic-like) reactions	8	2253	Risk Ratio (M-H, Random, 95% CI)	3.89 [0.83, 18.30]
7 Serious cardiac events, cumulative at latest follow-up	7	1358	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.66, 2.05]

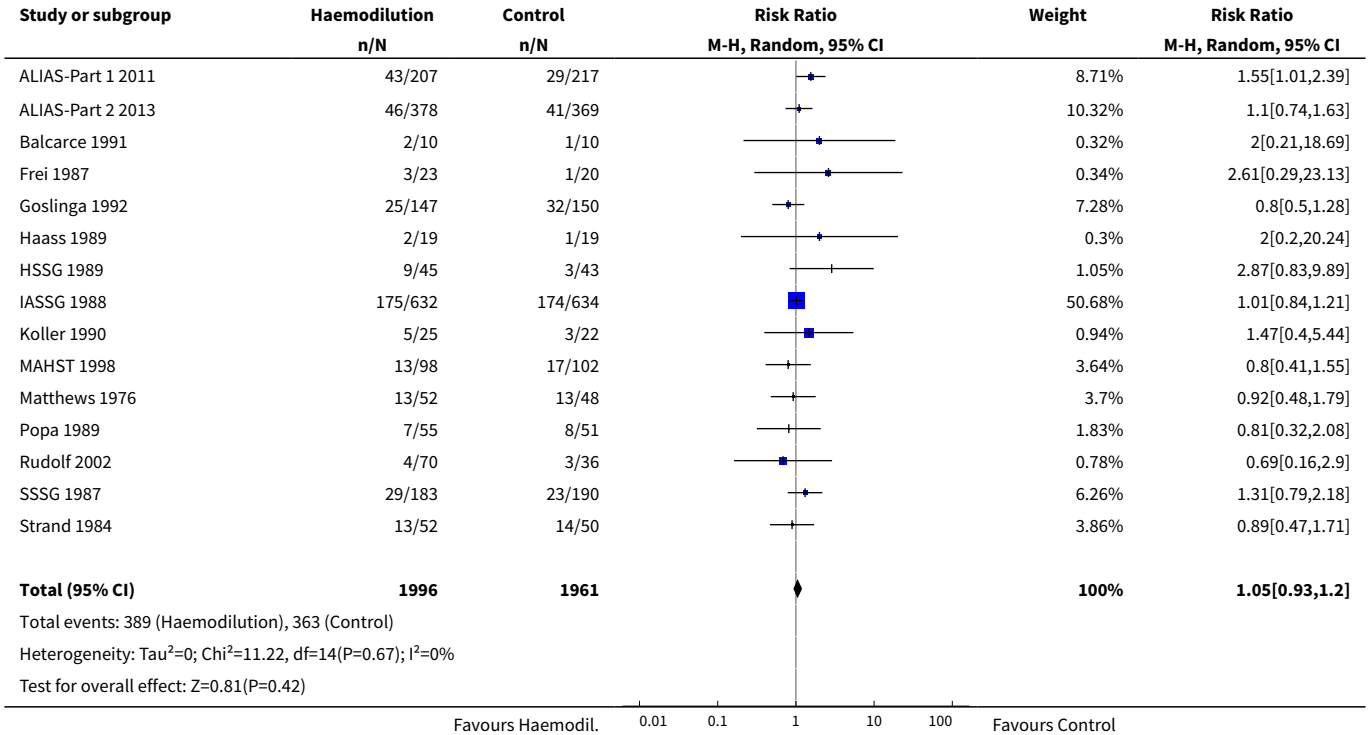
Analysis 1.1. Comparison 1 Haemodilution, all types, versus control, Outcome 1 Mortality at early follow-up (not later than 28 days).

Study or subgroup	Haemodilution n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
ALIAS-Part 1 2011	13/207	9/217		5.58%	1.51[0.66,3.47]
ALIAS-Part 2 2013	13/404	13/407		6.69%	1.01[0.47,2.15]
Bornstein 1981	1/28	4/29		0.84%	0.26[0.03,2.18]
Frei 1987	1/23	0/20		0.39%	2.63[0.11,61.05]
Gilroy 1969	2/46	8/54		1.7%	0.29[0.07,1.31]



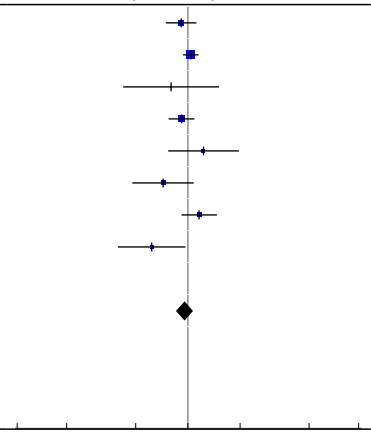


Analysis 1.2. Comparison 1 Haemodilution, all types, versus control, Outcome 2 Mortality at late follow-up (3-6 months).



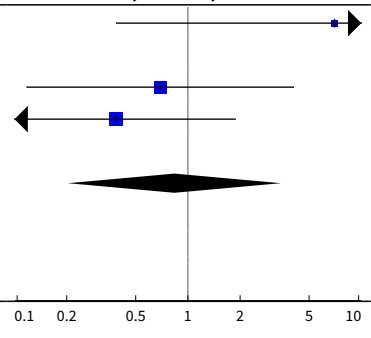
Analysis 1.3. Comparison 1 Haemodilution, all types, versus control, Outcome 3 Dead or dependent/institutionalised (3-6 months).

Study or subgroup	Haemodilution n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Goslinga 1992	78/147	87/150		16.97%	0.91[0.75,1.12]
IASSG 1988	343/632	331/634		27.99%	1.04[0.94,1.15]
Koller 1990	10/25	11/22		3.02%	0.8[0.42,1.51]
MAHST 1998	68/98	77/102		20.06%	0.92[0.77,1.09]
Matthews 1976	24/52	18/48		5.21%	1.23[0.77,1.97]
Rudolf 2002	28/70	20/36		6.53%	0.72[0.48,1.08]
SSSG 1987	85/183	76/190		14.59%	1.16[0.92,1.47]
Strand 1984	18/52	28/50		5.64%	0.62[0.4,0.97]
Total (95% CI)	**1259**	**1232**		**100%**	**0.96[0.85,1.07]**
Total events: 654 (Haemodilution), 648 (Control)					
Heterogeneity: Tau^2=0.01; Chi^2=11.81, df=7(P=0.11); I^2=40.73%					
Test for overall effect: Z=0.74(P=0.46)					



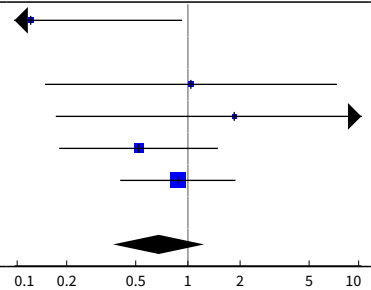
Analysis 1.4. Comparison 1 Haemodilution, all types, versus control, Outcome 4 Venous thromboembolic events at early follow-up (within 28 days).

Study or subgroup	Haemodilution n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Kaste 1976	3/20	0/20		19.02%	7[0.38,127.32]
Rudolf 2002	0/70	0/36			Not estimable
SSSG 1987	2/183	3/190		37.96%	0.69[0.12,4.09]
Strand 1984	2/52	5/50		43.03%	0.38[0.08,1.89]
Total (95% CI)	**325**	**296**		**100%**	**0.83[0.2,3.44]**
Total events: 7 (Haemodilution), 8 (Control)					
Heterogeneity: Tau^2=0.55; Chi^2=3.07, df=2(P=0.22); I^2=34.79%					
Test for overall effect: Z=0.25(P=0.8)					



Analysis 1.5. Comparison 1 Haemodilution, all types, versus control, Outcome 5 Venous thromboembolic events at late follow-up (3-6 months).

Study or subgroup	Haemodilution n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Frei 1987	1/23	7/20		8.7%	0.12[0.02,0.93]
Koller 1990	0/25	0/22			Not estimable
MAHST 1998	2/98	2/102		9.29%	1.04[0.15,7.24]
Matthews 1976	2/52	1/48		6.33%	1.85[0.17,19.71]
SSSG 1987	5/183	10/190		28.21%	0.52[0.18,1.49]
Strand 1984	10/52	11/50		47.47%	0.87[0.41,1.88]
Total (95% CI)	**433**	**432**		**100%**	**0.68[0.37,1.24]**

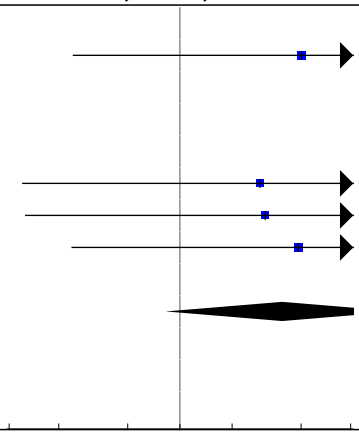


Study or subgroup	Haemodilution n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 20 (Haemodilution), 31 (Control)					
Heterogeneity: Tau²=0.05; Chi²=4.41, df=4(P=0.35); I²=9.22%					
Test for overall effect: Z=1.25(P=0.21)					

Favours Haemodil. Favours Control

Analysis 1.6. Comparison 1 Haemodilution, all types, versus control, Outcome 6 Anaphylactic (or anaphylactic-like) reactions.

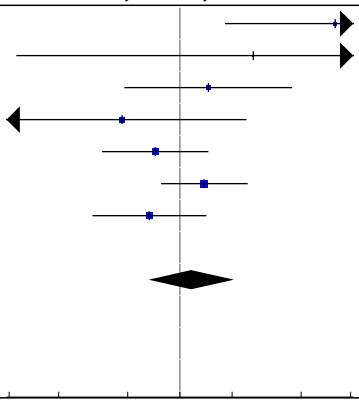
Study or subgroup	Haemodilution n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Gilroy 1969	0/46	0/54			Not estimable
IASSG 1988	2/632	0/634		26.05%	5.02[0.24,104.27]
Koller 1990	0/25	0/22			Not estimable
MAHST 1998	0/98	0/102			Not estimable
Rudolf 2002	0/70	0/36			Not estimable
Spudis 1973	1/30	0/29		24%	2.9[0.12,68.5]
SSSG 1987	1/183	0/190		23.51%	3.11[0.13,75.96]
Strand 1984	2/52	0/50		26.44%	4.81[0.24,97.8]
Total (95% CI)	**1136**	**1117**		**100%**	**3.89[0.83,18.3]**
Total events: 6 (Haemodilution), 0 (Control)					
Heterogeneity: Tau²=0; Chi²=0.1, df=3(P=0.99); I²=0%					
Test for overall effect: Z=1.72(P=0.09)					



Favours Haemodil. Favours Control

Analysis 1.7. Comparison 1 Haemodilution, all types, versus control, Outcome 7 Serious cardiac events, cumulative at latest follow-up.

Study or subgroup	Haemodilution n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
ALIAS-Part 1 2011	15/207	2/217		10.12%	7.86[1.82,33.96]
Koller 1990	1/25	0/22		2.93%	2.65[0.11,62]
MAHST 1998	7/98	5/102		14.11%	1.46[0.48,4.44]
Popa 1989	2/55	4/51		8.52%	0.46[0.09,2.42]
Rudolf 2002	14/70	10/36		20.93%	0.72[0.36,1.46]
SSSG 1987	24/183	18/190		23.44%	1.38[0.78,2.46]
Strand 1984	9/52	13/50		19.96%	0.67[0.31,1.42]
Total (95% CI)	**690**	**668**		**100%**	**1.16[0.66,2.05]**
Total events: 72 (Haemodilution), 52 (Control)					
Heterogeneity: Tau²=0.27; Chi²=12.76, df=6(P=0.05); I²=52.98%					
Test for overall effect: Z=0.52(P=0.6)					



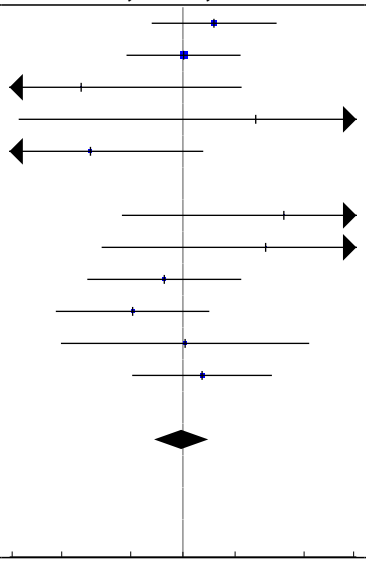
Favours treatment Favours control

Comparison 2. Hypervolaemic haemodilution (without venesection) versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality at early follow-up (not later than 28 days)	12	2055	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.68, 1.40]
2 Mortality at late follow-up (3-6 months)	8	1746	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.94, 1.51]
3 Dead or dependent/institutionalised (3-6 months)	3	406	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.74, 1.14]

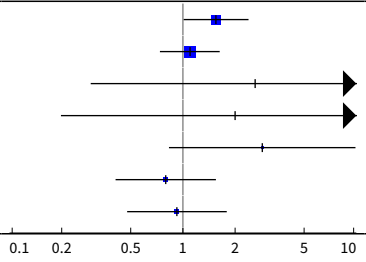
Analysis 2.1. Comparison 2 Hypervolaemic haemodilution (without venesection) versus control, Outcome 1 Mortality at early follow-up (not later than 28 days).

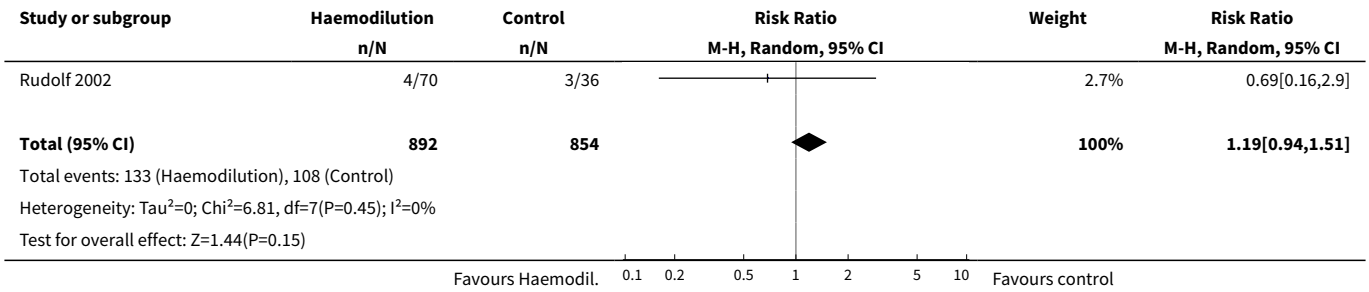
Study or subgroup	Haemodilution n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
ALIAS-Part 1 2011	13/207	9/217		18.51%	1.51[0.66,3.47]
ALIAS-Part 2 2013	13/404	13/407		22.14%	1.01[0.47,2.15]
Bornstein 1981	1/28	4/29		2.84%	0.26[0.03,2.18]
Frei 1987	1/23	0/20		1.3%	2.63[0.11,61.05]
Gilroy 1969	2/46	8/54		5.71%	0.29[0.07,1.31]
Hartmann 1987	0/15	0/12			Not estimable
HSSG 1989	4/45	1/43		2.78%	3.82[0.44,32.85]
Kaste 1976	3/20	1/20		2.71%	3[0.34,26.45]
MAHST 1998	6/98	8/102		12.23%	0.78[0.28,2.17]
Matthews 1976	5/52	9/48		12.26%	0.51[0.18,1.42]
Rudolf 2002	4/70	2/36		4.72%	1.03[0.2,5.35]
Spudis 1973	8/30	6/29		14.81%	1.29[0.51,3.26]
Total (95% CI)	**1038**	**1017**		**100%**	**0.98[0.68,1.4]**
Total events: 60 (Haemodilution), 61 (Control)					
Heterogeneity: Tau^2=0; Chi^2=10.06, df=10(P=0.43); I^2=0.64%					
Test for overall effect: Z=0.13(P=0.9)					



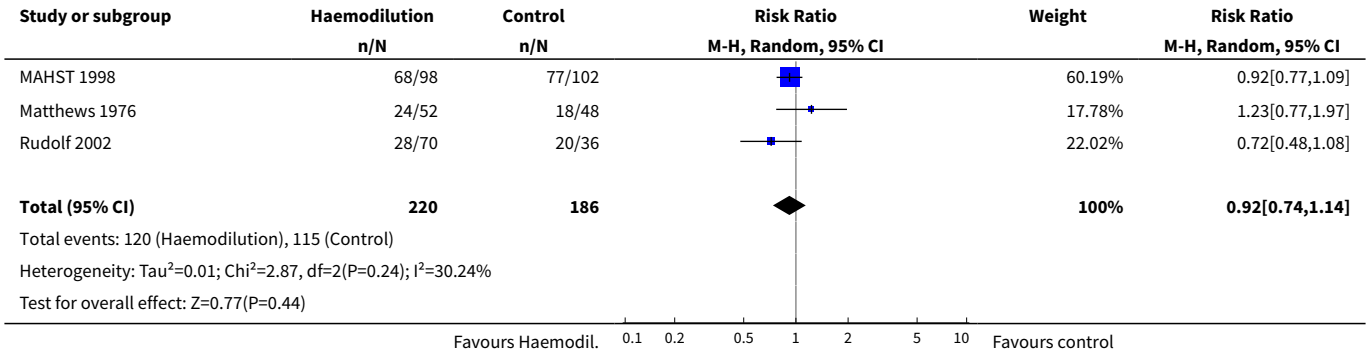
Analysis 2.2. Comparison 2 Hypervolaemic haemodilution (without venesection) versus control, Outcome 2 Mortality at late follow-up (3-6 months).

Study or subgroup	Haemodilution n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
ALIAS-Part 1 2011	43/207	29/217		30.21%	1.55[1.01,2.39]
ALIAS-Part 2 2013	46/378	41/369		35.78%	1.1[0.74,1.63]
Frei 1987	3/23	1/20		1.18%	2.61[0.29,23.13]
Haass 1989	2/19	1/19		1.05%	2[0.2,20.24]
HSSG 1989	9/45	3/43		3.66%	2.87[0.83,9.89]
MAHST 1998	13/98	17/102		12.61%	0.8[0.41,1.55]
Matthews 1976	13/52	13/48		12.82%	0.92[0.48,1.79]





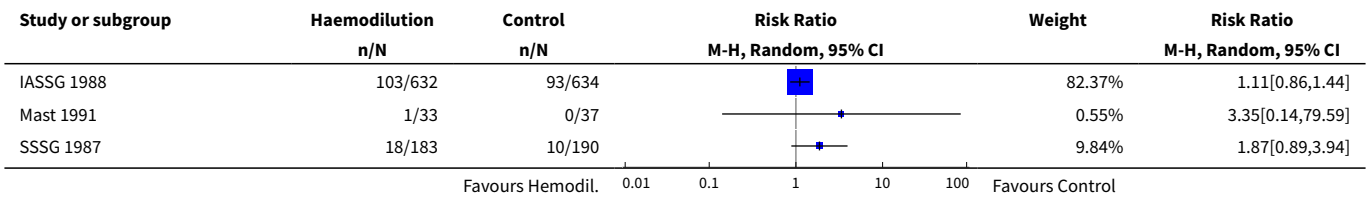
Analysis 2.3. Comparison 2 Hypervolaemic haemodilution (without venesection) versus control, Outcome 3 Dead or dependent/institutionalised (3-6 months).



Comparison 3. Isovolaemic haemodilution (including venesection) versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality at early follow-up (not later than 28 days)	4	1811	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.91, 1.46]
2 Mortality at late follow-up (3-6 months)	7	2211	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.86, 1.17]
3 Dead or dependent/institutionalised (3-6 months)	5	2085	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.83, 1.13]

Analysis 3.1. Comparison 3 Isovolaemic haemodilution (including venesection) versus control, Outcome 1 Mortality at early follow-up (not later than 28 days).

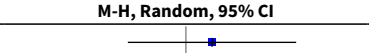


Study or subgroup	Haemodilution n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Strand 1984	8/52	9/50		7.24%	0.85[0.36,2.04]
Total (95% CI)	**900**	**911**		**100%**	**1.15[0.91,1.46]**
Total events: 130 (Haemodilution), 112 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.59, df=3(P=0.46); I^2=0%					
Test for overall effect: Z=1.2(P=0.23)					

Favours Hemodil. Favours Control

Analysis 3.2. Comparison 3 Isovolaemic haemodilution (including venesection) versus control, Outcome 2 Mortality at late follow-up (3-6 months).

Study or subgroup	Haemodilution n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Balcarce 1991	2/10	1/10		0.45%	2[0.21,18.69]
Goslinga 1992	25/147	32/150		10.23%	0.8[0.5,1.28]
IASSG 1988	175/632	174/634		71.21%	1.01[0.84,1.21]
Koller 1990	5/25	3/22		1.32%	1.47[0.4,5.44]
Popa 1989	7/55	8/51		2.57%	0.81[0.32,2.08]
SSSG 1987	29/183	23/190		8.79%	1.31[0.79,2.18]
Strand 1984	13/52	14/50		5.42%	0.89[0.47,1.71]
Total (95% CI)	**1104**	**1107**		**100%**	**1[0.86,1.17]**
Total events: 256 (Haemodilution), 255 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.98, df=6(P=0.81); I^2=0%					
Test for overall effect: Z=0.05(P=0.96)					



Favours Hemodil. Favours Control

Analysis 3.3. Comparison 3 Isovolaemic haemodilution (including venesection) versus control, Outcome 3 Dead or dependent/institutionalised (3-6 months).

Study or subgroup	Haemodilution n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Goslinga 1992	78/147	87/150		25.26%	0.91[0.75,1.12]
IASSG 1988	343/632	331/634		38.36%	1.04[0.94,1.15]
Koller 1990	10/25	11/22		5.05%	0.8[0.42,1.51]
SSSG 1987	85/183	76/190		22.12%	1.16[0.92,1.47]
Strand 1984	18/52	28/50		9.21%	0.62[0.4,0.97]
Total (95% CI)	**1039**	**1046**		**100%**	**0.97[0.83,1.13]**
Total events: 534 (Haemodilution), 533 (Control)					
Heterogeneity: Tau^2=0.01; Chi^2=7.72, df=4(P=0.1); I^2=48.19%					
Test for overall effect: Z=0.39(P=0.7)					

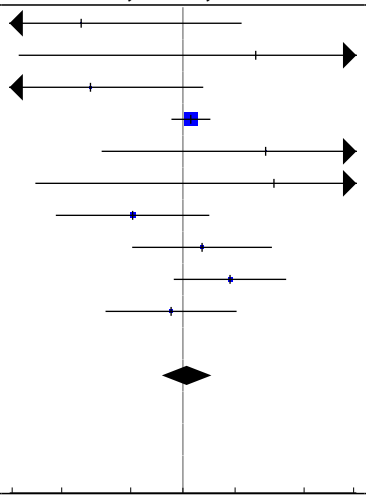
Favours Haemodil. Favours Control

Comparison 4. Haemodilution using low-molecular-weight dextran (dextran 40) versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality at early follow-up (not later than 28 days)	10	2210	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.76, 1.46]
2 Mortality at late follow-up (3-6 months)	7	2037	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.88, 1.20]
3 Dead or dependent/institutionalised (3-6 months)	5	1888	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.84, 1.20]

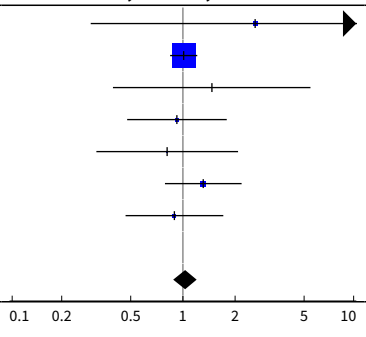
Analysis 4.1. Comparison 4 Haemodilution using low-molecular-weight dextran (dextran 40) versus control, Outcome 1 Mortality at early follow-up (not later than 28 days).

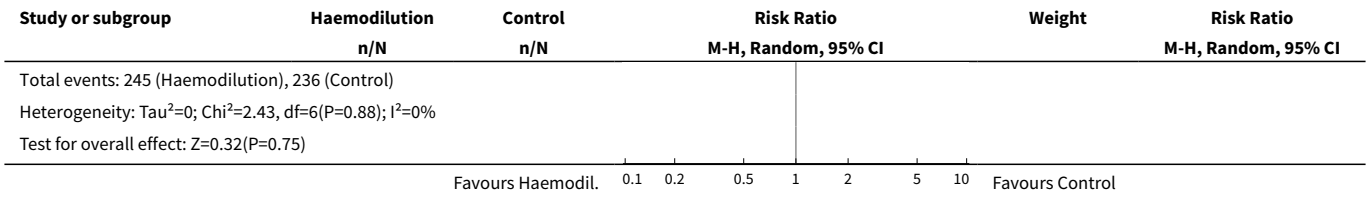
Study or subgroup	Haemodilution n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Bornstein 1981	1/28	4/29		2.28%	0.26[0.03,2.18]
Frei 1987	1/23	0/20		1.07%	2.63[0.11,61.05]
Gilroy 1969	2/46	8/54		4.43%	0.29[0.07,1.31]
IASSG 1988	103/632	93/634		43.73%	1.11[0.86,1.44]
Kaste 1976	3/20	1/20		2.19%	3[0.34,26.45]
Mast 1991	1/33	0/37		1.05%	3.35[0.14,79.59]
Matthews 1976	5/52	9/48		8.81%	0.51[0.18,1.42]
Spudis 1973	8/30	6/29		10.34%	1.29[0.51,3.26]
SSSG 1987	18/183	10/190		14.61%	1.87[0.89,3.94]
Strand 1984	8/52	9/50		11.49%	0.85[0.36,2.04]
Total (95% CI)	**1099**	**1111**		**100%**	**1.05[0.76,1.46]**
Total events: 150 (Haemodilution), 140 (Control)					
Heterogeneity: Tau^2=0.05; Chi^2=10.87, df=9(P=0.28); I^2=17.19%					
Test for overall effect: Z=0.29(P=0.77)					



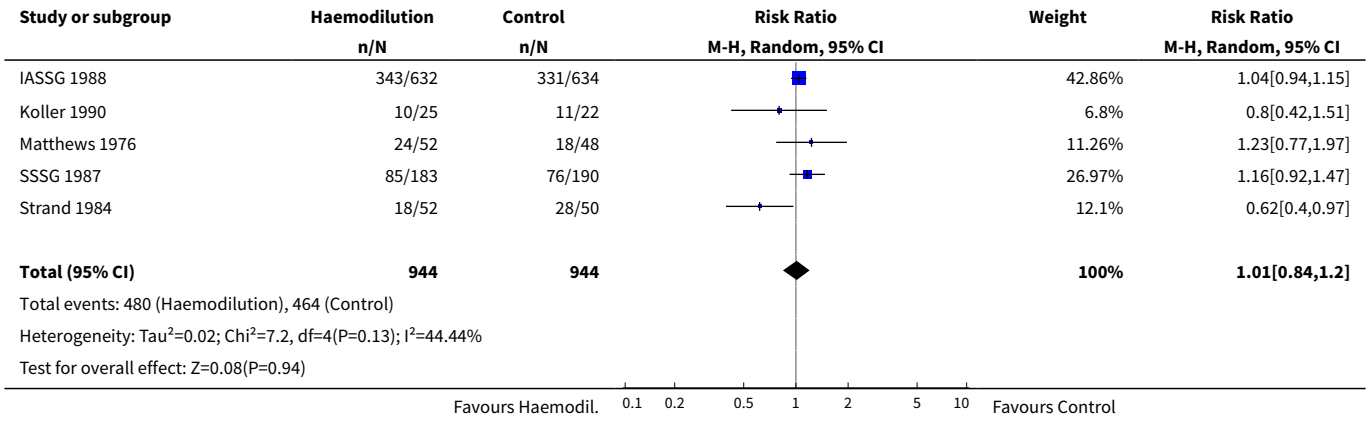
Analysis 4.2. Comparison 4 Haemodilution using low-molecular-weight dextran (dextran 40) versus control, Outcome 2 Mortality at late follow-up (3-6 months).

Study or subgroup	Haemodilution n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Frei 1987	3/23	1/20		0.5%	2.61[0.29,23.13]
IASSG 1988	175/632	174/634		74.97%	1.01[0.84,1.21]
Koller 1990	5/25	3/22		1.39%	1.47[0.4,5.44]
Matthews 1976	13/52	13/48		5.47%	0.92[0.48,1.79]
Popa 1989	7/55	8/51		2.71%	0.81[0.32,2.08]
SSSG 1987	29/183	23/190		9.26%	1.31[0.79,2.18]
Strand 1984	13/52	14/50		5.7%	0.89[0.47,1.71]
Total (95% CI)	**1022**	**1015**		**100%**	**1.03[0.88,1.2]**





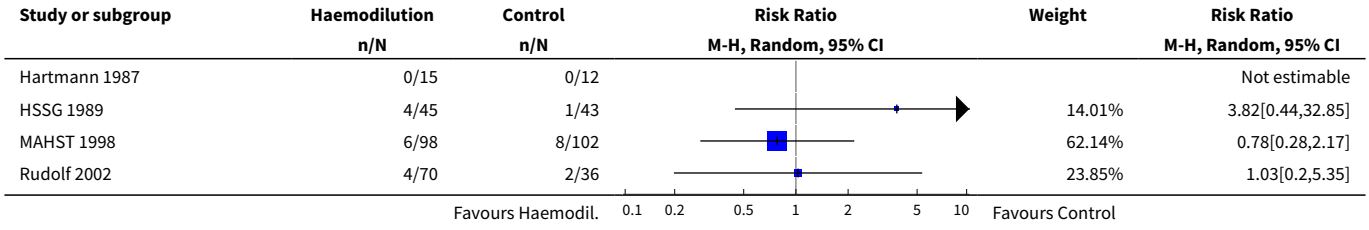
Analysis 4.3. Comparison 4 Haemodilution using low-molecular-weight dextran (dextran 40) versus control, Outcome 3 Dead or dependent/institutionalised (3-6 months).

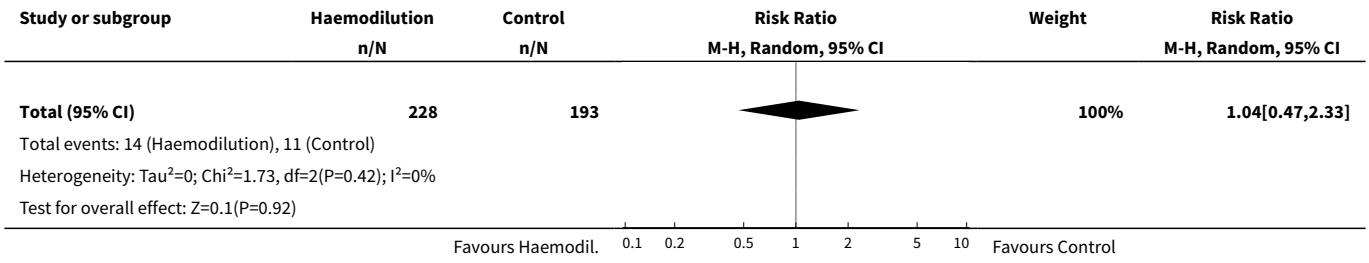


Comparison 5. Haemodilution using hydroxyethyl starch (HES) versus control

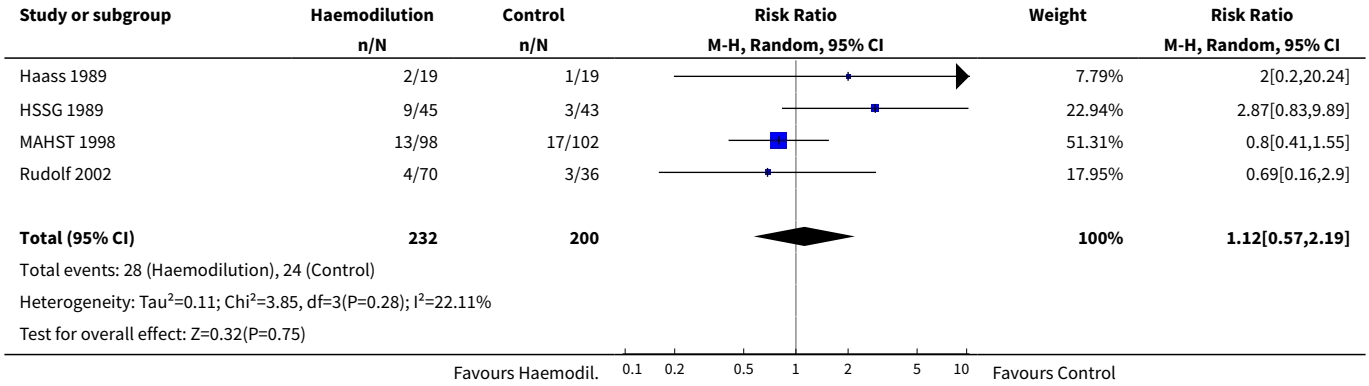
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality at early follow-up (not later than 28 days)	4	421	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.47, 2.33]
2 Mortality at late follow-up (3-6 months)	4	432	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.57, 2.19]
3 Dead or dependent/institutionalised (at 3-6 months)	2	306	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.71, 1.07]

Analysis 5.1. Comparison 5 Haemodilution using hydroxyethyl starch (HES) versus control, Outcome 1 Mortality at early follow-up (not later than 28 days).

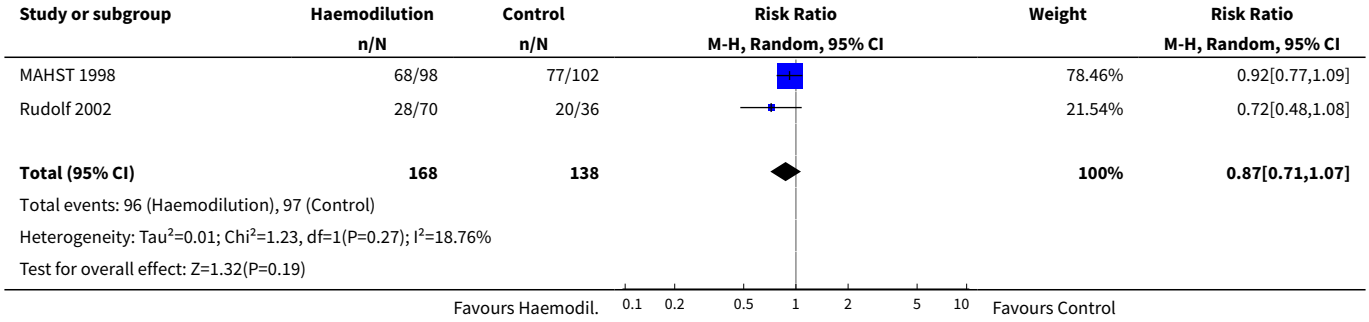




Analysis 5.2. Comparison 5 Haemodilution using hydroxyethyl starch (HES) versus control, Outcome 2 Mortality at late follow-up (3-6 months).



Analysis 5.3. Comparison 5 Haemodilution using hydroxyethyl starch (HES) versus control, Outcome 3 Dead or dependent/institutionalised (at 3-6 months).

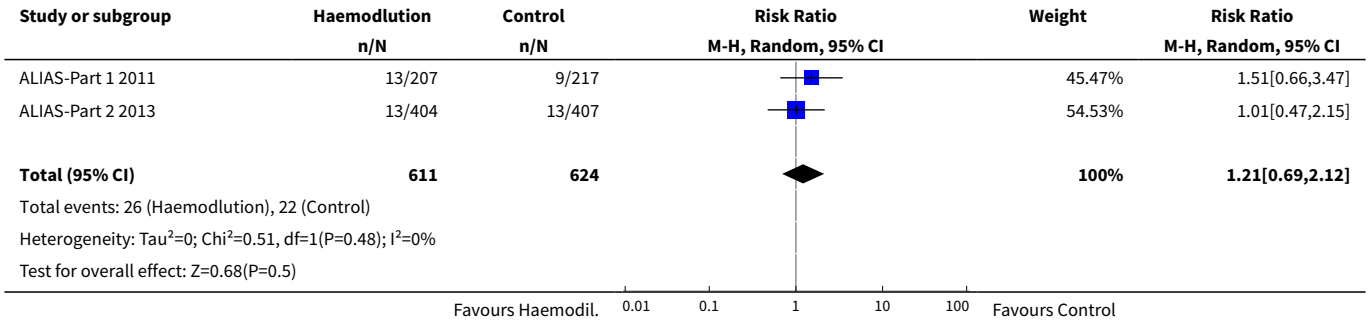


Comparison 6. Haemodilution using albumin versus control

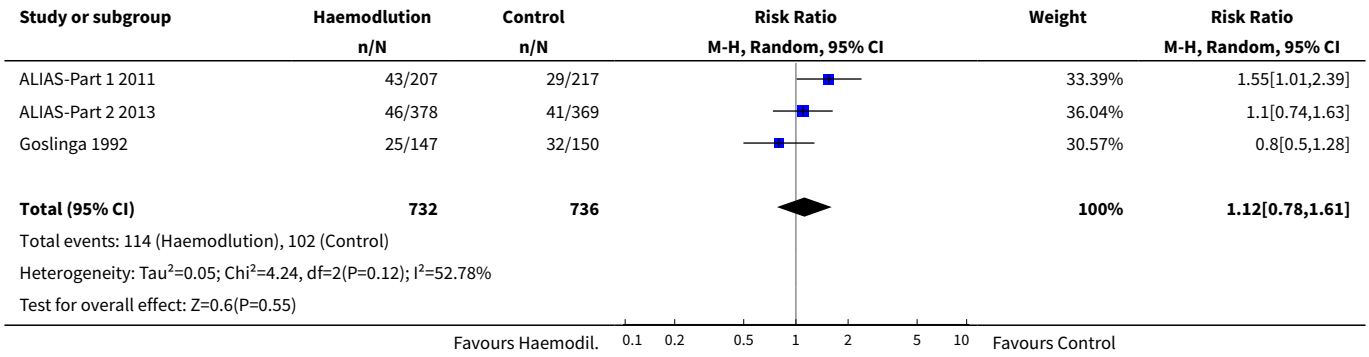
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality at early follow-up (not later than 28 days)	2	1235	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.69, 2.12]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Mortality at late follow-up (3-6 months)	3	1468	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.78, 1.61]

Analysis 6.1. Comparison 6 Haemodilution using albumin versus control, Outcome 1 Mortality at early follow-up (not later than 28 days).



Analysis 6.2. Comparison 6 Haemodilution using albumin versus control, Outcome 2 Mortality at late follow-up (3-6 months).

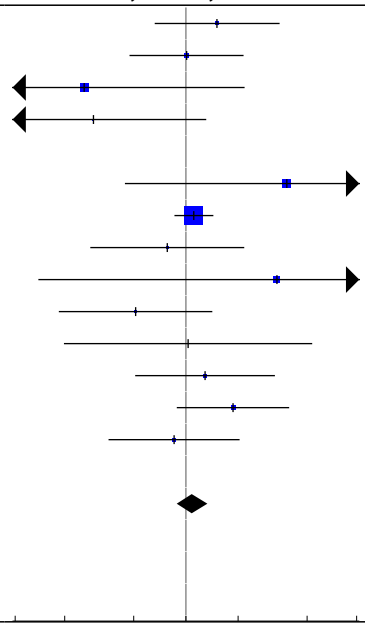


Comparison 7. Unconfounded haemodilution (with no other therapeutic modality) versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality at early follow-up (not later than 28 days)	14	3783	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.89, 1.33]
2 Mortality at late follow-up (3-6 months)	14	3914	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.93, 1.19]
3 Dead or dependent/institutionalised (at 3-6 months)	8	2491	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.85, 1.07]

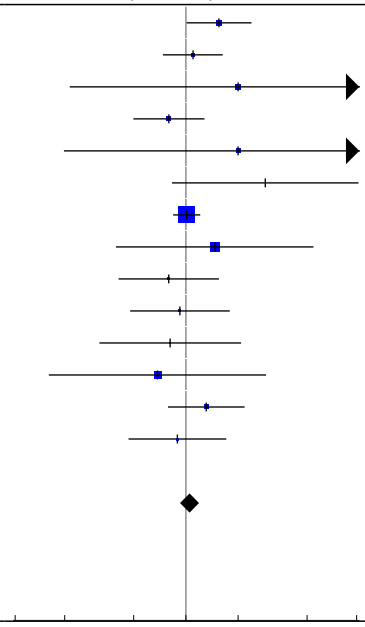
Analysis 7.1. Comparison 7 Unconfounded haemodilution (with no other therapeutic modality) versus control, Outcome 1 Mortality at early follow-up (not later than 28 days).

Study or subgroup	Haemodilution n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
ALIAS-Part 1 2011	13/207	9/217		5.91%	1.51[0.66,3.47]
ALIAS-Part 2 2013	13/404	13/407		7.07%	1.01[0.47,2.15]
Bornstein 1981	1/28	4/29		0.9%	0.26[0.03,2.18]
Gilroy 1969	2/46	8/54		1.82%	0.29[0.07,1.31]
Hartmann 1987	0/15	0/12			Not estimable
HSSG 1989	4/45	1/43		0.88%	3.82[0.44,32.85]
IASSG 1988	103/632	93/634		56.35%	1.11[0.86,1.44]
MAHST 1998	6/98	8/102		3.9%	0.78[0.28,2.17]
Mast 1991	1/33	0/37		0.41%	3.35[0.14,79.59]
Matthews 1976	5/52	9/48		3.91%	0.51[0.18,1.42]
Rudolf 2002	4/70	2/36		1.5%	1.03[0.2,5.35]
Spudis 1973	8/30	6/29		4.72%	1.29[0.51,3.26]
SSSG 1987	18/183	10/190		7.27%	1.87[0.89,3.94]
Strand 1984	8/52	9/50		5.36%	0.85[0.36,2.04]
Total (95% CI)	**1895**	**1888**		**100%**	**1.08[0.89,1.33]**
Total events: 186 (Haemodilution), 172 (Control)					
Heterogeneity: Tau^2=0; Chi^2=12.1, df=12(P=0.44); I^2=0.84%					
Test for overall effect: Z=0.78(P=0.44)					

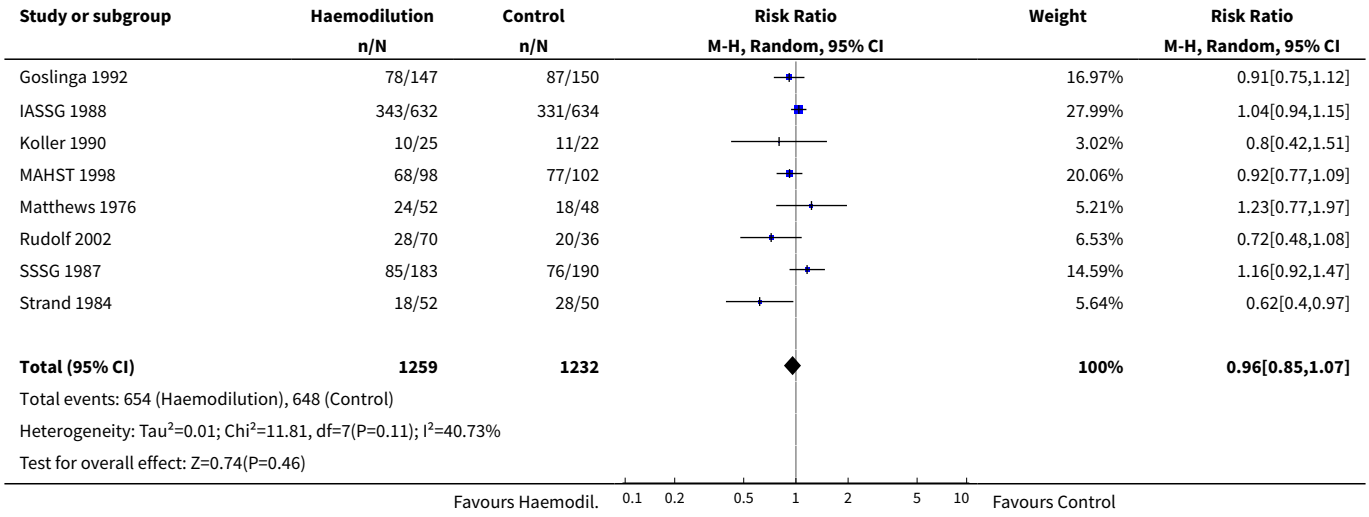


Analysis 7.2. Comparison 7 Unconfounded haemodilution (with no other therapeutic modality) versus control, Outcome 2 Mortality at late follow-up (3-6 months).

Study or subgroup	Haemodilution n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
ALIAS-Part 1 2011	43/207	29/217		8.74%	1.55[1.01,2.39]
ALIAS-Part 2 2013	46/378	41/369		10.35%	1.1[0.74,1.63]
Balcarce 1991	2/10	1/10		0.32%	2[0.21,18.69]
Goslinga 1992	25/147	32/150		7.31%	0.8[0.5,1.28]
Haass 1989	2/19	1/19		0.3%	2[0.2,20.24]
HSSG 1989	9/45	3/43		1.06%	2.87[0.83,9.89]
IASSG 1988	175/632	174/634		50.85%	1.01[0.84,1.21]
Koller 1990	5/25	3/22		0.94%	1.47[0.4,5.44]
MAHST 1998	13/98	17/102		3.65%	0.8[0.41,1.55]
Matthews 1976	13/52	13/48		3.71%	0.92[0.48,1.79]
Popa 1989	7/55	8/51		1.83%	0.81[0.32,2.08]
Rudolf 2002	4/70	3/36		0.78%	0.69[0.16,2.9]
SSSG 1987	29/183	23/190		6.28%	1.31[0.79,2.18]
Strand 1984	13/52	14/50		3.87%	0.89[0.47,1.71]
Total (95% CI)	**1973**	**1941**		**100%**	**1.05[0.93,1.19]**
Total events: 386 (Haemodilution), 362 (Control)					
Heterogeneity: Tau^2=0; Chi^2=10.55, df=13(P=0.65); I^2=0%					
Test for overall effect: Z=0.76(P=0.45)					



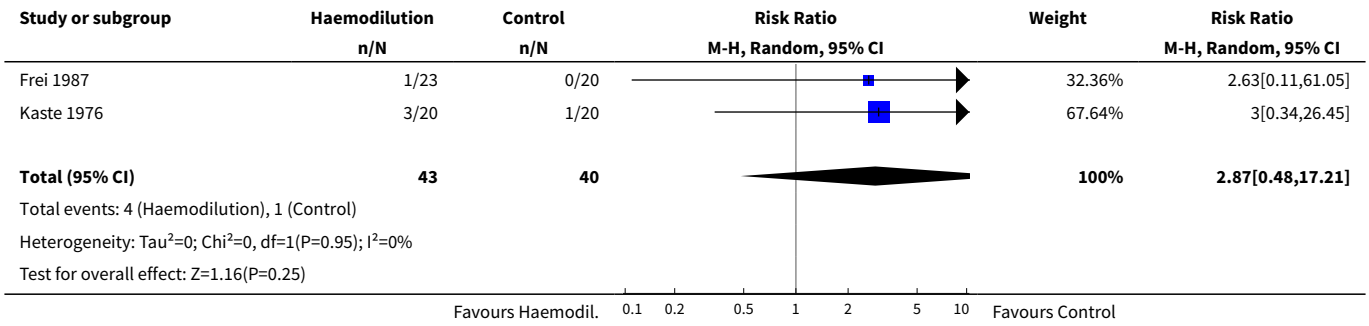
Analysis 7.3. Comparison 7 Unconfounded haemodilution (with no other therapeutic modality) versus control, Outcome 3 Dead or dependent/institutionalised (at 3-6 months).



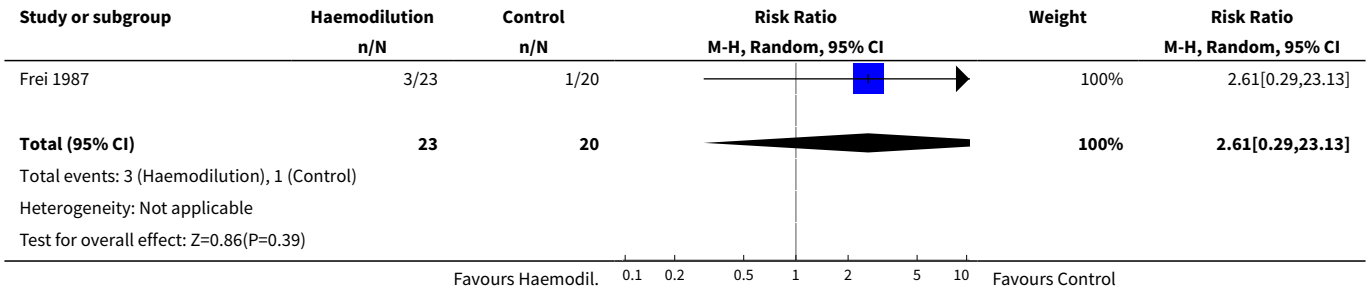
Comparison 8. Haemodilution combined with other treatment modalities

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality at early follow-up (not later than 28 days)	2	83	Risk Ratio (M-H, Random, 95% CI)	2.87 [0.48, 17.21]
2 Mortality at late follow-up (3-6 months)	1	43	Risk Ratio (M-H, Random, 95% CI)	2.61 [0.29, 23.13]

Analysis 8.1. Comparison 8 Haemodilution combined with other treatment modalities, Outcome 1 Mortality at early follow-up (not later than 28 days).



Analysis 8.2. Comparison 8 Haemodilution combined with other treatment modalities, Outcome 2 Mortality at late follow-up (3-6 months).



APPENDICES

Appendix 1. Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

1. [mh ^"cerebrovascular disorders"] or [mh "basal ganglia cerebrovascular disease"] or [mh "brain ischemia"] or [mh "carotid artery diseases"] or [mh"intracranial arterial diseases"] or [mh "intracranial embolism and thrombosis"] or [mh "intracranial hemorrhages"] or [mh ^stroke] or [mh "brain infarction"]

2. (stroke* or apoplex* or cerebral vasc* or cerebrovasc* or cva):ti,ab

3. ((brain or cerebr* or cerebell* or vertebrobasil* or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or middle next cerebr* or mca* or anterior next circulation) near/5 (ischemi* or ischaemic* or infarct* or thrombo* or emboli* or occlus* or hypoxi*)):ti,ab

4. ((brain* or cerebr* or cerebell* or intracerebral or intracran* or parenchymal or intraventricular or infratentorial or supratentorial or basal next gangli* or putaminal or putamen or posterior next fossa) near/5 (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*)):ti,ab

5. #1 or #2 or #3 or #4

6. [mh ^hemodilution]

7. [mh ^"plasma exchange"] or [mh "plasma substitutes"]

8. [mh ^"blood substitutes"]

9. [mh ^hetastarch] or [mh ^dextrans] or [mh ^polygeline] or [mh ^povidone] or [mh albumins] or [mh ^"sodium chloride"] or [mh ^"saline solution, hypertonic"] or [mh colloids]

10. [mh ^phlebotomy] or [mh ^bloodletting]

11. (hemodilut* or haemodilut*):ti,ab

12. (plasma near/3 (expand* or expansion or exchange* or substitut* or replace*)):ti,ab

13. (blood near/3 (expand* or expansion or exchange* or substitute* or replace* or remov* or dilut*)):ti,ab

14. (hetastarch or pentastarch or hydroxyethylstarch or "hydroxyethyl-starch" or dextran* or polygeline or povidone or albumin or saline or colloid*):ti,ab

15. (phlebotomy or bloodletting or "blood-letting" or venesection or venipuncture):ti,ab

16. {OR #6-#15}

17. #5 and #16

Appendix 2. MEDLINE (Ovid) (January 2008 to October 2013) search strategy

1. cerebrovascular disorders/ or exp basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp carotid artery diseases/ or exp intracranial arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp intracranial hemorrhages/ or stroke/ or exp brain infarction/

2. (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva).tw.

3. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.

4. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or intraventricular or infratentorial or supratentorial or basal gangli$ or putaminal or putamen or posterior fossa) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed $)).tw.

5. 1 or 2 or 3 or 4

6. hemodilution/

7. plasma exchange/ or exp plasma substitutes/

8. blood substitutes/

9. hetastarch/ or dextrans/ or polygeline/ or povidone/ or exp albumins/ or sodium chloride/ or saline solution, hypertonic/ or exp colloids/

10. phlebotomy/ or bloodletting/

11. (hemodilut$ or haemodilut$).tw.

12. (plasma adj3 (expand$ or expansion or exchange$ or substitut$ or replace$)).tw.

13. (blood adj3 (expand$ or expansion or exchange$ or substitute$ or replace$ or remov$ or dilut$)).tw.

14. (hetastarch or pentastarch or hydroxyethylstarch or hydroxyethyl-starch or dextran$ or polygeline or povidone or albumin or saline or colloid$).tw.

15. (phlebotomy or bloodletting or blood-letting or venesection or venipuncture).tw.

16. or/6-15

17. 5 and 16

18. Randomized Controlled Trials as Topic/

19. random allocation/

20. Controlled Clinical Trials as Topic/

21. control groups/

22. clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/

23. double-blind method/

24. single-blind method/

25. Placebos/

26. placebo effect/

27. Therapies, Investigational/

28. Research Design/

29. randomized controlled trial.pt.

30. controlled clinical trial.pt.

31. (clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv).pt.

32. random$.tw.

33. (controlled adj5 (trial$ or stud$)).tw.

34. (clinical$ adj5 trial$).tw.

35. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.

36. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.

37. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)).tw.

38. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.

39. (coin adj5 (flip or flipped or toss$)).tw.

40. placebo$.tw.

41. controls.tw.

42. or/18-41

43. 17 and 42

44. stroke volume/ or stroke volume.tw.

45. 43 not 44

46. exp animals/ not humans.sh.

47. 45 not 46

Appendix 3. EMBASE (Ovid) (January 2008 to October 2013) search strategy

1. cerebrovascular disease/ or basal ganglion hemorrhage/ or exp brain hematoma/ or exp brain hemorrhage/ or exp brain infarction/ or exp brain ischemia/ or exp carotid artery disease/ or cerebral artery disease/ or cerebrovascular accident/ or occlusive cerebrovascular disease/ or stroke/

2. stroke patient/ or stroke unit/

3. (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva).tw.

4. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.

5. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or intraventricular or infratentorial or supratentorial or basal gangli$ or putaminal or putamen or posterior fossa) adj10 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed $)).tw.

6. or/1-5

7. hemodilution/

8. exp plasma substitute/ or plasmapheresis/

9. blood substitute/ or dextran/ or dextran 40/ or dextran 60/ or dextran 70/ or hetastarch/ or polygeline/ or rheodextran/

10. albumin/ or serum albumin/ or sodium chloride/ or exp colloids/

11. phlebotomy/

12. (hemodilut$ or haemodilut$).tw.

13. (plasma adj3 (expand$ or expansion or exchange$ or substitut$ or replace$)).tw.

14. (blood adj3 (expand$ or expansion or exchange$ or substitut$ or replace$ or remov$ or dilut$)).tw.

15. (hetastarch or pentastarch or hydroxyethylstarch or hydroxyethyl-starch or dextran$ or polygeline or povidone or albumin or saline or colloid$).tw.

16. (phlebotomy or bloodletting or blood-letting or venesection or venipuncture).tw.

17. or/7-16

18. 6 and 17

19. Randomized Controlled Trial/

20. Randomization/

21. Controlled Study/

22. control group/

23. clinical trial/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/ or controlled clinical trial/

24. Double Blind Procedure/

25. Single Blind Procedure/ or triple blind procedure/

26. latin square design/

27. Parallel Design/

28. placebo/

29. random$.tw.

30. (controlled adj5 (trial$ or stud$)).tw.

31. (clinical$ adj5 trial$).tw.

32. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.

33. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.

34. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)).tw.

35. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.

36. (coin adj5 (flip or flipped or toss$)).tw.

37. placebo$.tw.

38. controls.tw.

39. or/19-38

40. 18 and 39

41. heart stroke volume/ or stroke volume.tw.

42. 40 not 41

43. limit 42 to human

Appendix 4. MEDLINE (Ovid) (1966 to June 2002) search strategy

1. (stroke or cerebrovascular disorders).mp
2. (haemodilution or hemodilution).mp
3. (plasma expanders or dextran or hydroxyethyl starch or albumin).mp
4. (bloodletting or venesection).mp
5. 2 or 3 or 4
6. 1 and 5

WHAT'S NEW

Date	Event	Description
29 April 2014	New citation required but conclusions have not changed	New review author team completed this update
9 March 2014	New search has been performed	Compared with the previous version of the review, this update includes three additional randomised trials and uses random-effects risk ratios instead of fixed-effect odds ratios. The review now includes 21 trials involving 4174 participants. Other additions include the 'Risk of bias' tool, reformatting of methods, sensitivity analyses, and new sections throughout the text

HISTORY

Protocol first published: Issue 2, 1995
Review first published: Issue 2, 1995

Date	Event	Description
25 August 2008	Amended	Converted to new review format.
14 August 2002	New search has been performed	Compared to the previous version, this update includes two additional randomised trials (of which one is not yet published), a plain language summary has been added, more background information is provided and an additional end-point (cardiac adverse effects) is presented.

CONTRIBUTIONS OF AUTHORS

Kjell Asplund published the first review in 1995 with the aid of Karin Israelsson and Ingrid Schampi, who were both medical students. They contributed to the literature search and with independent abstracting of data from the articles. Kjell Asplund updated this review in 2002.

Matthew Jensen took charge of this review in 2011. He was involved in co-ordinating the review, data collection, analysis of data, interpretation of data, writing the review and general advice on the review. Timothy Chang was involved in data collection, data management, analysis of data, interpretation of data and writing the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Swedish Medical Research Council, Swedish Social Research Council, Chest and Heart Fund, Vardalstiftelsen, Sweden.
- Clinical and Translational Science Award program, previously through the National Center for Research Resources grant 1UL1RR025011, and now by the National Center for Advancing Translational Sciences grant 9U54TR000021, USA.
- National Heart Lung and Blood Institute Fellowship F30HL112491, USA.
- National Institute of Health T32 GM008692, USA.
- National Institute of Health, USA.

1K08NS079622-01A1

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The 2002 version stated in the methods that "Only studies which reported clinical end-points of direct relevance for the patients (death, neurological outcome, functional outcome, need for institutional care, vascular or other events, adverse reactions) have been included." and "Many studies reported on changes in neurological and functional scores. A plethora of scores and measures of distribution have been used. Therefore, it has not been possible to report on changes of score sums in a uniform manner." All studies containing neurological outcome also had other outcomes including mortality, need for institutional care, etc. Therefore, these studies could be included in the data and analyses.

We decided not to include studies that only had neurological score outcomes, which may have been implicit in the 2002 methods. These studies could not be added to the data and analyses given the varying scores. Therefore, we added the following in the current version's methods "...studies that only included neurological examination scale outcomes because these outcomes could not be combined given the variety of neurological scores (see Types of outcome measures)."

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Brain Ischemia [complications] [mortality] [*therapy]; Combined Modality Therapy [methods]; Hemodilution [*methods] [mortality]; Phlebotomy [methods]; Plasma Substitutes [therapeutic use]; Randomized Controlled Trials as Topic; Stroke [etiology] [mortality] [*therapy]

MeSH check words

Humans